

# An efficient and one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$

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## Abstract

$\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  was found to be a mild and effective catalyst for the efficient, one-pot, three component synthesis of 2,4,5-trisubstituted imidazoles at room temperature. Moreover, the utility of this protocol was further explored conveniently for the one-pot, four component synthesis of 1,2,4,5-tetrasubstituted imidazoles in high yields.

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**Keywords:** Multicomponent reaction; One-pot synthesis; 2,4,5-Trisubstituted imidazoles; 1,2,4,5-Tetrasubstituted imidazoles;  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$

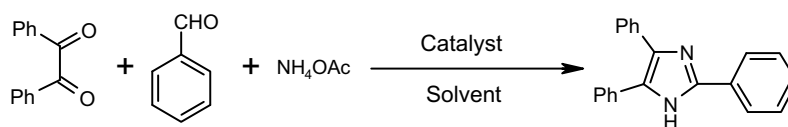
Multicomponent reactions enjoy an outstanding status in organic and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel.<sup>1</sup> Naturally occurring substituted imidazoles, as well as synthetic derivatives thereof, exhibit wide ranges of biological activities, making them attractive compounds for organic chemists. They act as inhibitors of p38 MAP kinase,<sup>2a</sup> B-Raf kinase,<sup>2b</sup> transforming growth factor  $\beta 1$  (TGF- $\beta 1$ ) type 1 activin receptor-like kinase (ALK5),<sup>2c</sup> cyclooxygenase-2 (COX-2)<sup>2d</sup> and biosynthesis of interleukin-1 (IL-1).<sup>2e</sup> Appropriately substituted imidazoles are extensively used as glucagon receptors<sup>3a</sup> and CB<sub>1</sub> cannabinoid receptor antagonists,<sup>3b</sup> modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR),<sup>3c</sup> antibacterial<sup>3d</sup> and antitumor<sup>3e</sup> agents and also as pesticides.<sup>3f</sup> Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids<sup>4</sup> and N-heterocyclic carbenes.<sup>5</sup>

This versatile applicability highlights the importance of access to efficient synthetic routes to well designed highly substituted imidazole derivatives. A number of methods have been developed for the synthesis of 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles. 2,4,5-Trisubstituted imidazoles are generally synthesized by three component cyclocondensation of a 1,2-diketone,  $\alpha$ -hydroxyketone or  $\alpha$ -ketomoxime with an aldehyde and ammonium acetate, which comprise the use of microwaves,<sup>6a-d</sup> ionic liquids,<sup>6c</sup> refluxing in acetic acid,<sup>6f-h</sup> silica sulfuric acid,<sup>6i</sup> and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ .<sup>6j</sup> Moreover, they have also been prepared by the reaction of aryl nitriles and  $\alpha, \alpha$ -dilithioarylnitromethanes<sup>7a</sup> or by multistep syntheses.<sup>7b,c</sup> On the other hand, the syntheses of 1,2,4,5-tetrasubstituted imidazoles are carried out by four-component condensation of a 1,2-diketone,  $\alpha$ -hydroxyketone or  $\alpha$ -ketomoxime with an aldehyde, primary amine and ammonium acetate using microwaves,<sup>8a</sup> heteropolyacid,<sup>8b</sup> silica gel/ $\text{NaHSO}_4$ <sup>8c</sup> or  $\text{HClO}_4 \cdot \text{SiO}_2$ .<sup>8d</sup> In addition, they can also be accessed by the cycloaddition reaction of mesoionic 1,3-oxazolium-5-olates with *N*-(arylmethylene)-benzenesulfonamides,<sup>9a</sup> hetero-Cope rearrangement,<sup>9b</sup> condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation<sup>9c</sup> and by *N*-alkylation of trisubstituted imidazoles.<sup>9d</sup>

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Table 1

Condensation of benzil, benzaldehyde and ammonium acetate using different catalysts and solvents<sup>a</sup>

Entry	Catalyst	Catalyst loading (mol %)	Solvent	Time (h)	Yield <sup>b</sup> (%)
1	InCl <sub>3</sub> ·3H <sub>2</sub> O	20	MeOH	12.0	73
2	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	MeOH	8.3	82
3	InCl <sub>3</sub> ·3H <sub>2</sub> O	30	MeOH	12.0	69
4	InCl <sub>3</sub> ·3H <sub>2</sub> O	5	MeOH	12.0	67
5	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	EtOH	12.0	77
6	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	<i>iso</i> -PrOH	13.0	62
7	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	<i>t</i> -BuOH	13.4	50
8	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	CHCl <sub>3</sub>	24.0	N.R. <sup>c</sup>
9	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	CH <sub>2</sub> Cl <sub>2</sub>	24.0	Trace
10	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	Toluene	24.0	N.R. <sup>c</sup>
11	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	CH <sub>3</sub> CN	12.0	55
12	InCl <sub>3</sub> ·3H <sub>2</sub> O	10	H <sub>2</sub> O	24.0	N.R. <sup>c</sup>
13	SnCl <sub>2</sub> ·2H <sub>2</sub> O	10	MeOH	18.0	48
14	CoCl <sub>2</sub> ·2H <sub>2</sub> O	10	MeOH	18.0	39
15	NiCl <sub>2</sub> ·2H <sub>2</sub> O	10	MeOH	18.0	41
16	AlCl <sub>3</sub> ·6H <sub>2</sub> O	10	MeOH	18.0	38
17	H <sub>3</sub> BO <sub>3</sub>	10	MeOH	18.0	34
18	Mg(OAc) <sub>2</sub> ·2H <sub>2</sub> O	10	MeOH	18.0	51
19	CAN	10	MeOH	10.0	72
20	CAN	10	EtOH	10.0	70
21	CAN	5	MeOH	10.0	75
22	No catalyst	—	MeOH	24.0	10

<sup>a</sup> Benzil:benzaldehyde:NH<sub>4</sub>OAc (1 mmol:1 mmol:2 mmol).<sup>b</sup> Isolated yield.<sup>c</sup> No reaction.

Most of these synthetic methods suffer from one or more serious drawbacks, such as laborious and complex work-up and purification, significant amounts of waste materials, strongly acidic conditions, occurrence of side reactions, low yields and the use of expensive reagents. Additionally, most require elevated temperatures created either by microwave irradiation<sup>6a–d,8a,c,9c</sup> at 180–200 °C or by refluxing<sup>6g–j,7a–c,8b,9b</sup> and heating<sup>6e,8c,d,9a</sup> the reaction mixture at high temperatures. Therefore, the development of a new catalytic system to overcome these shortcomings and fulfill the criteria of a mild, efficient and environmentally benign protocol for the synthesis of highly substituted imidazoles is an important task for organic chemists.

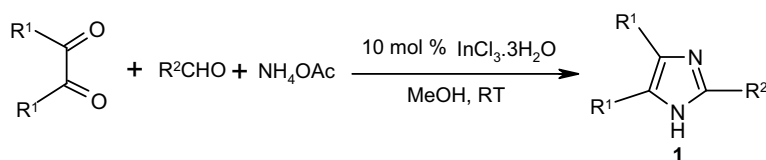
In recent years, indium chloride<sup>10</sup> has invoked enormous interest as a green and mild Lewis acid of high potential to construct carbon–carbon or carbon–heteroatom bonds in various organic transformations due to its low toxicity, cost effectiveness, air and water compatibility, ease of handling, good reactivity, experimental simplicity and excellent solubility in water and organic solvents. Moreover, it has a remarkable ability to suppress side reactions in acid sensitive substrates.

In continuation of our effort to develop Lewis and Brønsted acid<sup>11</sup> catalyzed synthetic methodologies, we report herein, for the first time, a simple, mild and expeditious synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles in high yields using InCl<sub>3</sub>·3H<sub>2</sub>O as a

catalyst at ambient temperature. It may be mentioned that InCl<sub>3</sub> was found to be completely ineffective for the synthesis of highly substituted imidazoles as recently reported by Singh et al.<sup>12</sup>

Initially, we sought a mild and convenient method for the synthesis of trisubstituted imidazoles at room temperature. Our investigation began with the evaluation of InCl<sub>3</sub>·3H<sub>2</sub>O as a catalyst in the reaction of benzil (1 equiv), benzaldehyde (1 equiv) and ammonium acetate (2 equiv) at ambient temperature. The use of 20 mol % of InCl<sub>3</sub>·3H<sub>2</sub>O in methanol afforded a 73% yield (Table 1, entry 1) of the desired product. Optimization of the reaction conditions was undertaken to increase the yield employing different catalyst loadings in a wide variety of solvents. The results are summarized in Table 1. The yield was increased to 82% using 10 mol % of InCl<sub>3</sub>·3H<sub>2</sub>O (Table 1, entry 2). However, the addition of 30 mol % of the catalyst was found to have an inhibitory effect on the formation of the 2,4,5-trisubstituted imidazole (Table 1, entry 3), whereas a reduction in yield was observed by decreasing the catalyst loading to 5 mol % (Table 1, entry 4). The influence of other Lewis acids were also examined. It is noteworthy that ceric ammonium nitrate (CAN) was found to give quite high yields for this transformation (Table 1, entries 19–21). In the absence of the catalyst, the reaction proceeded sluggishly (Table 1, entry 22). The choice of reaction solvent was crucial. Changing the solvent from

Table 2  
 $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  catalyzed synthesis of 2,4,5-trisubstituted imidazoles<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	Products	Time (h)	Yield <sup>b</sup> (%)
a	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<b>1a</b>	8.3	82
b	C <sub>6</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>1b</b>	9.0	77
c	C <sub>6</sub> H <sub>5</sub>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>1c</b>	8.2	76
d	C <sub>6</sub> H <sub>5</sub>	4-BrC <sub>6</sub> H <sub>4</sub>	<b>1d</b>	9.0	76
e	C <sub>6</sub> H <sub>5</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1e</b>	9.4	71
f	C <sub>6</sub> H <sub>5</sub>	2-HOC <sub>6</sub> H <sub>4</sub>	<b>1f</b>	9.1	69
g	C <sub>6</sub> H <sub>5</sub>	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>1g</b>	8.5	73
h	C <sub>6</sub> H <sub>5</sub>	2-ClC <sub>6</sub> H <sub>4</sub>	<b>1h</b>	9.1	68
i	C <sub>6</sub> H <sub>5</sub>	4-HOC <sub>6</sub> H <sub>4</sub>	<b>1i</b>	8.4	71
j	C <sub>6</sub> H <sub>5</sub>	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>1j</b>	9.3	76
k	4-MeC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>4</sub>	<b>1k</b>	8.4	78
l	4-MeC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>1l</b>	9.0	73
m	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	<b>1m</b>	8.4	64
n	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	<b>1n</b>	9.0	61
o	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	<b>1o</b>	9.4	54
p	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	<b>1p</b>	9.3	58
q	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>1q</b>	8.4	61
r	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )	<b>1r</b>	9.0	57

<sup>a</sup> Benzil:aldehyde:NH<sub>4</sub>OAc (1 mmol:1 mmol:2 mmol).

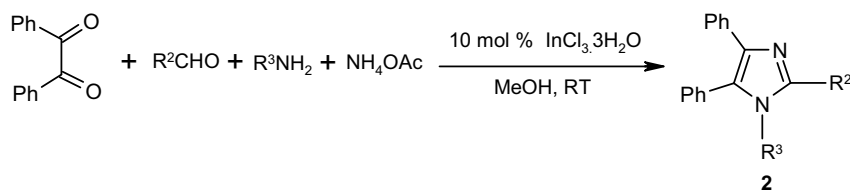
<sup>b</sup> Isolated yield.

methanol to ethanol was not beneficial as the yield was reduced to 77% (Table 1, entry 5). The use of *iso*-propanol and *t*-butanol as solvents furnished poor yields (Table 1, entries 6 and 7). The results indicated that the yield gradually decreased as we moved from highly polar to less polar alcoholic solvents. Other solvents, such as CH<sub>3</sub>CN, CHCl<sub>3</sub>

CH<sub>2</sub>Cl<sub>2</sub> and toluene were ineffective for this transformation. Hence, the conditions of entry 2, shown in Table 1, were the optimized reaction conditions.

We next examined a wide variety of aldehydes (both aromatic and aliphatic) and 1,2-diketones to establish the scope of this catalytic transformation (Table 2).<sup>13</sup> A broad

Table 3  
 $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles<sup>a</sup>



Entry	R <sup>2</sup>	R <sup>3</sup>	Products	Time (h)	Yield <sup>b</sup> (%)
a	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<b>2a</b>	6.4	83
b	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	<b>2b</b>	6.1	84
c	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> CH <sub>2</sub>	<b>2c</b>	6.0	84
d	C <sub>6</sub> H <sub>5</sub>		<b>2d</b>	7.2	77
e	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>2e</b>	7.4	79
f	4-MeC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>2f</b>	8.0	75
g	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	<b>2g</b>	6.0	80
h	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CH <sub>2</sub>	<b>2h</b>	6.0	81
i	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>2i</b>	7.5	73
j	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>2j</b>	8.4	51
k	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>2k</b>	9.0	49
l	CH <sub>3</sub>	CH <sub>3</sub>	<b>2l</b>	8.2	47

<sup>a</sup> Benzil:benzaldehyde:primary amine:NH<sub>4</sub>OAc (1 mmol:1 mmol:1 mmol:1 mmol).

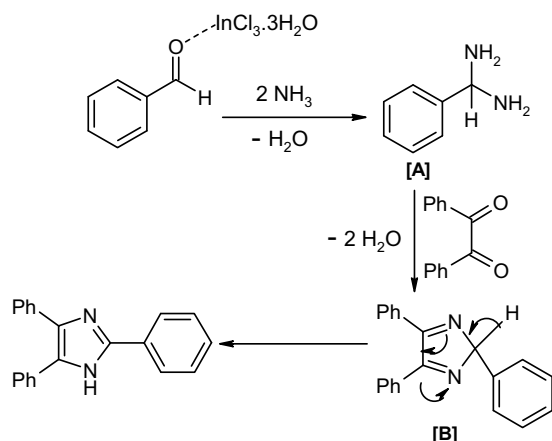
<sup>b</sup> Isolated yield.

range of aromatic aldehydes bearing electron donating and electron withdrawing substituents underwent this one-pot, three-component cyclocondensation to furnish 2,4,5-trisubstituted imidazoles in high yields. Aliphatic aldehydes afforded the corresponding imidazoles in moderate yields. Various functional groups were found to be compatible under the reaction conditions. In general, the reactions were clean and no side products were detected. In all cases, the reactions proceeded efficiently at room temperature.

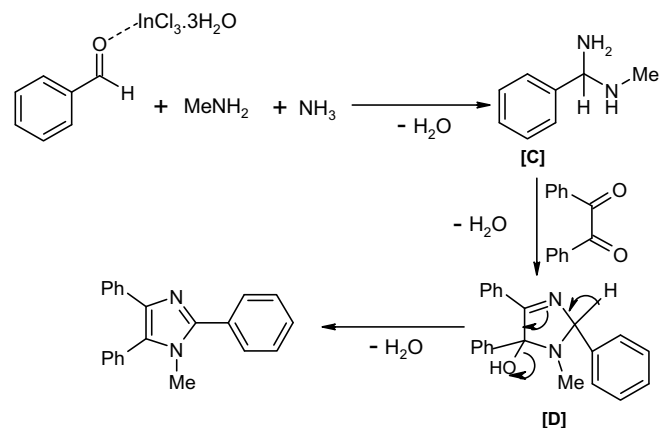
The same reaction conditions were applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the one-pot, four component condensation of benzil, an aldehyde, a primary amine and ammonium acetate.<sup>14</sup> To our delight, the 1,2,4,5-tetrasubstituted imidazoles were obtained in high yields at room temperature. The substrate scope of the reaction was then evaluated using a variety of structurally diverse aldehydes and primary amines (Table 3). Both aliphatic and aromatic aldehydes and primary amines could be subjected successfully to this protocol. Aromatic aldehydes produced high yields of 1,2,4,5-tetrasubstituted imidazoles, whereas aliphatic aldehydes produced moderate to lower yields of the corresponding imidazoles. In each case, no side product formation, for example, 2,4,5-trisubstituted imidazoles was observed, as is normally the case in such reactions under the influence of strong acids.

In accordance with the mechanism delineated by Srinivasan et al.<sup>6c</sup> it may be proposed that the  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  catalyst facilitates the formation of diamine intermediate [A] by increasing the electrophilicity of the carbonyl group of the aldehyde. Intermediate [A], in the presence of  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$ , condenses with benzil to form intermediate [B], which in turn rearranges to the trisubstituted imidazole by a [1,5] hydrogen shift (Scheme 1).

Similarly, the plausible mechanism for the synthesis of the tetrasubstituted imidazole involves the formation of intermediate [C] by the reaction of an aldehyde, primary amine and ammonium acetate in the presence of  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  catalyst. Intermediate [C] condenses with benzil to



Scheme 1. A plausible mechanism for the formation of trisubstituted imidazoles.



Scheme 2. A plausible mechanism for the formation of tetrasubstituted imidazoles.

form intermediate [D], which in turn liberates a water molecule to form the tetrasubstituted imidazole (Scheme 2).

In conclusion, a one-pot, multicomponent methodology has been developed for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by 10 mol % of  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  in high yields. Compared to previously reported methods, most of which required elevated temperatures, this protocol proceeded smoothly at room temperature. Moreover, the mild reaction conditions, easy work-up, clean reaction profiles, lower catalyst loading and cost efficiency render this approach as an interesting alternative to the existing methods. Further studies on the application of this method for the synthesis of highly functionalized biologically active imidazoles are underway.

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## Supplementary data

Experimental procedures and characterization data of all the compounds are available. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.02.053](https://doi.org/10.1016/j.tetlet.2008.02.053).

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13. *General procedure for the synthesis of 2,4,5-trisubstituted imidazoles:* In a 50 ml round-bottom flask, 1,2-diketone (1 mmol), aldehyde (1 mmol) and ammonium acetate (2 mmol) were stirred in the presence of 10 mol % of  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  in methanol (2 ml) at room temperature for the stipulated time (Table 2). The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with water (3 ml) and extracted with ethyl acetate ( $2 \times 15$  ml). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , concentrated and recrystallized from ethanol to afford pure product.
- 2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (1j):* Mp 215 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 300 MHz):  $\delta$  3.85 (s, 3H), 3.89 (s, 3H), 7.21–7.81 (m, 13H), 12.52 (br s, 1H); FT-IR (KBr,  $\text{cm}^{-1}$ ): 1545, 1633, 3446; ESI-MS ( $m/z$ ): 357 ( $\text{M}^+ + 1$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ : C, 77.51; H, 5.66; N, 7.86. Found: C, 77.57; H, 5.62; N, 7.89.
- 2-(1-Phenylethyl)-4,5-diphenyl-1H-imidazole (1r):* Mp 185–187 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 300 MHz):  $\delta$  1.17 (d,  $J = 7.2$  Hz, 3H), 4.31 (q,  $J = 7.2$  Hz, 1H), 7.14–7.79 (m, 15H), 12.44 (br s, 1H); FT-IR (KBr,  $\text{cm}^{-1}$ ): 1526, 1631, 3431; ESI-MS ( $m/z$ ): 325 ( $\text{M}^+ + 1$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2$ : C, 85.15; H, 6.21; N, 8.63. Found: C, 85.19; H, 6.27; N, 8.69.
14. *General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles:* In a 50 ml round-bottom flask, 1,2-diketone (1 mmol), aldehyde (1 mmol), primary amine (1 mmol) and ammonium acetate (1 mmol) were stirred in the presence of 10 mol % of  $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$  in methanol (2 ml) at room temperature for the stipulated time (Table 3). The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate ( $2 \times 25$  ml). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The products were separated and purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane mixture as an eluent to afford pure tetrasubstituted imidazoles.
- 1-Methyl-2,4,5-triphenylimidazole (2b):*<sup>8a</sup> Mp 144–145 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  3.51 (s, 3H), 7.16–7.76 (m, 15H); FT-IR ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ): 1602, 1581; ESI-MS ( $m/z$ ): 311 ( $\text{M}^+ + 1$ ). Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2$ : C, 85.13; H, 5.85; N, 9.03. Found: C, 85.18; H, 5.89; N, 9.02.