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**Research Article**

**Theme-** *New horizons in chemical sciences.*

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**Copper Silicate Catalyzed Efficient Synthesis of 2, 4, 5-Trisubstituted imidazole Derivatives via Multicomponent approach.**

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**ABSTRACT**

A new and efficient method has been developed for the synthesis of 2,4,5-trisubstituted imidazole derivatives from substituted aldehydes, benzyl and ammonium acetate in ethanol and copper silicates as a catalyst. The catalyst is separated simply by filtration process. High yield of products, reusable catalyst and easy workup procedure are the main features of developed process. The catalyst was recycled for four times without considerable loss of its catalytic activity. These advantages make the methodology more useful from the synthetic and environmental points of view.

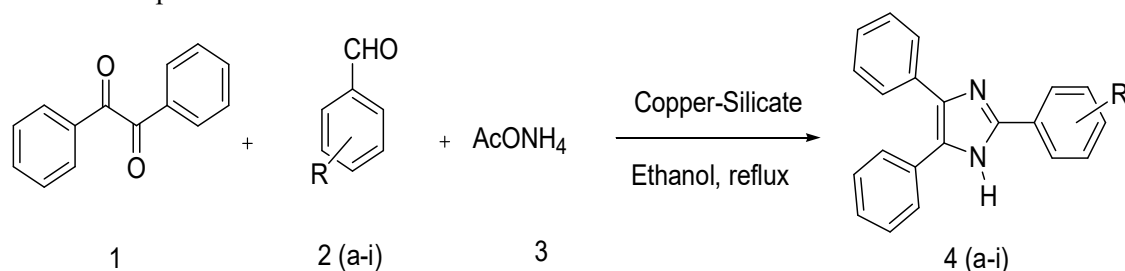
**KEYWORDS**

2, 4, 5-Trisubstituted imidazole, Copper silicate, Multicomponent, Heterogeneous catalyst.

## 1. INTRODUCTION

Imidazole plays important role in the field of medicinal chemistry because imidazole nucleus forms a central part in many drugs molecules.[1] Medicinal properties of imidazole derivatives mainly include antibacterial,[2] anti-inflammatory [3] and glucagon receptors.[4] During last decade numerous methodologies have been developed for the synthesis of substituted imidazole derivatives using various catalytic systems such as molecular iodine,[5] hetero polyacids,[6] L-proline,[7] MoO<sub>3</sub>-SiO<sub>2</sub>,[8] InCl<sub>3</sub>.3H<sub>2</sub>O,[9] ceric ammonium nitrate,[10] zeolite,[11] microwave irradiation[12], sonication[13] and ionic liquids[14]. Several methodologies have been reported for the synthesis of imidazole. These methods have some demerits such as longer reaction time, expensive or hazardous catalyst and use of tedious purification process. Thus there is need to develop new method for the synthesis of imidazole derivatives. Present protocol offers several advantages such as simplicity of procedure, short reaction time, high yield and easy workup procedure.

Due to heterogeneous behavior, this catalyst is easy to separate. Nontoxic, reusability, high reactivity and ease of handling are some additional advantages of this catalyst. Here, we present a simple and efficient methodology for synthesis of 2, 4, 5- Trisubstituted imidazoles using copper silicate catalyst. The reaction scheme is represented as shown below in Scheme - 1.



**Scheme 1.** Synthesis of 2, 4, 5-trisubstituted imidazole derivatives (4a-i).

## 2. MATERIALS AND METHODS

### 2.1. Experimental section

Chemicals were purchased from SD Fine and used without further purification. Melting points of the products were recorded in open capillaries in liquid paraffin bath and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) in 20% (ethyl acetate:n-hexane) on silica gel precoated aluminum foil (Merck). Infrared spectra were recorded in KBr disc on Shimadzu-FT-IR Spectrophotometer and absorption bands are expressed in cm<sup>-1</sup>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance II 400 NMR Spectrometer instrument in DMSO-d<sub>6</sub> as solvent and TMS as internal standard. Mass spectra were recorded on Waters Q-TOF micromass spectrophotometer.

### 2.2. General procedure for the synthesis of 2,4,5 tri substituted imidazole derivatives.

In round bottom flask 1 mmole of benzil, 1 mmole of aldehyde (2a-i), 2 mmole of ammonium acetate and 15 mole % copper silicate catalyst was added to 5 ml ethanol. This reaction mixture was reflux. The progress of the reaction was monitored by thin layer chromatography using hexane: ethyl acetate (8:2) as a mobile phase. After completion of the reaction, the reaction mixture was filtered to isolate the catalyst and then poured over crushed ice to obtain solid product. Obtained solid product is isolated by filtration method. Isolated crude product was purified by recrystallization using hot ethanol. Other analogs of this series were prepared and tabulated data of various derivatives is mention in table 4. Their structures have been confirmed by analyzing method such as <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS and IR spectra.

### 2.3. Spectral analysis

2-(4-Nitro-phenyl)-4,5-diphenyl- *1H* -imidazole (4a), M P = 243-246<sup>0</sup>C, Yield 92 %, IR (KBr, cm<sup>-1</sup>) 3350 (-N-H) 1950 (-C=N), 1620 (C=C), 1570 (-NO<sub>2</sub>). <sup>1</sup>H-NMR (400 MHz, DMSO) δ 7.25(d, 3H, Ar-H), 7.35(d, 3H, Ar-H), 7.55(dd, 4H, Ar-H), 7.72(d, 1H, Ar-H), 7.91(d, 1H, Ar-H), 8.15(d, 1H, Ar-H), 8.35(d, 1H, Ar-H). <sup>13</sup>C NMR (100 MHz, DMSO) 147.32, 146.40, 143.36, 138.45, 136.05, 134.60, 130.48, 129.06, 128.45, 126.82, 132.64. ES-MS (m/z): M+1= (342.12).

2-(4-Chloro-phenyl)-4,5-diphenyl- *1H* -imidazole (4f), M P = 260-262<sup>0</sup>C, Yield 87 %, IR (KBr, cm<sup>-1</sup>) 3340 (-N-H), 1950 -C=N (stretch), 1620 -C=C, 850 C-Br. <sup>1</sup>H-NMR (400 MHz, DMSO) δ 7.15(d, 3H, Ar-H), 7.30(d, 3H, Ar-H), 7.45(dd, 4H, Ar-H), 7.65(d, 1H, Ar-H), 7.90(d, 1H, Ar-H), 8.10(d, 1H, Ar-H), 8.25(d, 1H, Ar-H). <sup>13</sup>C NMR (100 MHz DMSO) 145.50, 145.40, 142.34, 137.40, 137.00, 134.10, 129.48, 128.20, 127.40, 127.80, 131.50. ES-MS (m/z) M+1 = (330.09).

### 3. RESULTS AND DISCUSSION

Reaction of benzil (1), 4-nitro benzaldehyde (2a) and ammonium acetate (3) is considered as a model reaction (Scheme 1). For the screening of various catalysts, initially we used ferric chloride at room temperature; it gives moderate yield (Table 1, entry 1). There is a scope to change the catalyst for the reaction aluminum chlorides and Eaton's reagents with dichloromethane as a solvent gives moderate yield (Table 1, entry 2-3). To decrease the time and increase the yield of this reaction, we used copper silicate in ethanol as a heterogeneous catalyst better result was observed (Table 1, entry 4).

**Table 1.** Screening of various catalysts for the synthesis of 2,4,5-trisubstituted imidazole derivatives.

Entry	Catalysts	Solvent	Temp (°C)	Time (h)	Yield (%)
1	FeCl <sub>3</sub>	Ethanol	R T	7	45
2	AlCl <sub>3</sub>	DCM	Reflux	6	62
3	Eaton's reagent	DCM	Reflux	5	51
4	Copper silicate	Ethanol	Reflux	3	92

In order to study screening of solvent, reactions were carried out in various solvents for the synthesis of substituted imidazole derivatives. Selection of solvent, initially we use dichloromethane and 15 mole % catalyst at room temperature. 52 % yield was obtained (Table 2, entry 1). To raising the temperature and screening, various solvents good yield was obtained (Table 2, entry 2-6).The best results was obtained in ethanol as a solvent at reflux condition (Table 2, entry 7) making it the most suitable solvent.

**Table 2.** Screening of solvent for the synthesis of 2,4,5-trisubstituted imidazole derivatives.

Entry	Solvent	Catalyst	Time (h)	Temp (°C)	Yield (%)
1	DCM	15%	7	RT	52
2	Methanol	15 %	3	Reflux	90
3	Toluene	15 %	5	Reflux	63
4	Acetonitrile	15 %	4	Reflux	85
5	DMF	15 %	2	Reflux	78
6	Water	15 %	3	Reflux	30
7	Ethanol	15 %	3	Reflux	92

To optimize the concentration of catalyst in the model reaction, we investigated 5,10, 15, and 20mol % catalyst (Table 3). When the reaction was carried out in the absence of catalyst, the product formed was only a trace amount (Table 3, entry 1). Optimal results were obtained with 15 mole % catalyst (Table 3, entry 4).

**Table 3.** Effect of concentration of catalyst for the synthesis of 2,4,5-trisubstituted imidazole derivatives.

Entry	Catalyst (Mole %)	Solvent	Time (h)	Temp ( <sup>0</sup> C)	Yield (%)
1	-	Ethanol	8	Reflux	30
2	5	Ethanol	7	Reflux	69
3	10	Ethanol	5	Reflux	85
4	15	Ethanol	3	Reflux	92
5	20	Ethanol	3	Reflux	92

To explore the scope of the method, different substituted aldehyde 2(a-i) were reacted with benzil and ammonium acetate in the presence of 15 mol % of copper silicateas a catalyst and using ethanol as a solvent as indicated in table 4.

**Table 4.** Synthesis of imidazole derivatives using benzil (2 mmol), aldehyde 2a-i (2 mmole), ammonium acetate (5 mmol) and catalyst (15 mol %) at reflux condition.

Entry	Aldehyde (2a-i)	Time (h)	Yield <sup>a</sup> (%)	M. P. ( <sup>0</sup> C)
1	4-NO <sub>2</sub>	3	92	243-246
2	2-OH	3	89	200-203
3	4-OCH <sub>3</sub>	4	82	231-233
4	4-OH	3	86	235-238
5	3,4-(OCH <sub>3</sub> ) <sub>2</sub>	5	80	217-218
6	4-Cl	3	87	260-262
7	3-OCH <sub>3</sub> , 4-OH	3	93	220-221
8	4-F	4	87	188-190
9	4-Br	3	88	261-263
10	-H	4	85	268-270

<sup>a</sup>Isolated yield

After optimizing the reaction conditions, we examined the recycling of catalyst. The results are summarized in Table 5. Data indicate that there is marginal decrease in the yield of the product as the number of cycle increases.

**Table 5.** Data for recycling of catalysts for the synthesis of 2,4,5-trisubstituted imidazole derivatives.

Entry	Number of cycles	Temp ( <sup>0</sup> C)	Yield (%)
1	Fresh	Reflux	92
2	1	Reflux	90
3	2	Reflux	88

4	3	Reflux	81
5	4	Reflux	76

#### 4. CONCLUSION

Synthesis of 2,4,5-trisubstituted imidazole derivatives has been reported via multicomponent reaction approach. High yield, easy work up procedure, easily separable and reusable catalyst are some advantages of this synthetic protocol. The catalyst was recycled for four times without considerable loss of its catalytic activity. These advantages make the methodology more useful from the synthetic and environmental points of view.

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