



## **Potassium Dihydrogen Phosphate: An Inexpensive Catalyst for the Synthesis of 2, 4, 5- Trisubstituted Imidazoles under Solvent Free Condition**

**Jayashri D. Bhirud<sup>1</sup> and Hemant P. Narkhede<sup>2\*</sup>**

1. Moolji Jaitha College, Jalgaon, Dist-Jalgaon, (M. S.), 425002, **INDIA**

2. Smt. P. K. Kotecha Mahila Mahavidyalaya, Bhusawal, Dist-Jalgaon, (M. S.), 425201, **INDIA**

Email: [narkhede.hemant@rediffmail.com](mailto:narkhede.hemant@rediffmail.com), [ingale.jayashri@rediffmail.com](mailto:ingale.jayashri@rediffmail.com)

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### **ABSTRACT**

*An efficient procedure was described for the synthesis of 2, 4, 5-trisubstituted imidazoles through a three component one pot reaction of benzyl, benzaldehyde and NH<sub>4</sub>OAc, in the presence of catalytic amount of potassium dihydrogen phosphate (10 mol %) under solvent-free condition at room temperature. The notable advantages of this method are the experimental simplicity, inexpensive reagents, short reaction times and easy workup procedure.*

**Keywords:** Trisubstituted imidazole, KH<sub>2</sub>PO<sub>4</sub>, Grinding method, solvent free.

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### **INTRODUCTION**

Multicomponent reactions are the processes that trigger the conversion of three or more starting materials in onepot to a highly functionalized product displaying maximum molecular diversity, complexity and impressive selectivity. Therefore, these reactions are highly atom economical eco-friendly and synthetically efficient in terms of decreasing the time, the number of reaction steps, and the consumption of chemicals and solvents used [1-3]

Someazole derivatives containing imidazole moieties shows wide spectrum of biological activities[4,5]. Besides, imidazole derivatives display various bioactive effects such as fungicid, herbicid[6], antitumor[7]. There are several methods reported in the literature for the synthesis of 2,4,5-triphenylimidazoles by using catalyst such as iodine[8], glacial acetic Acid[4], InCl<sub>3</sub>.3H<sub>2</sub>O[9], TiCl<sub>4</sub>-SiO<sub>2</sub>[10], poly(AMPS-co-AA) [11], ionic liquids[12], nano particles[13]

To achieve the goal of sustainability, greener chemical processes has become a major issue in all over the world. Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions and uses of chemicals that reduce risks to humans and the environment. Organic solvents are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store [14] By avoiding solvents, the most important is a grinding method for synthesis of

various organic compounds. Many articles about solid state reactions with grinding have been reported [15-16].

Imidazole ring system is one of the most important structures found in a large number of natural products and pharmacologically active compounds. Thus, the development of a greener method for the synthesis of imidazoles derivatives would be highly desirable. The use of solid acid catalysts has attracted a vast importance in organic synthesis due to their several advantages including operationally simplicity, no toxicity, low cost. Potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ) was used as buffer neutralizing agent and yeast food also applied as an efficient heterogeneous acid catalyst [14, 15]. In continuation of our work [17-18], during the course of present study, we wish to report a simple and efficient method for the synthesis of 2, 4, 5-triaryl imidazoles by using  $\text{KH}_2\text{PO}_4$  as a catalyst. Potassium dihydrogen phosphate has been found as a mild and effective catalyst in synthesis of 2, 4, 5-triaryl-1H-imidazoles (Scheme-1).

## MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates in chloroform: methanol system (9:1). The spot was visualized by exposing dry plate in UV chamber. IR spectra were recorded on Shimadzu IR affinity model 1 spectrometer using KBr pellets.  $^1\text{H}$  NMR spectra were recorded on a Bruker Avance II 400 MHz NMR spectrometer (SAIF, Panjab University Chandigarh) in  $\text{CDCl}_3$  using TMS as internal standard. All reagents were obtained from commercial sources.

**General procedure for synthesis of 2,4,5-trisubstituted imidazoles catalyzed by  $\text{KH}_2\text{PO}_4$ :** A mixture of benzaldehyde (1 mmol), benzyl (1 mmol),  $\text{NH}_4\text{OAc}$  (2 mmol) and  $\text{KH}_2\text{PO}_4$  (10 mol %) were ground together in a mortar with a pestle at room temperature for appropriate time (Table 2). After completion of reaction confirmed by TLC, the mixture was treated with water to furnish the crude product. Recrystallised from methanol.

### Spectral data of 2, 4, 5-trisubstituted imidazoles

**2,4,5-triphenyl-1H-imidazole:** White solid; m.p.: 273–275  $^\circ\text{C}$ , lit.[13] m.p.: 274–277  $^\circ\text{C}$ ; IR (KBr) ( $\text{cm}^{-1}$ ): 3434 (NH), 3061 (C=C–H), 1484 (C=N), 1586 (C=C aromatic);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 7.24–8.08 (m, 15H, Ar–H), 12.70 (s, 1H, NH).

**2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 229–231  $^\circ\text{C}$ , lit.[13] m.p.: 231–232  $^\circ\text{C}$ ; IR (KBr) ( $\text{cm}^{-1}$ ): 3422 (NH), 3045 (C=C–H), 1490 (C=N), 1609 (C=C aromatic);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 3.12 (s, 3H), 7.02–7.05 (d, J= 8.4 Hz, 2H), 7.29–7.61 (m, 10H), 8.00–8.03 (d, J=8.1 Hz, 2H), 12.62 (s, 1H, NH).

**2-(4-Methyl-phenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 230–232  $^\circ\text{C}$ , lit.[13] m.p.: 232–236  $^\circ\text{C}$ ; IR (KBr) ( $\text{cm}^{-1}$ ): 3435 (NH), 3031 (C=C–H), 1490 (C=N), 1613 (C=C aromatic);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 2.41 (s, 3H), 7.06–7.76 (m, 12H), 7.99–8.01 (d, J=8.2 Hz, 2H), 12.58 (s, 1H, NH).

**2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 260–262  $^\circ\text{C}$ , lit.[13] m.p.: 260–261  $^\circ\text{C}$ ; IR (KBr) ( $\text{cm}^{-1}$ ): 3419 (NH), 3058 (C=C–H), 1488 (C=N), 1608 (C=C aromatic), 1067 (C–Cl);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 7.15–8.07 (m, 12H), 8.12–8.15 (d, J=8.4 Hz, 2H), 12.69 (s, 1H, NH).

**2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 212–214  $^\circ\text{C}$ , lit.[8] m.p.: 215  $^\circ\text{C}$ ; IR (KBr) ( $\text{cm}^{-1}$ ): 3417 (NH), 3032 (C=C–H), 1484 (C=N), 1635 (C=C aromatic);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 7.18–7.86 (m, 10H), 7.76–7.78 (d, J=8 Hz, 2H), 8.03–8.06 (d, J=8 Hz, 2H), 12.72 (s, 1H, NH).

**2-(2-chloro-phenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 195–197 °C, lit.[13] m.p.: 196–199 °C; IR (KBr) ( $\text{cm}^{-1}$ ): 3432 (NH), 3065 (C=C–H), 1479 (C= N), 1610 (C=C aromatic), 1059 (C–Cl);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 7.21–7.67 (m, 14H), 11.74 (s, 1H, NH).

**2-(2-Hydroxy-phenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 118– 121 °C, lit.[13] m.p.: 118–120 °C; IR (KBr) ( $\text{cm}^{-1}$ ): 3427 (NH), 3035 (C=C–H), 1486 (C= N), 1610 (C=C aromatic);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 7.01–7.98 (m, 14H), 12.02 (s, 1H, NH).

**2-(3-Nitro-phenyl)-4,5-diphenyl-1H-imidazole:** White solid; m.p.: 194– 196 °C, lit.[8] m.p.: 198–200 °C; IR (KBr) ( $\text{cm}^{-1}$ ): 3439 (NH), 3056 (C=C–H), 1491 (C= N), 1608 (C= C aromatic);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): ( $\delta$ ) 8.23(s, 1H), 7.25–8.13 (m, 13H), 12.20 (s, 1H, NH).

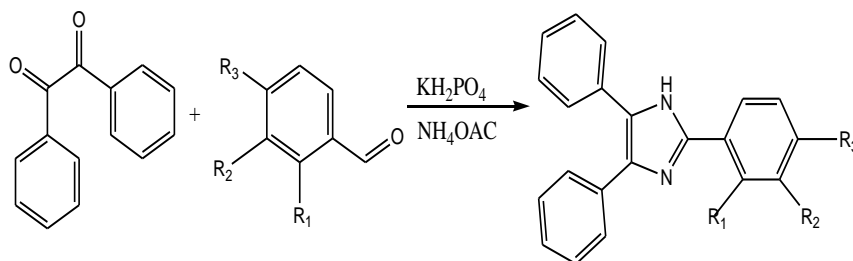
## RESULTS AND DISCUSSION

To the best of our knowledge, there are no examples on the use of  $\text{KH}_2\text{PO}_4$  for the synthesis of 2,4,5-trisubstituted imidazole by grinding approach. A model study was carried out on the synthesis of 2,4,5-triphenyl-1H-imidazole by condensation reaction of benzyl (1 mmol) with benzaldehyde (1 mmol) and ammonium acetate (2 mmol), under solvent-free condition, by grinding approach. Yield was very poor. So, for examination of the catalytic activity we select  $\text{KH}_2\text{PO}_4$ . To determine the most appropriate reaction conditions and evaluate the catalytic efficiency of  $\text{KH}_2\text{PO}_4$  a model study was carried out on the synthesis of 2,4,5-triphenyl-1H-imidazole by condensation reaction of 1 mmol benzyl with 1 mmol benzaldehyde and 2 mmol ammonium acetate in the presence of  $\text{KH}_2\text{PO}_4$  under solvent free condition, the mixture was ground together in a mortar with a pestle at room temperature for several minutes. The amounts of the catalyst have a great influence on the model reaction. It is clear that in the absence of catalyst, even if the time was prolonged to 80 min, poor yields were observed. As indicated, the best result has been obtained with amount of 10 mol % of  $\text{KH}_2\text{PO}_4$  (Table-1).

**Table-1** Synthesis of 2,4,5-trisubstituted imidazoles using  $\text{KH}_2\text{PO}_4$

Entry	$\text{KH}_2\text{PO}_4$ mol%	Time (min)	Yield
1	No catalyst	80	20
2	2	60	Trace
3	5	60	67
4	10	10	89
5	15	10	89

By using this criteria, present study describe the synthesis of series of trisubstituted imidazole from substituted benzaldehyde, benzyl and ammonium acetate in presences of  $\text{KH}_2\text{PO}_4$  as a catalyst (scheme - I).



**Scheme 1.** Synthesis of 2,4,5-trisubstituted imidazoles by using  $\text{KH}_2\text{PO}_4$  as a catalyst under solvent free conditions.

The results of  $\text{KH}_2\text{PO}_4$  catalyzed synthesis of 2,4,5-trisubstituted imidazoles are presented in table 2.

**Table 2**  $\text{KH}_2\text{PO}_4$  catalyzed synthesis of 2,4,5-trisubstituted imidazoles

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Time(min)	Yield
1	H	H	H	10	89
2	H	H	OCH <sub>3</sub>	14	84
3	H	H	CH <sub>3</sub>	15	79
4	H	H	Cl	14	83
5	H	H	Br	12	80
6	Cl	H	H	14	86
7	OH	H	H	17	78
8	H	NO <sub>2</sub>	H	09	89

The structure of compounds 1–8 was deduced from their  $^1\text{H}$  NMR and infrared spectral data. Also, their melting points were compared with literature reports. All of the products exhibited a singlet in  $^1\text{H}$  NMR spectra at about  $\delta$  11.74–12.72 ppm and also a distinguishing peak at 3417–3439  $\text{cm}^{-1}$  in IR spectra for NH.

### APPLICATIONS

These investigations involve use of solvent free method. The low cost, and ready availability of catalyst, an environmentally benign procedure makes this methodology, a useful contribution to the existing procedures available for the synthesis of trisubstituted imidazole derivatives.

### CONCLUSIONS

Potassium dihydrogen phosphate has been found as a mild and effective catalyst for three component, one pot condensation of benzyl, ammonium acetate and aromatic aldehydes, by grinding approach yield 2,4,5-Triaryl-1H-imidazoles. The notable merits offered by this methodology are solvent free reaction condition, high efficiency, short times of reaction, and high yields of products. Simplicity, making it an attractive alternative for the clean synthesis of 2, 4, 5-trisubstituted imidazoles as biologically and pharmaceutically relevant materials.

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#### AUTHORS' ADDRESSES

1. **Jayashri Dinkar Bhirud**

Asst. Professor

Moolji Jaitha College, Jalgaon, Dist-Jalgaon, (M. S.), 425002, India

Email: ingale.jayashri@rediffmail.com, Mobile no. 9420787219

2. **Hemant P. Narkhede**

Assosiate Professor

Smt. P. K. Kotecha Mahila Mahavidyalaya, Bhusawal, Dist-Jalgaon, (M. S.), India

Email: narkhede.hemant@rediffmail.com, Mobile no. 9420899055