

Synthesis of 2,4,5-triaryl-1H-imidazoles using a potent, green and reusable nano catalyst (FHS/SiO₂)

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ABSTRACT

A simple, green and efficient method for synthesis of 2,4,5-trisubstituted imidazoles is described via three-component cyclocondensation of benzil or benzoin, aldehyde and ammonium acetate by using the nano SiO₂-supported ferric hydrogen sulfate (FHS), as a catalyst, under solvent-free conditions. The nano SiO₂ support and catalyst were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM) and IR spectroscopy. In this project, the optimum conditions such as: reaction temperature, reaction time and amount of catalyst were investigated. The major advantages of the present method are high yields, shorter reaction times, easy work-up, purification of products by non-chromatographic method and the reusability of the catalyst.

Keywords: 2,4,5-Trisubstituted imidazoles; Heterogeneous catalyst; Solvent-free synthesis; Nano catalyst; Ferric hydrogen sulfate.

1. Introduction

The imidazole nucleus can be found in many biologically significant molecules. These molecules have many pharmacological properties and play important roles in biochemical processes. They can act as inhibitors of P38MAP kinase, fungicides, herbicides, anti-inflammatory agents, antithrombotic agents, plant growth regulators and therapeutic agents. In addition, they are used in photography as photosensitive compounds. Some substituted triarylimidazoles are selective antagonists of the glucagons receptor and inhibitors of IL-1 biosynthesis [1]. Radziszewski and Jaap [2, 3] introduced the first synthesis of the imidazole core in 1882. In recent years a lot of catalysts were recommended for synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles such as ZrCl₄ [4], zeolites HY/silica gel [5], NaHSO₃ [6], sulphanilic acid [7], iodine [8], ceric ammonium nitrate [9], oxalic acid [10], ionic liquids [11], microwave irradiation using acetic acid [12] and also polymeric catalyst [13].

Each of the above methods has its own merits, while some of the methods have drawbacks such as the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution [1]. Therefore, there is still an interest to develop a new mild method to overcome these disadvantages.

As known, solid acids have many advantages over liquid acids. They do less harm to the environment and have no corrosion or disposal of effluent problems. Many of them are reusable and easy to separate from liquid products. As economically and environmentally benign catalysts, their research and application have attracted much attention in chemistry and industry. The replacement of traditional homogeneous catalysts with heterogeneous solid acids is becoming an inevitable trend [14].

In our previous works [15-17], we demonstrated the catalytic activity of supported ferric hydrogen sulfate (FHS) in organic synthesis. Some of the advantages of using supported FHS rather than a homogeneous catalyst are easier recovery and recycling after reactions, and easier separation of product. The use of supported FHS could increase the specific surface area of the catalyst and modify their catalytic properties [18]. The immobilization of FHS on nano SiO₂, can be used to produce a novel heterogeneous catalyst system

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that has both high separation efficiency and a relatively high surface area to maximize catalyst loading and activity.

With these assumptions, we report here the one-pot synthesis of 2,4,5-trisubstituted imidazoles using a nano SiO₂-supported FHS as a novel catalyst (Fig. 1). We examined aromatic aldehydes with various substituents to establish the catalytic importance of the catalyst for this reaction.

2. Experimental

The FHS was prepared according to the literature [19]. Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were recorded with a Varian 3100 FT-IR spectrometer. ¹H NMR was recorded with a BRUKER DRX-400 AVANCE spectrometer at 298 K. NMR spectra were obtained on solutions in DMSO-d₆. All the products are known compounds [20–23], which were characterized by IR and NMR spectral data and their m.p.s compared with literature reports. The particle size and shape of nanostructures of SiO₂ were studied by transmission electron microscopy (TEM, LEO 912 AB). The X-ray diffraction (XRD) pattern of the nano SiO₂ was obtained using a PW3710-Philips powder diffractometer.

2.1. Synthesis of SiO₂ nanoparticles

The SiO₂ nanoparticles were synthesized according to the literature [24]. The sol-gel precursor solution was obtained by mixing of tetraethyl orthosilicate (TEOS) and ethanol (EtOH) with EtOH/TEOS molar ratio of 4. The mixture was stirred using magnetic stirring and at a pH value of 2 forms a clear solution. The molar ratio of water to TEOS was 12. After the specified solution

was obtained for 20 min, it was poured in a clean container and left at ambient temperature for gelation. After the gel had formed, the sample was dried at 220°C for 6 h.

2.2. Catalyst preparation

FHS (1.0 g) and absolute ethanol (30 mL) were poured in a round-bottomed flask. The mixture was stirred at room temperature for 30 min. The nano SiO₂ (1.7 g) was then added to the mixture and stirred for 24 h. The mixture was filtered and the residue was dried at 100 °C for 2 h. A yellowish homogeneous powder was obtained and stored in a desiccator.

2.3. General procedure for preparation of 2a–h

A mixture of aldehyde (1 mmol), benzil or benzoin (1 mmol), ammonium acetate (5 mmol) and nano-SiO₂-supported FHS (0.04 g) as a catalyst, in a 20ml glass tube was stirred at 110 °C for 30 min. After completion of the reaction, appropriate amounts of hot EtOH (96%) was added and the mixture was stirred for 10 min and then, the catalyst was separated by filtration. The filtrate was concentrated in vacuo to remove the ethanol. The residue was washed with cold water and crystallized from hot ethanol to afford the pure product.

Selected spectral data

2,4,5-Triphenyl-1H-imidazole (2a):

Color: white. m.p.= 273–275°C. IR (KBr): $\bar{\nu}$ = 3428, 3037, 2962, 1601, 1490 cm⁻¹. ¹HNMR (400 MHz, DMSO-d₆): δ = 12.71 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 2H), 7.57–7.22 (m, 13H) ppm.

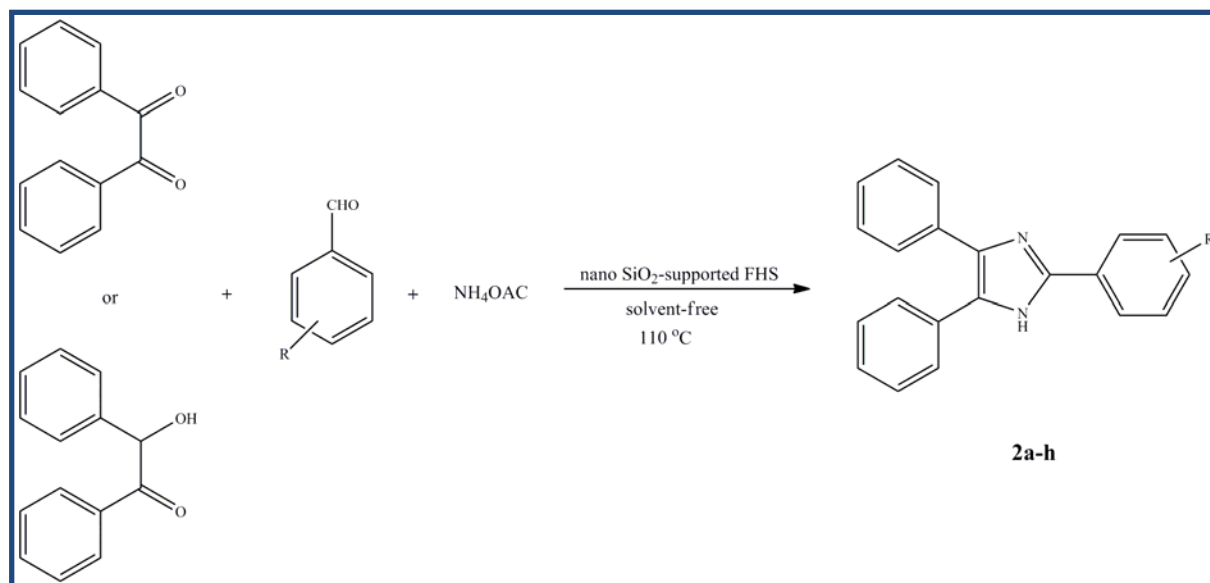


Fig. 1. The nano SiO₂-supported FHS catalyzed synthesis of 2,4,5-trisubstituted imidazole.

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (2b):

Color: white. m.p.= 264–266°C. IR (KBr): $\bar{\nu}$ = 3080, 1597, 1485 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 12.67 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.63–7.21 (m, 12H) ppm.

2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (2d):

Color: orange. m.p.= 238–240°C. IR (KBr): $\bar{\nu}$ = 3358, 3080, 2848, 1597, 1515 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 11.87 (s, 1H), 8.34–7.70 (m, 14H) ppm.

2-(4-(Diethylamino)phenyl)-4,5-diphenyl-1H-imidazole (2e):

Color: white. m.p.= 247–248°C. IR (KBr): $\bar{\nu}$ = 3409, 3060, 2970, 1616, 1508 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 12.27 (s, 1H), 7.86 (d, J = 8 Hz, 2H), 7.54–7.20 (m, 10H), 6.71 (d, J = 8 Hz, 2H), 3.36 (q, J = 8 Hz, 4H), 1.11 (t, J = 8 Hz, 4H) ppm.

2-(4-isopropylphenyl)-4,5-diphenyl-1H-imidazole (2f):

Color: white. m.p.= 255–257°C. IR (KBr): $\bar{\nu}$ = 3030, 2960, 1605, 1490 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 12.60 (s, 1H), 8.00 (d, J = 8.06 Hz, 2H), 7.51–7.24 (m, 12H), 2.93 (sep, J = 8 Hz, 1H), 1.25 (d, J = 8 Hz, 6H) ppm.

2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole (2h):

Color: yellow. m.p.= 301–302°C. IR (KBr): $\bar{\nu}$ = 3400, 3056, 1601, 1522 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 13.15 (s, 1H), 8.95 (s, 1H), 8.56 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H), 7.77–7.34 (m, 11H) ppm.

3. Results and discussion

The size and structure of obtained nano SiO_2 were characterized by transmission electron microscopy (TEM). The TEM images of SiO_2 nanoparticles are demonstrated in Fig. 2. This image shows uniformity and spherical morphology of nanoparticles. The size of SiO_2 nanoparticles according to the TEM was estimated 30–50 nm.

Also the x-ray diffraction (XRD) patterns of the synthesized SiO_2 nanoparticles were showed in Fig. 3. The XRD pattern of nano SiO_2 with sharp peaks in the 2θ range from 7° to 36° confirmed the crystalline nature of SiO_2 . In addition, lack of an XRD peak centered at 2θ angle 22° (typical for amorphous SiO_2) confirmed the crystallinity. The patterns of the spherical products confirm the SiO_2 structure.

The FHS in the nano SiO_2 particles was confirmed by IR spectroscopy. The FT-IR spectra of nano SiO_2 , FHS and nano SiO_2 -supported FHS are shown in Fig. 4. The FT-IR spectrum of nano SiO_2 exhibits strong bands in the low-frequency region (1200 – 500 cm^{-1}). The characteristic band of Si–O is observed at 1109 cm^{-1} . In the FT-IR spectra of FHS, the peak at 1620 is related to the bond of Fe–O. The broad OH stretching absorptions of FHS were observed at around 3600 – 3000 cm^{-1} . Also, the absorptions of the O=S=O stretching mode of FHS was observed at 1180 cm^{-1} . In the FT-IR spectrum of nano SiO_2 -supported FHS, bands corresponding to SiO_2 and FHS are observed but slightly shifted.

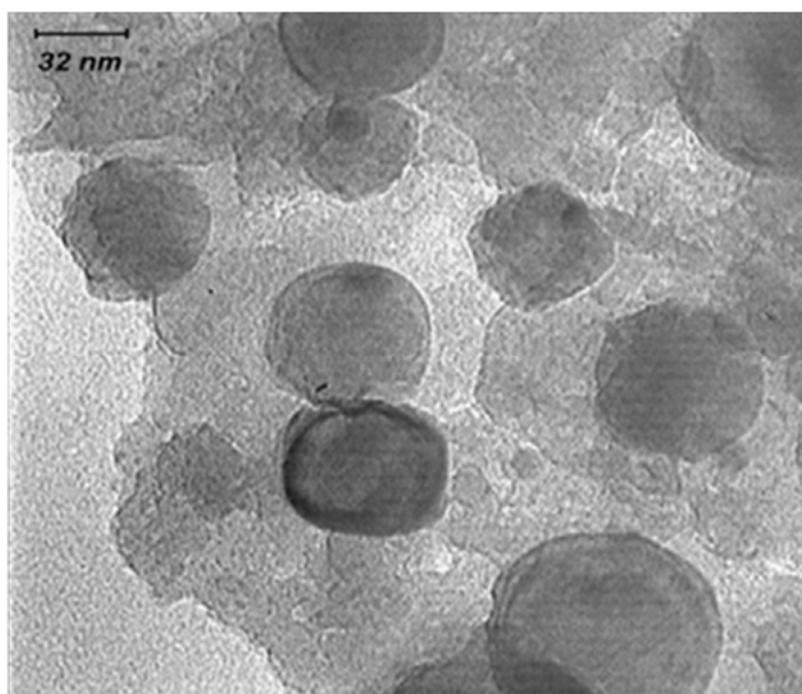


Fig. 2. TEM image of the synthesized nano SiO_2 .

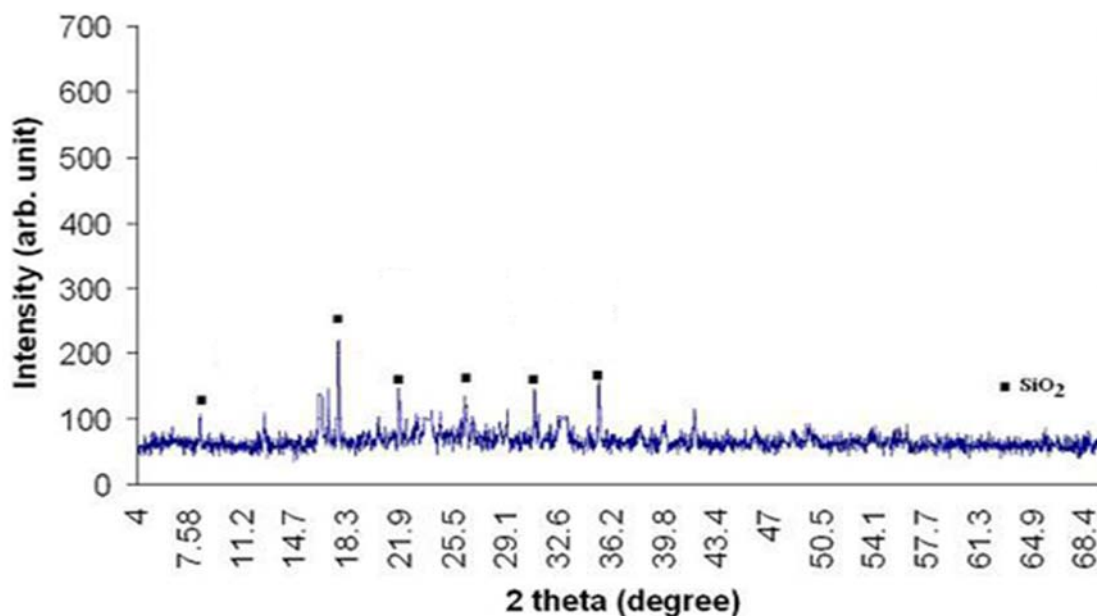


Fig. 3. X-ray diffraction (XRD) pattern of SiO₂ nanoparticles.

Efficiency of this reaction is mainly affected by the amount of catalyst, temperature and reaction time. For getting the best conditions, initially we started the condensation of benzil (1 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (5 mmol) in the presence of the nano SiO₂-supported FHS (0.01 g) as a catalyst at room temperature. However we did not obtain any product even after 24 hours. Hence the reaction temperature was increased up to 70°C. In this situation, the desired product i.e. **2d** was gained in 30% yield but it was very low. For this

reason, the reaction temperature was again increased to 130°C. With increasing the reaction temperature, the reaction time decreased and the productivity increased but was not very high (Table 1, entry 4). Hence, it was thought worthwhile to carry out the reaction in the presence of higher amount of the catalyst. As indicated in Table 1, maximum yield was obtained (95%) when the reaction was loaded with 0.04 g of the nano catalyst at the 110°C. A further increasing of catalyst loading does not affect the yield (Table 1, entry 8).

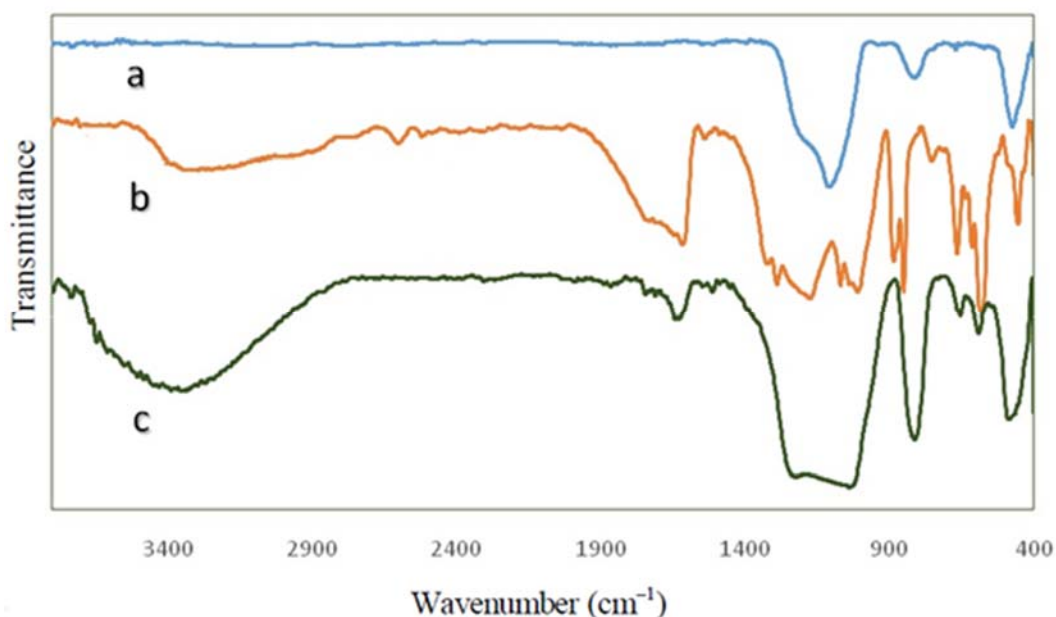


Fig. 4. FT-IR spectra of nano SiO₂ particles (a), FHS (b) and nano SiO₂-supported FHS (c).

Table 1. Optimization of one-pot synthesis of trisubstituted imidazoles by the nano catalyst.^a

Entry	Nano catalyst (g)	Temp. (°C)	Time (min)	Yield (%)
1	0.01	r.t.	24 h	0
2	0.01	70	180	30
3	0.01	110	30	40
4	0.01	130	30	40
5	0.02	110	30	55
6	0.03	110	30	80
7	0.04	110	30	95
8	0.05	110	30	95

^aBenzil (1 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (5 mmol).

After optimizing the conditions, we applied this catalyst for synthesis of trisubstituted imidazoles by using different aromatic aldehydes with a wide range of substitutions under to establish the catalytic importance of the nano SiO₂-supported FHS for this reaction. The corresponding results are given in Table 2. Also, due to direct use of benzoin rather than benzil in the synthesis of imidazoles a significant improvement in the synthesis toward the greener chemistry is represented. We have repeated the reaction with benzoin instead of benzil and the desired product has been efficiently produced. As indicated in Table 2, when we used benzoin instead of benzil, the yield of the reaction decreased partially. In the next step, we investigated the reusability of the nano

catalyst. For this purpose, the catalyst was used for the synthesis of product 2b. When the reaction was completed, the catalyst was separated by simple filtration by diluting with hot ethanol and after washing with water dried in oven 100°C. The recycled catalyst was employed consecutively in subsequent reactions and the results showed for 4 times using, the yield was 95, 90, 83 and 75%.

Finally, the efficiency of the nano SiO₂-supported FHS catalyst was compared with that of other catalysts reported elsewhere for synthesis of 2,4,5-triphenyl-1H-imidazole by one-pot three-component condensation of 2-chlorobenzaldehyde, benzil, and ammonium acetate. The data listed in Table 3 show that the nano SiO₂-supported FHS is a suitable catalyst for this reaction.

Table 2. Synthesis of 2,4,5-triaryl-1H-imidazoles (**2a–h**) using the nano catalyst (0.04 g).

Products ^a	R	Yield (%) ^{b,c}			m.p. (°C)	
		Benzil	Benzoin	Found	Reported	Ref.
2a	4-H	90	90	273–275	272–274	[20]
2b	4-Cl	95	90	264–266	262–264	[20]
2c	4-OCH ₃	90	85	230–233	228–231	[20]
2d	4-NO ₂	85	80	238-240	239-242	[21]
2e	4-N(CH ₂ CH ₃) ₂	90	80	247-248	----	
2f	4-CH(CH ₃) ₂	85	80	255-257	253-255	[22]
2g	2-Cl	95	85	196–198	197-199	[22]
2h	3-NO ₂	90	85	301-302	>300	[23]

^aAll the isolated products were characterized on the basis of their physical properties and IR, ¹H NMR spectral analysis and by direct comparison with authentic materials.

^bReaction Time (30 min).

^cYield (without catalyst condition) = 0 %.

Table 3. Comparison of results using the nano catalyst with literature results.

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	ZrCl ₄	CH ₃ CN, RT	600	93	[4]
2	Zeolites HY/silica gel	Microwave irradiation	6	85	[5]
3	NaHSO ₃	Ethanol/Water, 80°C	30	90	[6]
4	Sulphanilic acid	Ethanol/Water, 80°C	50	95	[7]
5	Iodine	Ethanol, 75°C	28	98	[8]
6	Ceric ammonium nitrate	Ethanol/Water, 65°C	50	95	[9]
7	Oxalic acid	Ethanol/Water, 80°C	60	90	[10]
8	Polymeric catalyst	Solvent free, 110°C	30	90	[25]
9	Nano SiO ₂ -supported FHS	Solvent free, 110°C	30	95	Present work

Possible mechanism for the nano SiO₂-supported FHS catalyzed synthesis of trisubstituted imidazoles has been given in Fig. 5 [13]. In summary, this paper describes a convenient and efficient process for the

one-pot synthesis of trisubstituted imidazoles through the three-components coupling of benzil or benzoin, aldehydes and ammonium acetate using the nano SiO₂-supported FHS as a catalyst. Reaction profile is

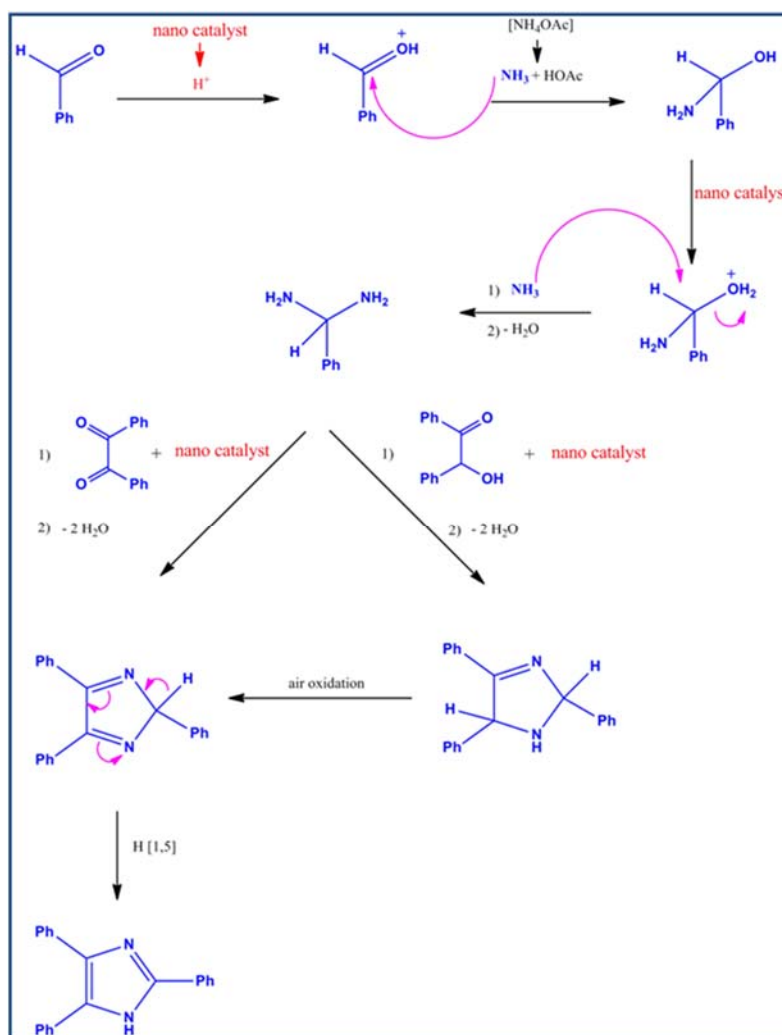


Fig. 5. Probable mechanism in synthesis of trisubstituted imidazoles using the nano SiO₂-supported FHS.

very clean and no by-products are formed. All the synthesized imidazoles have been characterized on the basis of elemental and spectral studies. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of trisubstituted imidazoles of biological and medicinal importance.

4. Conclusions

We have been able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active trisubstituted imidazoles via condensation of benzil or benzoin with various aromatic aldehydes and ammonium acetate using the nano SiO₂-supported FHS as catalyst. High yields, easy work-up, purification of compounds by non-chromatographic method (crystallization only) and the reusability of the catalyst are the key advantages of this method.

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