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Magnetic Nano Cobalt Ferrite: An efficient recoverable catalyst for synthesis of 2,4,5-trisubstituted imidazoles

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ABSTRACT

An efficient three-component synthesis of 2,4,5-trisubstituted imidazolesis described by one-pot condensation of aldehydes, diketones and ammonium acetate using $CoFe_2O_4$ magnetic nanoparticles as an efficient and environmentally benign catalyst.The easy recovery of the catalyst and reusability, broad substrate scopes, high yields of products and ethanol as solvent make this protocol practical, environmentally friendly and economically attractive.

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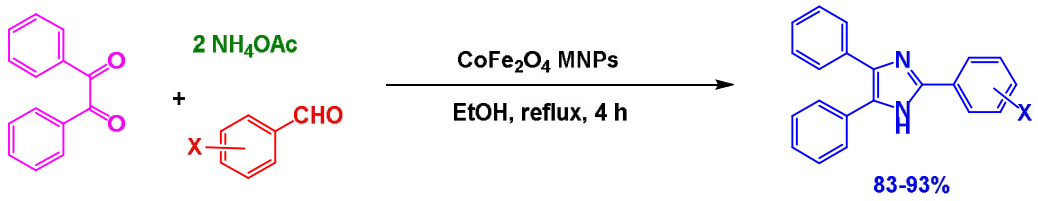
GRAPHICAL ABSTRACT



1. Introduction

Heterocycles are of immense importance not both biologically and industrially and also due to their functioning of any developed human society as well.[1] Imidazole are one of the most well-known heterocyclic scaffolds, since a large number of these molecular frameworks show interesting biological activities and are often part of various pharmaceutical compositions.[2-5] Imidazole derivatives are well-known as inhibitors of P38MAP kinase, fungicides, herbicides, anti-inflammatory agents, antithrombotic agents, plant growth regulators and therapeutic agents.[5-6] In recent years, a variety of methods has been reported for the synthesis of imidazole derivatives in the literature.[1]

Multicomponent reactions (MCRs) are one of the most efficient strategies in organic synthesis especially in the synthesis of medicinal and natural heterocyclic molecules, because they have all features that contribute to an ideal synthesis: high atom efficiency, quick and simple implementation, time and energy saving, environment-friendly and they offer a target and diversity-oriented synthesis.[7-8] During the last decade, sustainable and practical chemistry using recyclable catalysts has been one of the most fascinating developments in chemistry in both the academic area and industry.[9] In recent times, magnetic nanoparticles (MNPs) have received considerable attention, due to the easy preparation of such catalysts and their functionalization, good stability, large surface-to-volume ratio, and efficient recovery procedure by magnetic attraction.[10-14] The most important future of MNPs is their easy separation, because magnetic catalysts can be readily recovered with an external magnet due to their paramagnetic character.[15] Among magnetic nanoparticles, cobalt spinel ferrites ($CoFe_2O_4$) are attractive candidates due to their strong anisotropy, high coercivity, moderate saturation magnetization, good mechanical and excellent chemical stabilities at higher temperature.[15]

Now, in this paper, we describe a fascinating protocol for the synthesis of 2,4,5-trisubstituted imidazoles via the multi-component reaction in the presence of $CoFe_2O_4$ magnetic nanoparticles as an new, efficient and green magnetically separable catalyst.

2. Results and discussion

The $CoFe_2O_4$ nanoparticles were prepared by a previously reported method in the literature, and characterized by FT-IR spectroscopy and scanning electron microscopy (SEM).FT-IR spectra of $CoFe_2O_4$ MNPs shows a characteristic peak at 580 cm^{-1}, which is attributed to the Fe–O bond.The morphology and structure of the as-prepared cobalt ferrite magnetic nanoparticles were characterized by scanning electron

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microscopy (SEM).The results show that the diameter of the $CoFe_2O_4$ MNPs, is about 25-45 nm (Fig. 1).

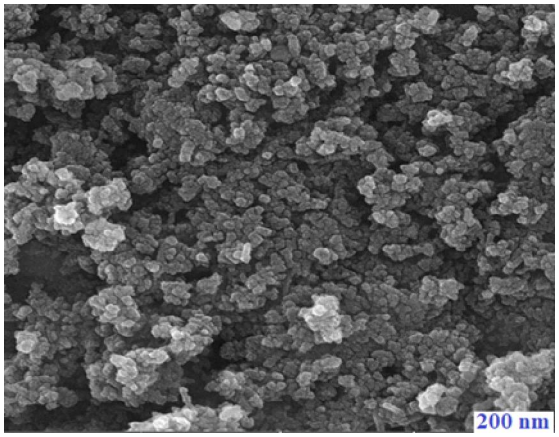
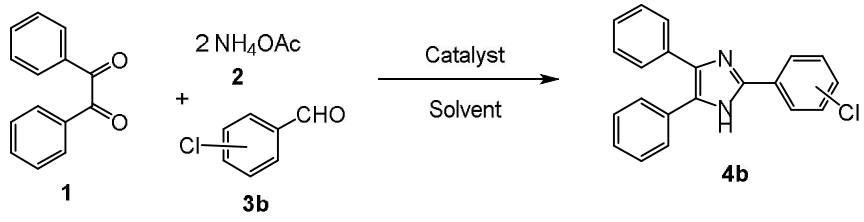


Fig 1. SEM image of $CoFe_2O_4$ MNPs in 200 nm.

Table 1. Optimization of reaction conditions [a]

Entry	Catalyst (mg)	Solvent	Yield (%) [b]
1	10	EtOH	76
2	10	Water	27
3	10	CH_3CN	34
4	10	DMF	58
5	10	THF	17
6	5	EtOH	60
7	15	EtOH	84
8	20	EtOH	91
9	25	EtOH	91
10	--	EtOH	Trace

[a] Reaction conditions:Benzil (1 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (2mmol), solvent (2 mL) at reflux temperature for 4 h.[b] Isolated yield.



Scheme 1. $CoFe_2O_4$ MNPs catalyzed the model reaction.

After preparation and characterization of cobalt ferrite magnetic nanoparticles, its catalytic activity was explored in the multi-component synthesis of 2,4,5-trisubstituted imidazoles. In the continuation of this research, in order to optimize reaction conditions, the reaction of 4-chloro benzaldehyde, ammonium acetate and benzil was selected as a model reaction (Scheme 1), and then the effect of catalyst loading and solvent was investigated (Table 1). After surveying a variety of experiments, we found that 20 mg of $CoFe_2O_4$ MNPs in EtOH under solvent-free conditions is the optimal conditions for this reaction. Next, a variety of aromatic aldehydes were examined under the optimized reaction conditions (Scheme 2), and the results are listed in Table 2. As shown in Table 2, aromatic aldehydes with electron donating as well as electron withdrawing group react smoothly giving high yields of 2,4,5-trisubstituted imidazoles.

Table 1. $CoFe_2O_4$ MNPs catalyzed the multi-component synthesis of 2,4,5-trisubstituted imidazoles in EtOH.[a]

Entry	Aldehyde	Product	Yield (%) [b]	Melting point (°C)
1	C_6H_5CHO	**4a**	88	270-272 [6]
2	4-Cl C_6H_5CHO	**4b**	91	261-263 [6]
3	4-MeC_6H_5CHO	**4c**	86	229-232 [6]
4	4-OMeC_6H_5CHO	**4d**	87	230-232 [6]
5	4-FC_6H_5CHO	**4e**	90	251-254 [6]
6	4-BrC_6H_5CHO	**4f**	93	263-266 [6]
7	3-$NO_2C_6H_5CHO$	**4g**	83	300-302 [6]
8	3-BrC_6H_5CHO	**4h**	90	233-235 [6]
9	2-OMeC_6H_5CHO	**4i**	85	211-214 [6]
10	3,4-OMeC_6H_4CHO	**4k**	88	218-220 [6]

[a]All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H-and ^{13}C-NMR spectral analysis and by direct comparison with authentic materials. [b] Isolated yield.

The reusability of the catalyst was evaluated under the reaction conditions described above for the model reaction. Upon completion of the reaction, the catalyst can be easily removed using an external magnetic from the reaction

mixture. The recovered catalyst was washed with ethyl acetate, air-dried and then reused directly in model reaction for the next round without further purification. The catalyst can be used for five runs, and no obvious loss in the catalytic activity is observed (Fig. 2).

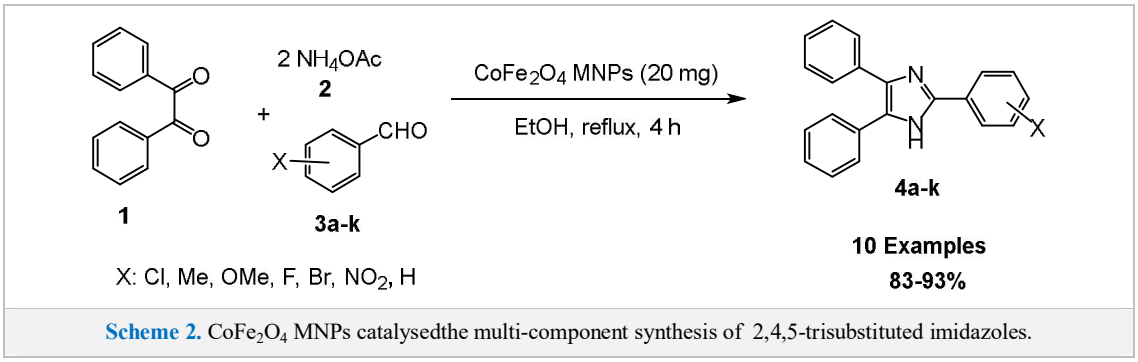
3. Conclusion

In conclusion, we have developed a simple and highly efficient procedure for the synthesis of 2,4,5-trisubstituted imidazoles using $CoFe_2O_4$ magnetic nanoparticles as an efficient and environmentally benign catalyst. Cobalt ferrite catalyst could be easily recovered by simple magnetic decant-ation and reused five times without significant loss of activity. This method provides a very fast, green and low-cost procedure for the synthesis of imidazoles.

4. Experimental

4.1. Preparation of magnetic CoFe2O4 MNPs

$CoFe_2O_4$ NPs were prepared by a chemical co-precipitation method using $FeCl_3{\cdot}6H_2O$ and $CoC_{12}{\cdot}6H_2O$ as precursors. $FeCl_3{\cdot}6H_2O$ (5.4g) and $CoCl_2{\cdot}\ 6H_2O$ (2.38 g) were dissolved in 100mL distilled water. Then, the mix-ture solution was transferred into a three-necked lask equipped with a mechanical stirrer. Fifty milliliters of 3 mol/L NaOH solution were added into the lask under vigorous stir-ring. The mixture was heated to relux for 1 h to yield a black dispersion. When the reaction had inished, the black product was washed with double-distilled water several times until the pH value of the solution became neutral. The black precipitate was separated by a per-manent magnet, followed by washing three times with ethanol and drying at 100°C in a vacuum for 24 h.



Scheme 2. $CoFe_2O_4$ MNPs catalysedthe multi-component synthesis of 2,4,5-trisubstituted imidazoles.

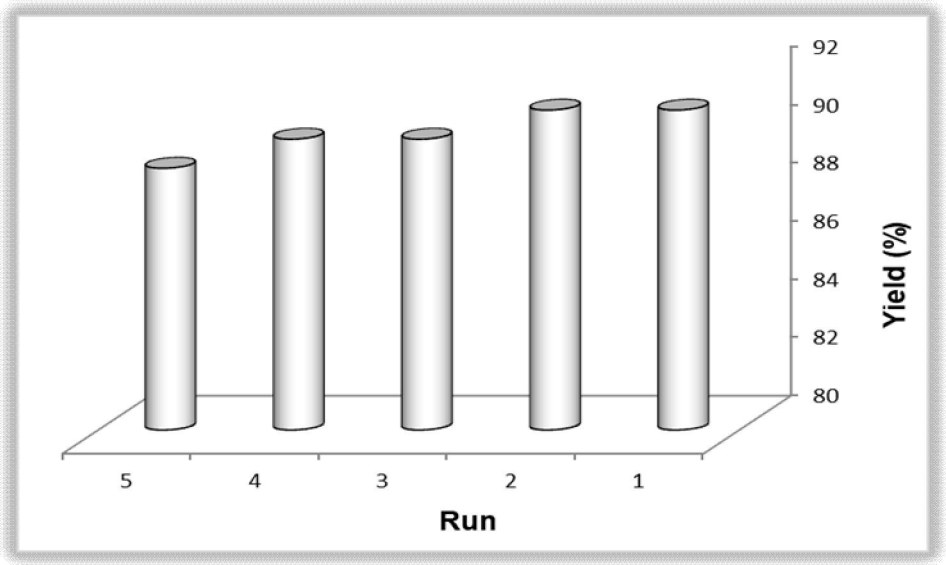


Fig 2. Reusability of catalyst in the model reaction.

4.2. General procedure for synthesis of 2,4,5-trisubstituted imidazoles

A mixture of 1,2-diketone (1 mmol), aldehyde(1 mmol), ammonium acetate (2 mmol) and CoFe2O4 MNPs (20 mg) in ethanol (2 ml) was stirred under reflux conditions. The mixture was stirred for the appropriate time (Table 2).

After completion of the reaction (monitored by TLC), the catalyst was separated using an external magnet, washed several times with water and ethanol and dried under vacuum at room temperature to be ready for a later run. The solvent was evaporated, and then the solid residue was recrystallized from ethanol to afford pure 2,4,5-trisubstituted imidazole derivatives.

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