

Nano copper and cobalt ferrites as heterogeneous catalysts for the one-pot synthesis of 2,4,5-tri substituted imidazoles

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Abstract. A simple one-pot synthesis has been developed for the synthesis of 2,4,5-trisubstituted imidazoles using magnetic recyclable spinel nano copper and cobalt ferrites by the condensation of benzil, aromatic aldehyde and ammonium acetate in ethanol as solvent. The reaction, with these catalysts was carried out under mild reaction conditions with very good yields of substituted imidazoles. These catalysts can be recycled very easily and reused, which makes this methodology environmentally benign.

Keywords. Heterogeneous catalysts; nano copper and cobalt ferrites; one-pot synthesis; 2,4,5-tri substituted imidazoles.

1. Introduction

Multi-component reactions carried out in one-pot process are of interest as they form a single product with high yields.^{1,2} These reactions are convenient and powerful tools for the preparation of a few biologically and pharmaceutically active organic compounds. Many biologically active natural products were found to contain substituted imidazole structures. Tri aryl imidazole is the main structural unit in some widely used drugs such as ketoconazole,³ proton pump inhibitors omeprazole,⁴ cimetidine,⁵ clotrimazole⁶ and metronidazole,⁷ potential inhibitor of P³⁸mapkinase,⁸ therapeutic agents⁹ and anti HIV-I protease.¹⁰

Numerous methods have been developed for the synthesis of substituted imidazoles. 2,4,5-trisubstituted imidazoles can be prepared by a three-component cyclo condensation in the presence of acetic acid,¹¹ silica supported sulphuric acid,¹² InCl₃.3H₂O,¹³ ceric ammonium nitrate,¹⁴ iodine,¹⁵ trichloroisocyanuric acid (TCCA),¹⁶ NiCl₂.6H₂O/Al₂O₃,¹⁷ ionic liquids,¹⁸ zeoliteHY/silica gel¹⁹ and ZrCl₄²⁰ under reflux conditions. Although these methods have a lot of potential, the reactions suffer from low yields, longer reaction times, use of expensive reagents, associated with a mixture of products and lack of generalization. Thus, they were not appropriate for synthesis of structurally diverse imidazoles. Development of clean and high yielding and environmentally benign approaches is still desirable and much in demand.

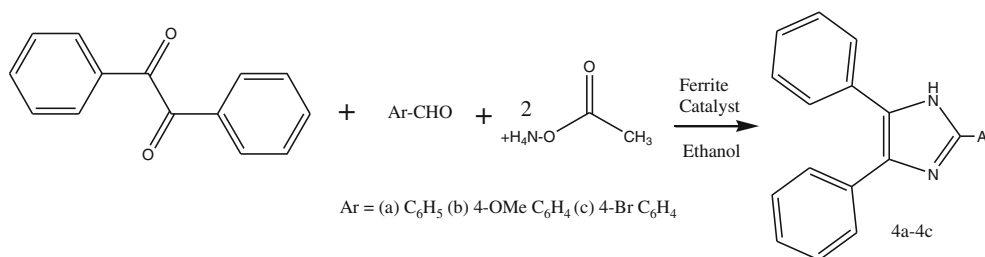
In continuation to our efforts to explore the catalytic activity of magnetically separable substituted nanoferrites for various organic transformations, it is observed that the efficacy of copper and cobalt nanoferrite catalysts for the synthesis of trisubstituted imidazoles has not been explored before. Hence, the influence of nanoferrite catalyst in the one-pot synthesis of 2,4,5-trisubstituted imidazoles by cyclocondensation of benzil, benzaldehyde and ammonium acetate (scheme 1) has been attempted. Previously, copper and cobalt nanoferrites were synthesized and used for various organic transformations.^{21–27} Now a one-pot synthesis of 2,4,5-trisubstituted imidazoles has been carried out using cobalt and copper substituted nanoferrites and the results are reported.

2. Experimental

2.1 Catalyst preparation

Solvents and reagents were of AR grade acquired from the commercial sources and used without purification. Magnetic spinel nanoferrite catalysts with composition MFe₂O₄ [M = Cu/Co] were chosen for this study. For the preparation of catalysts, aqueous solutions of stoichiometric amounts of copper and cobalt nitrates along with ferric citrate were reacted with citric acid in 1:1 molar ratio. pH of the solution was increased to 7 by addition of ammonia to complete the reaction and ethane diol was added. The solution was

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Scheme 1. One-pot synthesis of 2,4,5-,trisubstituted imidazoles.

evaporated very slowly over a period of ten to twelve hours to dryness. Viscosity and colour changed as the solution turned into a puffy and porous dry gel. As soon as the solvent removal completed, dried precursor underwent a self-ignition reaction to form a very fine powder known as as-synthesized powder. The as-synthesized powders, thus obtained were calcined in a muffle furnace at 500°C for 2 h to remove the residual carbon and furnace cooled.

2.2 Characterization

For the characterization of the calcined as-synthesized nanoferrites, the XRD spectra were recorded on PANalytical-Xpertpro diffractometer and the average crystallite size was determined from the corresponding XRD data. The microstructural morphology was studied with a scanning electron microscope (SEM) model JEOL-JSM 6610 LV. FTIR spectra were recorded on BRUKER ALPHA FT-IR with Opus 6.1 version. Magnetization $M(H)$ measurements were made using a commercial vibrating sample magnetometer (VSM) model BHV-50 of Riken Denshi Co. Ltd. Japan. Specific surface area (SBET) of samples was determined by BET surface area analyzer (Nova 2000 series, Quantachrome Instruments, UK). Melting points were determined on a capillary melting point apparatus and are uncorrected. ¹HNMR and ¹³CNMR spectral data were recorded on the Bruker-Avance 300-MHz spectrometer in DMSO-*d*₆. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. The mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector.

2.3 Characterization of nanoferrites

2.3a X-ray diffraction (XRD) analysis: Figures S1 and S2 (see supplementary information) show typical

XRD pattern for copper and cobalt nanoferrite samples respectively, which were sintered at 500°C. The pattern shows all the characteristic peaks of a spinel structure and confirms the phase formation indicating the absence of other impurity phases. The XRD parameters of various peaks were compared with the standard data of the cubic copper ferrites (JCPDS # 77-10) and found to be in cubic phase and cobalt ferrites nos. (JCPDS3-864 and 22-1086). The particle size and other characteristics of the copper and cobalt ferrite nano particles obtained from the XRD pattern using Scherer's formula²⁸⁻³⁰ was found to be 29 and 27 nm respectively and reported in table 1. The peaks can be indexed to (111), (220), (311), (222), (400), (422), (511) and (440) planes of a cubic unit cell.

2.3b Infrared Spectroscopy: In order to confirm the formation of the spinel phase and to understand the nature of the residual carbon in the samples, the FT-IR spectra of the as-synthesized powders and thermally treated powder were recorded and shown in figures S3 and S4. The as-synthesized sample shows characteristic absorptions of ferrite phase with a strong absorption around 600 cm⁻¹. Waldron studied the vibrational spectra of ferrites and attributed the sharp absorption band around 580 cm⁻¹ to the intrinsic vibrations of the tetrahedral groups and the other band of the octahedral groups. There are two weak and broad absorptions around 1040, 1400, 1600, 3400 cm⁻¹ corresponding to the presence of small amount of residual carbon in the samples. These absorptions in the present case are very weak which indicate that the residual carbon has mostly burnt away during the sintering process.

2.3c Morphological and elemental analysis (SEM & EDX): Figures S5 and S6 show the typical SEM image of the nano copper and cobalt nanoferrites sintered at 500°C. The crystallite size calculated from XRD is in the range of below 30 nm which is in agreement with the SEM image. The structural composition and crystallinity of the cobalt ferrite nano particles was further

Table 1. Particle size and other characteristics of copper and cobalt ferrites.

S No	Sample	Lattice Parameter	Density (%)	FWHM	Porosity (%)	Grain size (D) (μm)	Particle Size
1	CuFe ₂ O ₄	8.387	92.5	0.281	7.4	1.62	29
2	CoFe ₂ O ₄	8.389	91.9	0.272	7.3	1.58	27

examined by using SEM and TEM. The iron and copper or cobalt ratio in the nano crystals as determined by EDX analysis was very much close to the atomic ratio in the formula CuFe₂O₄ and CoFe₂O₄.

2.3d BET surface area analysis: The BET surface area of the CuFe₂O₄ and CoFe₂O₄ are found to be 127 and 135 m²/g respectively. The difference in the surface area of the samples is attributed to the atomic sizes of copper and cobalt. Further, copper ferrite shows decrease in surface area during calcination at 500°C. This may be due to the completion of dehydration associated with the completion of crystallization and growth of crystallite size by sintering.

2.4 One pot synthesis of 2,4,5, trisubstituted imidazoles

The one-pot synthesis of substituted imadazoles was carried out in a 50 mL round bottomed flask equipped with a reflux condenser in an oil bath with temperature control and refluxed. About 500 mg of the catalyst was taken and activated at 500°C for 2 h and cooled to room temperature before the experiment. 10 mmol each of benzil, aromatic aldehyde and 20 mmol of ammonium acetate were mixed together along with the catalyst and 10 mL of ethanol as solvent and refluxed. The completion of the reaction was checked with TLC (n-hexane: ethyl acetate 4:1) and the products were isolated by removing the catalyst magnetically from the reaction mixture. All the products are known in the literature and were identified by IR, ¹HNMR, ¹³CNMR and mass spectra of representative compounds and compared.

2.5 Spectral data of substituted imidazole derivatives (figures S7 and S15)

2.5a 2,4,5,triphenyl 1-H-Imidazole (4a): M.p. 273–275°C; ¹HNMR (Bruker) (CDCl₃/DMSO-*d*₆) δ = 7.97–7.34(m, 15H), 9.31(brs, N-H), ¹³CNMR (CDCl₃/DMSO-*d*₆); 122.5, 127.0, 128.7, 129.2, 136.4 ppm; FTIR (KBr, cm⁻¹): 3450(N-H), 3062(C-H), 1658 (C=C), 1578(C=N), NCMS (m/z) ; 297 (M⁺+1)

2.5b 2-(4-methoxy phenyl)-4,5,diphenyl-1-H Imidazole (4b): M.p. 222–224°C; ¹HNMR (Bruker) (CDCl₃/DMSO-*d*₆) δ = 3.85 (s, 3H), 6.97–6.95 (d, J = 8.8Hz, 2H), 7.54–7.25(m, 10H), 7.84–7.82 (d, J = 8.8Hz, 2H), ¹³CNMR (CDCl₃/DMSO-*d*₆), 55.7, 113.4, 122.6, 126.3, 126.6, 128.0, 128.3, 133.4, 145.7, 159.6 ppm; FTIR (KBr, cm⁻¹); 3450(N-H), 1612(C=C), 1579(C=N), 1385(C-O), NCMS (m/z) 327 (M⁺+1)

2.5c 2-(4-Bromo phenyl)-4,5,diphenyl-1-H Imidazole (4c): M.p. 260–262°C; ¹HNMR (Bruker) (CDCl₃/DMSO-*d*₆): δ = 7.76–7.05 (m,10H), 7.97–7.92 (d,J = 8.0Hz, 2H), 6.71–6.67(d, J = 8.6Hz, 2H); ¹³CNMR (CDCl₃/DMSO-*d*₆); δ = 122.2, 125.4, 126.5, 128.8, 129.9, 132.8, 144.3 ppm; FTIR (KBr,cm⁻¹); 3432(N-H), 1600(C=C), 1482(C=N), 729(C-Br), NCMS (m/z) 367 (M⁺+1)

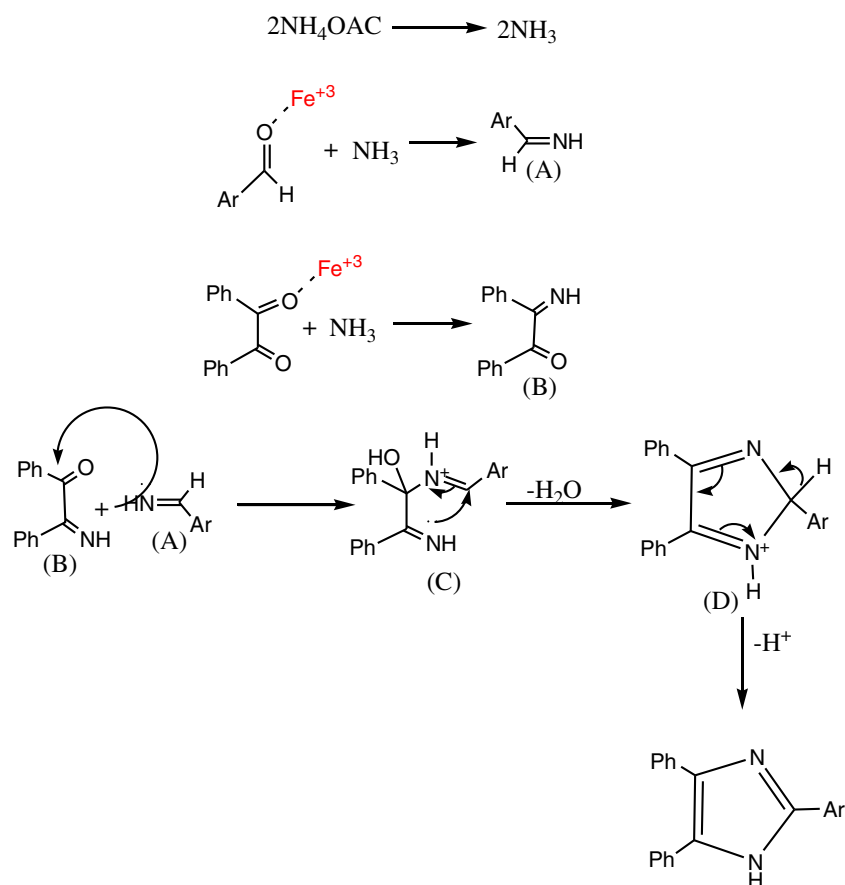
3. Results and Discussion

3.1 Catalytic Study

It can be understood from the similar studies reported in the literature,³¹ the plausible mechanism with the copper and cobalt catalyst in the reaction may be shown in scheme 2. The Aldehyde and 1,2-diketone are first activated by ferrite nanoparticles (Fe³⁺) to afford A and B respectively. The imine intermediate (A), condenses further with the carbonyl carbon or 1,2 diketone imine (B) and formation of carbocation (C) followed by attack of imine nitrogen to positive centre and dehydration to afford the imo-imidazole (D), which rearranges via^{1,5} sigmatropic shift followed by deprotonation gives the imidazole.

3.1a Comparison of effect of the present catalysts with other catalysts on synthesis of 2,4,5, tri-substituted imidazoles: It is observed from table 2, that copper and cobalt ferrites have shown similar effective yields when compared to iodine and TCCA with minimum reaction times, which is a significant contribution in this method.

3.1b Effect of solvent on synthesis of 2,4,5, trisubstituted imidazoles: Investigation of reaction medium



Scheme 2. Plausible mechanism for the formation of 2,4,5 tri-substituted imidazoles

for the process revealed that solvents played an important role in the reaction under investigation. The results are summarized in table 3. It was found that polar solvents such as acetic acid, CH₃CN, and C₂H₅OH were much better than non-polar solvents. Trace amounts of yield observed when H₂O was used as solvent, presumably due to the aggregation of the hydrophobic catalyst. Although acetic acid was effective, low yield was

obtained when the catalyst was reused. We therefore selected ethanol as solvent.

3.1c Effect of temperature on synthesis of 2,4,5-trisubstituted imidazoles: The reaction temperature has a great influence on the model reaction. The reactions were carried out in ethanol at different temperatures ranging from 30 to 70°C. The results are

Table 2. Comparative catalytic activity of copper and cobalt ferrites with other catalysts.

Sl. No.	Catalyst	Ar	Time (min)	Temp (°C)	Yield (%)
1	Iodine ¹⁵	Ph	15	75	99
2	TCCA ¹⁶	Ph	12hrs	85	90
3	CuFe ₂ O ₄	Ph	10	70	94
4	CoFe ₂ O ₄	Ph	10	70	98(4a)
5	Iodine ¹⁵	4-OMe C ₆ H ₄	25	75	99
6	TCCA ¹⁶	4-OMe C ₆ H ₄	12hrs	85	89
7	CuFe ₂ O ₄	4-OMe C ₆ H ₄	13	70	96
8	CoFe ₂ O ₄	4-OMe C ₆ H ₄	10	70	96(4b)
9	Iodine ¹⁵	4-Br C ₆ H ₄	–	–	–
10	TCCA ¹⁶	4-Br C ₆ H ₄	12hrs	85	90
11	CuFe ₂ O ₄	4-Br C ₆ H ₄	20	75	92
12	CoFe ₂ O ₄	4-Br C ₆ H ₄	15	75	94(4c)

Table 3. Effect of solvent.

Sl. No.	Catalyst	Ar	Solvent	Time (min)	Yield (%) ^a
1	CoFe ₂ O ₄	Ph	H ₂ O	60	trace
2	CoFe ₂ O ₄	Ph	CH ₂ Cl ₂	60	35
3	CoFe ₂ O ₄	Ph	CH ₃ CN	45	55
4	CoFe ₂ O ₄	Ph	CH ₃ COOH	25	86, 57 ^b
5	CoFe ₂ O ₄	Ph	C ₂ H ₅ OH	10	98

All reactions were carried out under reflux conditions with 500 mg of catalyst.

^a Isolated yields ^b Catalyst was reused

Table 4. Effect of temperature.

S.No.	Catalyst	Ar	Temperature (°C)	Time (min)	Yield (%) ^a
1	CoFe ₂ O ₄	Ph	R.T.	300	20
2	CoFe ₂ O ₄	Ph	45	120	45
3	CoFe ₂ O ₄	Ph	60	35	75
4	CoFe ₂ O ₄	Ph	70	10	98

All reactions are carried out using 500 mg of catalyst in ethanol.

^a Isolated yields

presented in table 4. It is clear that at lower temperatures, even if the times were prolonged to 8 h, only low yields were observed. Consequently, we chose 70°C as the optimal temperature for our reaction.

3.2 Recycling of the catalyst

Catalyst reusability is of major concern in heterogeneous catalysis. The recovery and reusability of the catalyst was investigated in this reaction with benzaldehyde (**4a**). Catalyst recycling was achieved by fixing the catalyst magnetically at the bottom of the flask with a strong magnet, after which the solution was taken off with a pipette, the solid washed twice with dichloromethane (DCM) and the fresh substrate dissolved in the same solvent was introduced into the flask, allowing the reaction to proceed for the next run. The catalyst was consecutively reused five times without any noticeable loss of its catalytic activity. These catalysts are highly magnetic and their saturation magnetization values are found to be 32.45 and 35.56 emu/g, which are much higher than other reported magnetic catalysts. Therefore, they could be easily and almost completely separated by an external magnet which is of a great advantage for a heterogeneous catalyst.

4. Conclusion

An efficient method has been developed for the synthesis of 2,4,5-tri aryl imidazoles using copper and

cobalt nanoferrites. This method offers several advantages including high yield, short reaction time, ease of separation and recyclability of the magnetic catalyst.

Supplementary Information

Supplementary information contains XRD, FTIR and SEM images of copper and cobalt ferrites (**S1–S6**) and FTIR, Mass and ¹HNMR spectra of substituted imidazoles (**S7–S15**). For details, see www.ias.ac.in/chemsci.

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References

- Ley S V, Baxendale I R, Bream R N, Jackson P S, Leach A G, Longbottom D A, Nesi M, Scott J S, Storer R I and Taylor S J 2000 *J. Chem. Soc. Perkin. Trans. 1* **23** 3815 and references cited therein
- Domling A 2006 *Chem. Rev.* **17** 106
- Heeres J, Backx L J J, Mostmans J H and Van Custem J 1979 *J. Med. Chem.* **22** 1003
- Tanigawara Y, Aoyama N, Kita T, Shirakawa K, Komada F, Kasuga M and Okumura K 1999 *Clin. Pharmacol. Ther.* **66** 528
- Brimblecombe R W, Duncan W A M, Durant G J, Cemmatt J C, Ganellin C R and Parsons M E 1975 *J. Int. Med. Res.* **3** 86
- Dorneanu O, Popovici I, Boiculese L and Bosnea D J 2003 *J. Prev. Med.* **11** 41
- Dinh H T, Kernbaum S and Frottier J 1978 *Lancet* **338** 3111
- Lee J, Laydon J, McDonnell P, Gallagher T, Kumar S, Green D, McNulty D, Blumenthal N, Heys J, Landvatter S, Strickler J, Mclaughlin M, Siemens I, Fisher S, Livi J, White J, Adams J and Young P 1994 *Nature* **372** 739
- Heeres J, Backx L, Mostmans J and Vancustem J 1979 *J. Med. Chem.* **22** 1003
- Baures P W 1991 *Org. Lett.* **2** 249

11. Sarshar S, Siev D and Mjalli M M 1996 *Tetrahedron Lett.* **37** 835
12. Shaabani A and Rahmati A 2006 *J. Mol. Catal. A Chem.* **246** 249
13. Sharma S D, Hazarika P and Konwar D 2008 *Tetrahedron Lett.* **49** 2216
14. Sangshetti J N, Kokare N D, Kotharkara S A and Shinde D B 2008 *J. Chem. Sci.* **120** 463
15. Kidwai M, Mothsra P, Bansal V, Rishi K S, Abdul S E, Sharmistha D and Tej P S 2007 *J. Mol. Catal. A: Chem.* **265** 177
16. Seyedeh F H, Seyede A N and Zahra B 2012 *Monatsh. Chem.* **144** 387
17. Heravi M M, Bekhtiari K, Oskooie H A and Taheri S 2007 *J. Mol. Catal. A Chem.* **263** 279
18. Siddiqui S A, Narkhede U C, Palimkar S S, Daniel T, Loholi R J and Srinivasan K V 2005 *Tetrahedron* **61** 3539
19. Balalaie S, Arabanian A and Hashtroudi M 2008 *Monatsh. Chem.* **139** 125
20. Sharma G, Jyothi Y and Lakshmi P 2006 *Syn. Comm.* **36** 2991
21. Kooti M and Afshari M 2012 *Catal. Lett.* **142** 319
22. Murthy Y L N, Diwakar B S, Govind B, Nagalakshmi K, Kasiviswanath I V and Rajendra singh 2012 *J. Chem. Sci.* **124** 639
23. Kantam M L, Yadav J, Soumi L, Srinivas P, Sreedhar B and Figueras F 2009 *J. Org. Chem.* **74** 4611
24. Shin H-C, Choi S-C, Jung K-D and Han S-H 2001 *Chem. Mater.* 2001 **13** 1238
25. Panda N, Jena A K, Mohapatra S and Rout S R 2011 *Tetrahedron Lett.* **52** 1924
26. Polshettiwar V, Baruwati B and Varma R S 2009 *Green Chem.* **11** 127
27. Nasir Baig R B and Varma R S 2013 *Chem. Commun.* **49** 752
28. Scherrer P 1918 *Mathematisch-Physikalische Klasse* **2** 98
29. Langford J and Wilson A 1978 *J. App. Cryst.* **11** 102
30. Jenkins R and Snyder R L 1996 In *X-ray powder Diffractometry: An introduction* (New York: John Wiley) 89
31. Javad S and Zohre Z 2012 *Iranian J. Catal.* **2(3)** 121