



Fe-CuO NANOCATALYST: A APPROACH TOWARDS SOLVENT-FREE SYNTHESIS OF PYRAZOLE DERIVATIVES VIA MICHAEL ADDITION REACTION SUSTAINABLE

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ABSTRACT:

In the present research work, ferrite functionalized copper oxide nanocatalyst has been synthesized well by co-precipitation method in benign media. The synthesized nanocat Fe-CuO was characterized by spectroscopic techniques like XRD, ICP-AES & SEM. Functionalized MNPs used for the synthesis of pyrazole derivatives *via* Michael addition reaction followed by cyclization with help of microwave irradiation. The proposed method were afford the advantages like solvent free approach, good reaction yield, short process time, simple work-up and recycling of the catalyst which thoroughly touch the sustainable transformation.

KEYWORDS:

Nanocat Fe-CuO, MNPs, Pyrazole aldehyde, Michael addition, Microwave irradiation.

INTRODUCTION:

In the past few decades magnetic nano particles (MNP_s) which are available from low-cost materials *via* simple synthesis and easily tunable by structural surface modifications, have drawn much attention due to their vast applications including drug delivery, biosensors, enzyme immobilization, environmental remediation and so on.¹ Recently, magnetic nano partials show the application as catalyst supports has become a hot topic due to their unique properties such as high surface area, good dispersion, super paramagnetic behavior as well as low toxicity.² The most attractive feature of nano particles supported catalysts is that they can be recycled by simple magnetically driven separation, thereby eliminating the requirement of catalyst filtration and centrifugation. Furthermore, improved activity is usually achieved in the nanometer-sized supported catalyst due to the high surface area and good dispersion properties.³

Recent investigation suggest that, several noble transition-metal catalysts like Mo, Co, Ni, Zn, Pd, Pt & Au, enzyme catalysts as well as organocatalyst⁴ have been successfully immobilized on magnetite with good catalytic activity and reusability.⁵ Up to now, most of these nano particles supported catalysts employed covalent immobilization strategies, requiring additional synthetic manipulation in most cases. Non-covalent immobilization, endowed with the merits such as easy modification and combinatorial flexibility.⁶



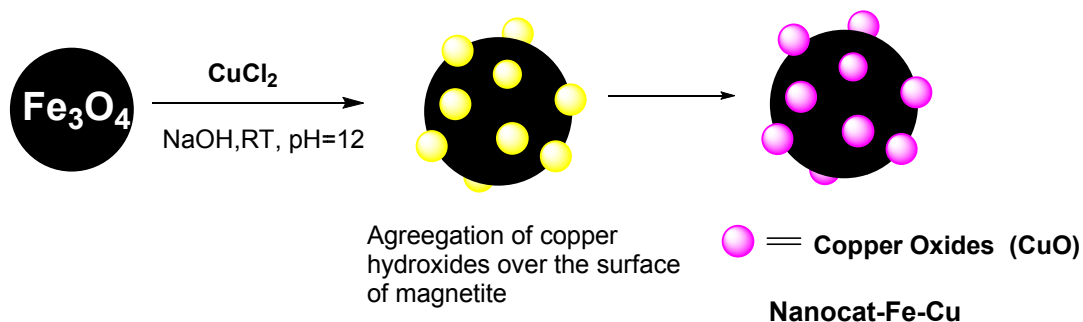
Literature survey reveals that, drugs supported on a pyrazole ring bearing two adjacent aryl groups in vicinal relation have often been occurred a position in the list of best-selling pharmaceutical products since the beginning of decades. Many pyrazole derivatives have been reported to possess diverse pharmacological activities as anti-inflammatory, antimicrobial, antihypertensive etc. however studies investigating the potential of pyrazole derivatives as dual anti-inflammatory,⁷ antimicrobial⁸ agent have only recently been investigated. Recently the multi-component, one-pot reactions are highly highlighted because of their wide range of applications in pharmaceutical chemistry for the production of structural scaffolds and combinatorial libraries for drug discovery.⁹⁻¹² On the way of such organic transformation supported by catalysis techniques have by-passed the problems related with inefficient heating and use of charging methods like mechano chemical grinding, ultrasonic and microwave (MW) irradiation for expenditure syntheses.¹³⁻¹⁵

In a continuation of our efforts in the field of green synthesis using nanocatalyst & in heterocycles synthesis¹⁶ herein we have developed our research extension as a novel and simple scheme for functionalization of MNPs ferrite with copper oxide for pyrazole derivatives synthesis *via* Michael addition followed by internal cyclization.

RESULTS AND DISCUSSION:

Magnetic nanocat-Fe-Cu Characterization

Magnetic nanocat-Fe-Cu were prepared by the simple wet impregnation method followed by chemical reduction as reported in the literature¹⁶ (Scheme 1) and well characterized by X-ray diffraction (XRD), inductive coupled plasma-atomic emission spectroscopy (ICP-AES), field-emission gun, scanning electron microscope, and electron dispersive spectrometry (FEG- SEM-EDS).



Scheme 1. Synthesis of Nanocat-Fe-Cu MNPs

The crystallite size of the Nanocat-Fe-Cu MNPs determined by Debye Scherrer equation was found to be 39.1 nm, which is in agreement with the result obtained from the TEM which shows a size distribution between 40-50 nm. Although signals of Cu were not discovered in the XRD scale (Figure 1) of Fe_3O_4 -Cu the weight percentage of Cu was determined to be 3.98 % by ICP-AES analysis.



INTERNATIONAL RESEARCH JOURNAL OF INDIA

ISSN 2454-8707 / IMPACT FACTOR 2.05 / VOLUME - II, ISSU –X, JUNE 2017

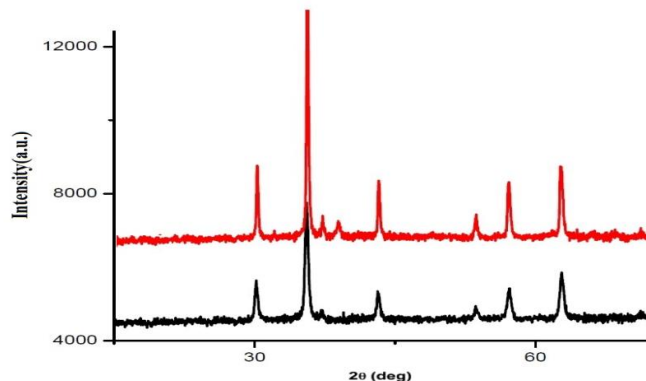


Figure 1. XRD of Fe₃O₄ (black line) and Nanocat-Fe-Cu

In the survey spectrum of the Fe₃O₄-CuO nanocatalyst the main lines of oxygen, iron and copper are clearly visible. Additionally, we observed carbon, being a common impurity, and sodium. The presence of the former is most probably due to the production process. The FEG-SEM analysis of nano magnetite-Cu sample was observed using 25kV acceleration voltage. The experiment shows uniform-size of nanoparticles, with particles image somewhat spherical morphology and seems a wooly cloud like clusters (Figure 2).

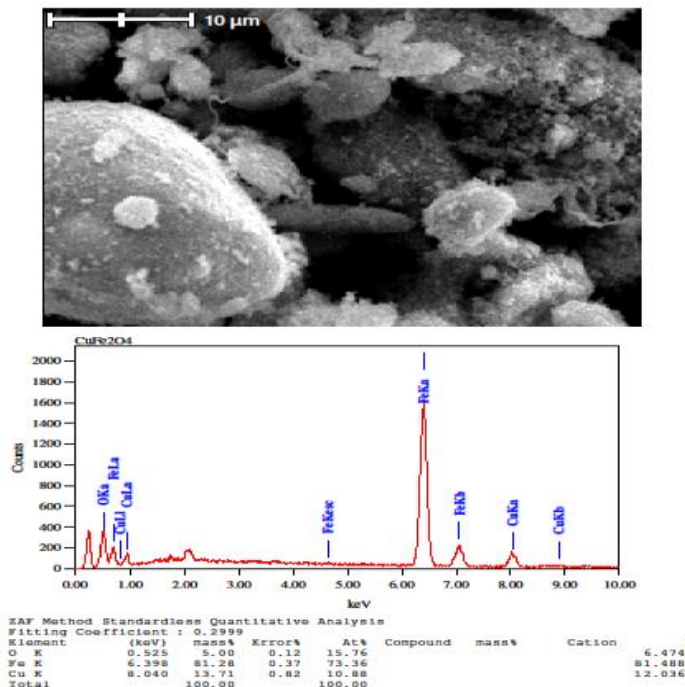


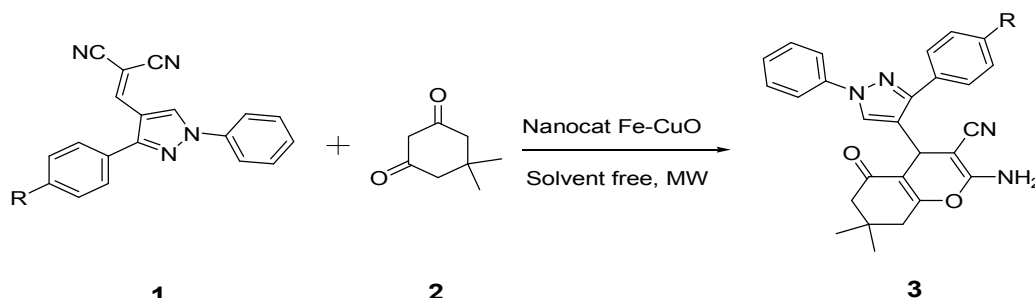
Figure 2. SEM image with EDS profile of nanocat Fe-Cu.

Nanocat-Fe-CuO catalyzed synthesis of pyrazole derivatives via Michael addition.

To validate the competency and scope of synthesized and well characterized nanocat Fe₃O₄-Cu in MCRs, aromatic aldehydes analogues with malononitrile & dimedone were subjected for one pot condensation in presence catalytic amount of nanocat-Fe-CuO to obtain the pyrazole analogues



(Scheme 2). All reaction proceeds smoothly under conventional way (100°C, 60min) and under microwave irradiation at 350W for 6-8 min. Reaction well goes under microwave irradiation & solvent free benign media with good product yield.



Scheme 2: Nanocat-Fe-CuO catalyzed synthesis of pyrazole analogue via Michael addition followed by cyclization.

In order to optimize the reaction conditions, aromatic aldehyde was selected as a demonstrative aldehyde along with malononitrile & dione with nanocat-Fe-Cu were reacted under solvent free conditions (table-1).

Table 1: Optimization of reaction condition ^a

No.	Catalysts	Solvent	Time(h/min)	Temp	Yield ^b
1	No catalysts	---	24 (h)	RT	NR
2	No catalysts	---	24 (h)	50°C	Trace
3	Nanocat-Fe-Cu	---	60 min	RT	Trace
4	Nanocat-Fe-Cu	---	24 (h)	RT	35
5	Nanocat-Fe-Cu	---	30 min	100°C	91
6	Nanocat-Fe-Cu	---	6-8 min (MW)	100°C	94
7	Nanocat-Fe-Cu	H ₂ O	50-60 min	100°C	80
8	Nanocat-Fe-Cu	EtOH	60 min	100°C	85

Reactions condition malononitrile (10 mmol), aromatic aldehyde (10 mmol), dione (10 mmol), Nanocat-Fe-CuO (100mg) MW irradiation ; NR (no reaction); ^b isolated yield of pure product.

To study the effect of temperature, the three component reaction was carried out at four different temperatures at 50, 100 and 150°C. Notably best results were obtained at 100°C (table-2, entry-2). With further increase in temperature, no considerable increase in yield was observed (table-2, entry-3). Therefore, all other reaction parameters were set up at 100°C.



INTERNATIONAL RESEARCH JOURNAL OF INDIA

ISSN 2454-8707 / IMPACT FACTOR 2.05 / VOLUME - II, ISSU -X, JUNE 2017

Table 2: Effect of temperature on reaction yield.

Entry	Reaction temperature (°C)	Reaction yield (%)
1	50	57
2	100	94
3	150	79

Initially, as a standard reaction when performed using nanocat as observed from Table-1&2, the compounds 3a-e are obtained in low yields when reactions were performed under conventional refluxing method (Table-1&2). In contrast the same reactions were supported in presence of MNPs by microwave irradiation method, products were obtained in very clean and appreciably higher yield. All experiments were operating three times to check the reliability of the results.

EXPERIMENTAL:

Resources and Reagents.

All reaction were carried out using a laboratory microwave oven (RAGA'S Scientific Microwave System-700W). All the noted melting points were determined on Melting Point apparatus Model: KI-11 (MP-D), Make: Kumar Sales Corporation, Mumbai (India) and are uncorrected. The progress of the reaction was monitored with the help of preparative TLC and was executed on pre-coated silica gel glass plates (Kieselgel 60 mit Fluoreszens-Indicator UV- 254, E. Merck, Germany). The spots were visualized using UV light.

Characterization techniques

XRD analysis was carried out for newly synthesized CuO-Ferrite nano catalyst. The X-ray powder diffraction pattern was attained using a conventional powder diffractometer RIGAKU, model: MiniFlex™ II benchtop X-ray Diffractometer; X-ray tube: Cu-K α (30 kV / 15 mA) radiation operating in Bragg-Brentano ($\theta/2\theta$) geometry. SEM images were acquired using a JEOL JSM7001F FEG-SEM. Elemental analysis was performed using a light elements EDS detector from ICT. The nanocat Fe₃O₄-CuO powder was spread on a double-sided carbon tape and analyzed using 25kV acceleration voltage. Elemental analysis was done by using ICP-AES (Inductively coupled plasma-atomic emission spectrometer) from ICT model equipped with a 40.68 MHz RF generator, Czerny-Turner monochromator with 1.00 m (sequential), autosampler AS500 and CMA (concomitant metals analyzer). The FT-IR spectra were scanned on PerkinElmer spectrum Version 10.4.2. The NMR spectra were recorded on a Bruker 300 MHz (¹HNMR) and 75 MHz (¹³CNMR) instrument with CDCl₃ or DMSO as a solvent and internal standard TMS; the chemical shifts (δ) are stated in ppm also coupling constants (J) are specified in Hertz. Signal splitting is signified by s (singlet), d (doublet), t (triplet), dd (double doublet), and m (multiplet).



Preparation of Ferrites MNPs¹⁶

The $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5.4 g) and urea (3.6 g) were dissolved in water (200 mL) for 2 h at 85 to 90°C. The solution becomes brown color. To this brown reaction content cooled at room temperature, was added $\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$ (2.8 g) and then further NaOH (0.1 M) adds until the pH become 10. In the above case the molar ratio of Fe (III) to Fe (II) was nearly 2.00. The resultant hydroxide content was treated by ultrasound sonication technique in sealed flasks at 30 to 35°C for 30 min. After that aging for 5h, the acquired black powder (Fe_3O_4) was purify and dried under vacuum.

Preparation of Nanocat-Fe-CuO MNPs¹⁶

The magnetite nanoparticles Fe_3O_4 (2 g) and Copper Chloride ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$), (to get 5 wt. % of Cu on magnetite) were stirred at room temperature in aqueous solution (50 mL) for 1 h. After impregnation, the suspension was adjusted to pH 12-13 by adding sodium hydroxide (1.0 M) and further stirred for 20 h. The solid was washed by distilled water (5 x 10 mL). The resulting Nanocat-Fe-Cu particles were sonicated for 10 min., washed with distilled water and subsequently with ethanol, and dried under vacuum at 60°C for 24 h. The Cu content was determined by ICP-AES and it was found to be 3.98%.

One pot MCR synthesis of pyrazole derivatives by using nanocat-Fe-CuO

The stoichiometric mixture of pyrazole aldehyde (2 mmol), malononitrile (2 mmol) and dimedone (2 mmol) were melted in MW oven at 350W for 6-8 min at about temperature 100°C under solvent free media. To check priority over non-conventional method the same reaction mixture was stirred and carried conventionally in benign media. The monitoring of reaction was done with the help of TLC. All synthesized product were check by the preparative TLCs, M.P & from NMR data.

Table-3: Ferrite-CuO catalyzed synthesis of pyrazole analogues (**3a-e**) yield and melting points.

Entry	-R	M.P (°C)	Time (min) / Yield (%)
4a	-H	232	6 / 94
4b	-CH ₃	240	5 / 92
4c	-F	227	5 / 90
4d	-Cl	198	6 / 89
4e	-Br	228	6 / 84

In another study, comparison of present catalyst Fe-CuO with respect to the other reported catalyst in literature for synthesis of pyrazole analogues *via* Michael reaction reaction (table 4) show clearly that our present investigation using nanocat Fe-CuO was more efficient over reported conditions.



INTERNATIONAL RESEARCH JOURNAL OF INDIA

ISSN 2454-8707 / IMPACT FACTOR 2.05 / VOLUME - II, ISSU -X, JUNE 2017

Table 4: Comparison result using nanocat Fe-CuO with other reported catalyst in the literature.

No.	Catalyst	Conditions	Ref. yield (%)
1	CH ₃ CN/ ACOH	Reflux, 2h	81 ¹⁷
2	N(Et) ₃	Ethanol	70 ¹⁸
3	Piperidine	MW, 6min	85 ¹⁹
4	Fe-CuO	Solvent free, MW, 6min	94 ^{present work}

However, catalyst stability was checked by recycling of the catalyst in suggesting reactions. In each cycle the catalyst was separated magnetically and washed with ethanol and finally dried at 60°C under vacuum to eradicate residual solvents. The result of various cycles with reaction yield showed in table-5.

Table 5: Reusability of Nanocat Fe-CuO.

Sr.no.	Cycle	Yield (%)
1	Fresh	95
2	1	94
3	2	92
4	3	90
5	4	86

This suggests that, the catalyst used up to five times without any considerable loss of the initial catalytic activity.

SPECTRAL DATA:

¹H-NMR (300 MHz CDCl₃, δ, ppm): 0.9 (3H, s, -CH₃), 1.3 (2H, s, -NH₂), 2.0 (2H, s, -CH₂), 2.1 (2H, s, -CH₂), 4.7(1H, s, -CH), 6.7-7.7 (11H, m, -ArH).

¹³C-NMR (75 MHz, CDCl₃, δ, ppm): 28.1, 28.5, 32.0, 40.8, 50.7, 118.8, 124.9, 126.1, 127.3, 129.2, 130.6, 130.8, 130.9, 139.9, 151.3, 160.9, 161.9, 164.2, 196.6.

CONCLUSION:

The magnetic nano catalyst Cu-Ferrite was easily prepared, stable to air and magnetically recovered by simple magnetic decantation. Cu-Ferrite nano catalyst has been showed good to use for the synthesis of pyrazole aldehyde derivative preparation with 82 to 94 % yield. The catalytic activity of the catalyst remains unaltered after six consecutive cycles making them environmentally friendly and with reusability due to their efficiency, ease of handling and cost effectiveness. We believe that this approach towards sustainable chemistry has great scope for future catalytic processes.



INTERNATIONAL RESEARCH JOURNAL OF INDIA

ISSN 2454-8707 / IMPACT FACTOR 2.05 / VOLUME - II, ISSU -X, JUNE 2017

ACKNOWLEDGMENT:

The authors are thankful to the Director of SAIF, Panjab University (Chandigarh, India) for the spectral analysis. Author also grateful to the principal and HOD, S.S.G.M. College, Kopargaon, Ahmednagar (MH) for providing research facilities and constant encouragement.

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