Multicomponent synthesis of pyrazole-3-one under mild conditions using an effective novel ceria-doped copper nanocatalyst

Gharat Vaishnav D.* and Patil Vishvanath D.
Organic Chemistry Research Laboratory, Department of Chemistry, C.K. Thakur A.C.S. College, New Panvel, Raigad, Maharashtra, INDIA
*vaishnavgharat@gmail.com

Abstract
Synthesis of pyrazole-3-one derivative was successfully catalyzed by a copper nanocatalyst that had been doped with cerium. With outstanding yields of pyrazol-3-one derivatives, this approach has been applied to a wide range of substrates including electrophilic and sterically hindered aromatic aldehydes. The remarkable selectivity under mild conditions of this commercially available inexpensive catalyst is an attractive feature of this method.

Keywords: Pyrazole-3-one, Doped copper nanocatalyst, Ceria dope, Multicomponent synthesis.

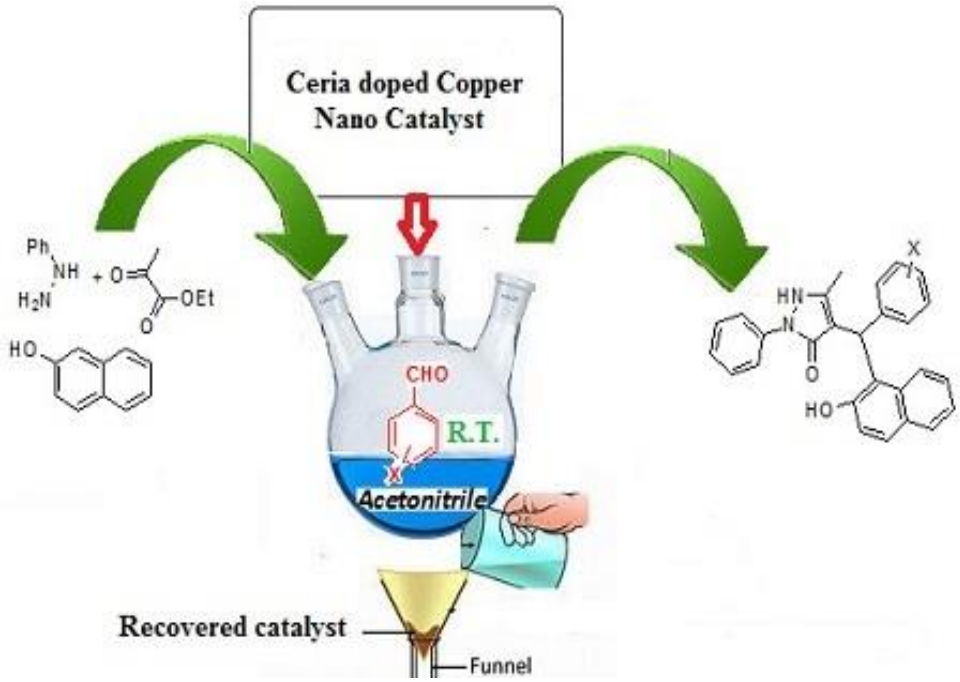
Introduction

Pyrazole is a pharmaceutical chemical that is incredibly valuable, since it has a wide range of biological effects including antibacterial, antiviral, sedative, antifungal, herbicidal, antiarrhythmic, hypoglycemia and anti-inflammatory ones.[11] Although various synthetic approaches have been reported[9] such as palladium-catalyzed alkynyl carbonylation of aryl iodides with the use of Mo $(CO)_6$[5], one-pot' synthesis of 4-substituted 1,5-diaryl-1H-pyrazole-3-carboxylates via lithium tert-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction[5] and Ce/SeO_2 with reflux[3]. Nitrogen-containing heterocyclic compounds are found promisingly biologically active pharmaceutical and natural products[2].

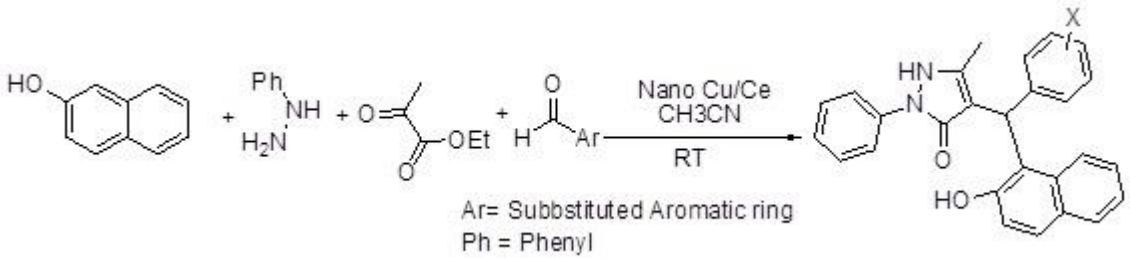
One-pot synthesis offers a significant advantage over conventional multistep synthesis[1,13]. The development of selective and reusable solid catalysts for the synthesis of hetero moieties is in great demand.[7,8,10,12] The suggested method has certain limitations such as challenging reaction situations and prolonged reaction times. In order to get over this restriction, we developed a general, efficient and novel method to synthesize pyrazol-3-one.

Material and Methods

AR grade chemicals from Loba, SD Fine Ltd., were utilized in the experiment. NMR spectra were obtained using $CDCl_3$ as a solvent. Parts per million (ppm) numbers were utilized to express chemical changes in the solvent. Every reaction was performed in a safe atmosphere. Thin layer chromatography (TLC) was performed on aluminum plates coated with silica and observed through an ultraviolet chamber. All solvents were used without purification unless otherwise indicated in the processes. No effort was taken to remove ambient moisture. Before being used, glassware was dried for at least an hour at 80°C in an oven. The catalyst was calcined at 600°C in Shimadzu's Muffle furnace.



Graphical Abstract



Scheme 1: Synthesis of pyrazolone derivative

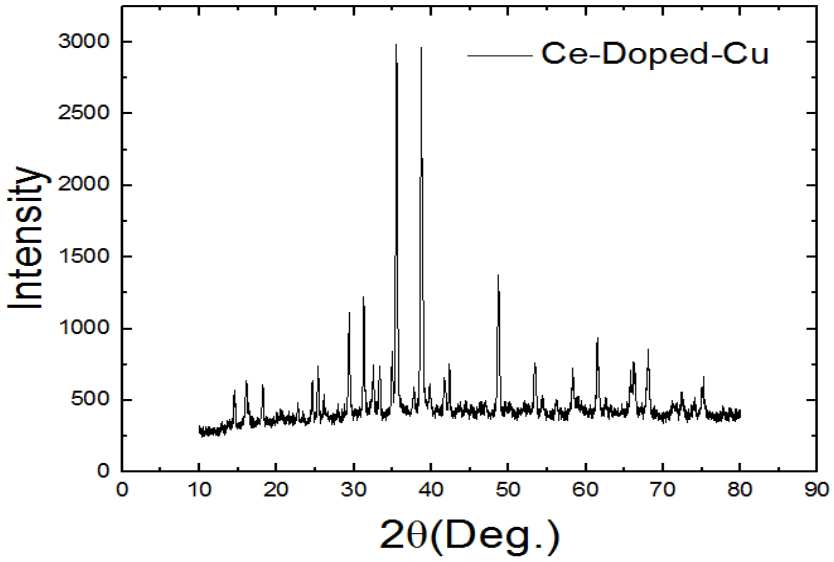


Fig. 1: XRD pattern of Ce-Doped-Cu Nano Catalyst

Preparation of Ce-doped-Cu nanocatalyst: Synthesis of Ce-doped-Cu nanocatalyst was done with the help of copper nitrate (1.596 gm.) as a source of Cu ion with cerium nitrate (0.332 gm) as a source of Ce ion and calculated amount of glycine along with L-ascorbic acid in minimum amount of distilled water. It was heated on a hot plate at 80°C to get homogenized gel after the removal of excess water. On further heating, gel gets swallowed and releases brownish gases within 2-3 seconds. In the end, the powder obtained was calcinated at 500°C in the Muffle furnace for 4 hours. The resultant crystalline powder of Ce-doped-Cu nanocatalyst has an average particle size of 9.8 nm). Characterization of nanomaterial was done with SEM, EDAX, XRD and IR.

General Experimental Procedure for pyrazolone derivatives: A mixture of phenylhydrazine (108 mg, 1 mmol), ethyl aceto acetate (130 mg, 1 mmol), beta naphthol (144 mg, 1mmol), aromatic aldehyde (1 mmol) and Ce-Doped-Cu nanocatalyst (1.5 mg 10 % w/w) with 3 ml acetonitrile as solvent was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). After 30 min, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was recrystallized with ethanol. The product obtained pyrazolone 2 (table 4, Entry 2).

Characterization of catalyst: The powder XRD pattern (Fig. 1) of Ce-doped-Cu nanocatalyst prepared by sol-gel method revealed that the product formed is single-phase and the crystallite size was estimated from broadening diffraction peak by using Scherrer's equation which is found to be 9.8 nm. FTIR spectra of Ce-doped-Cu Nano catalyst (fig 2) were in the range of 450-4000 cm^{-1} wave number which shows a characteristic peak at 460 cm^{-1} as Ce-O stretching band which shows the formation of CeO and peaks in the 600- 700 cm^{-1} revealing the formation of CuO with the peaks at 3415 cm^{-1}.

EDAX analysis of the prepared doped nanocatalyst (Fig. 3a) showed that the composition of Ce was 13.58% higher concerning Cu. Sulfur and oxygen were also detected along with Ce and Cu, showing successful doping and dispersion of Ce with Cu catalyst (Fig. 3b). Analysis using Scanning electron microscope (SEM) reveals that the produced particles had hollow rod morphology (Fig. 4a) and were nano-scale in size (Fig. 4b) due to their high catalytic activity.

Figure 5 depicts TEM images of doped materials. The crystalline cerium doped copper nanoparticles are shown in figure 5a and c. The average particle size of cerium-doped copper nanoparticles was found to be 10-50 nm. This value corresponds to the average particle size determined by XRD

and FE-SEM analysis. Because Ce doping reduces particle size while increasing particle surface area, more particles become involved in the chemical process. Figure 5d depicts the SAED pattern of Ce-doped-Cu nanoparticles. The SAED pattern with sharp circular rings corresponds to the nano-size particles.

The powder XRD pattern (Fig. 1) of the sol-gel generated Cd-doped-Zn nanocatalyst revealed that the product formed is single-phase and the crystallite size was calculated using Scherrer's equation from the broadening diffraction peak which was found to be 33.08 nm.

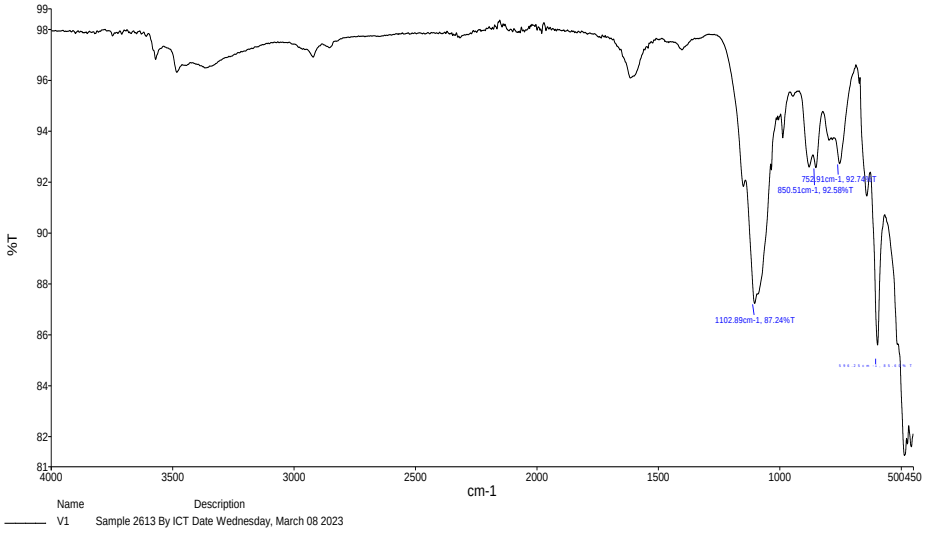
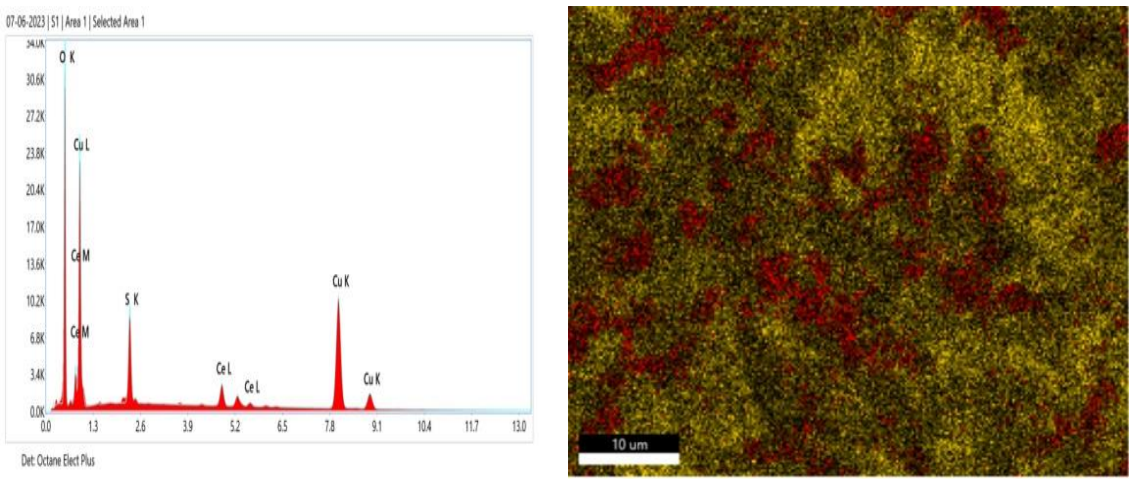
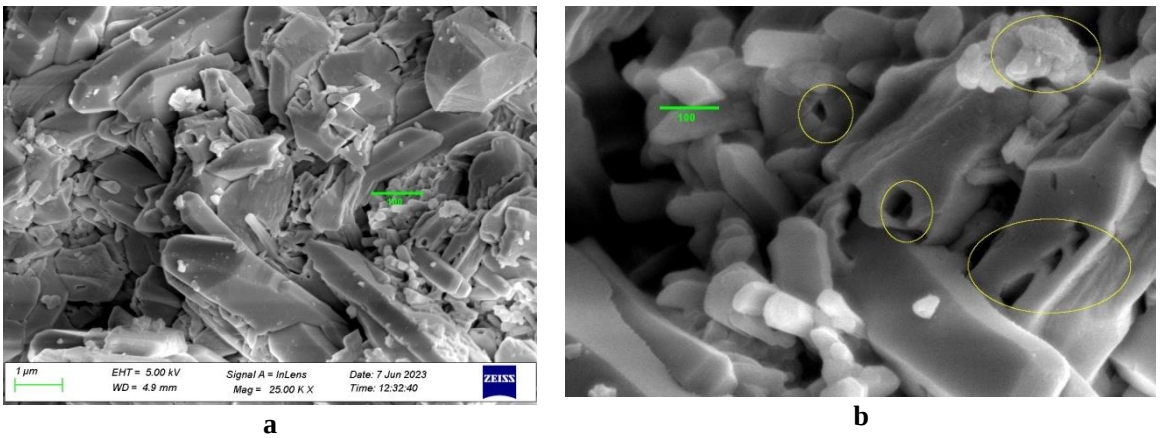


Fig. 2: IR of Ce-Doped-Cu Nano Catalyst



a **b**

Fig. 3: EDAX pattern (a) and Mapping (b) of Ce-Doped-Cu nano Catalyst CeL CuK



a **b**

Fig. 4: Scanning Electron Microscopy of Ce-doped-Cu nanocatalyst

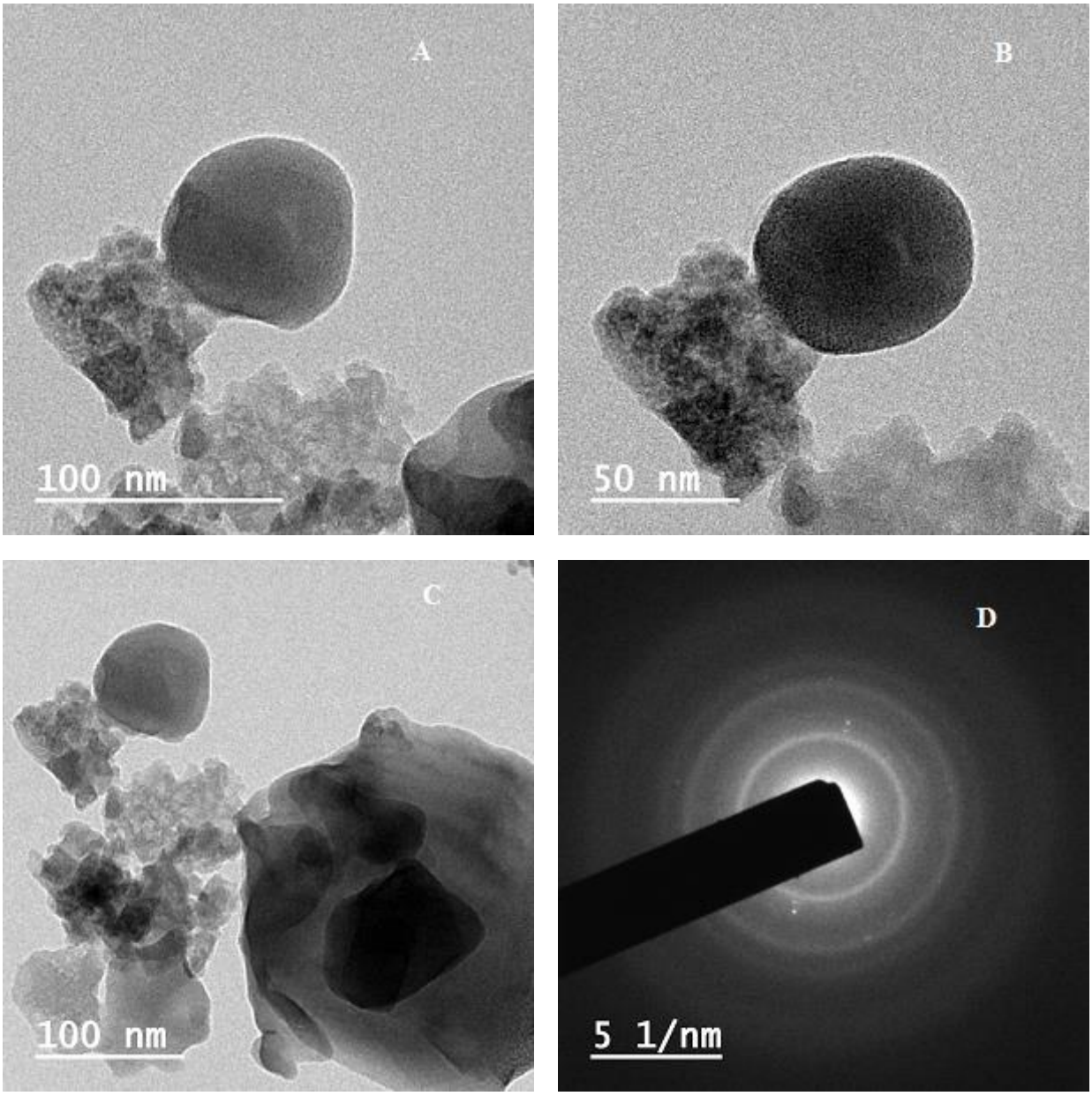


Fig. 5: TEM of Ce-Doped-Cu nanoparticles at different magnificence

Table 1
Catalytic effect of dopant (Ce) percentage in pyrazolone 2 synthesis (table no 4-entry 2) in acetonitrile at room temperature.

Entry	% (w/w) of Ce	Yield (%)[a]
1.	4	65
2.	8	70
3..	12	76
4.	**16**	**94**
5.	20	93
6.	24	85

[a] Isolated yield of the corresponding pyrazolone product

Results and Discussion

To find out the most effective combination of dopant (Ce) with Cu nanocatalyst for the synthesis of pyrazolone 2 (table 4, Entry 2), we employed various percentages of ceria metal oxides at room temperature (Table 1). According to the results obtained, the 16 % Ce combination was found to be the most efficient catalyst. However, other combinations exhibit less significant catalytic properties in the synthesis of pyrazolone 2 (Table 4, Entry 2). The desired percentage combination of 16% (w/w) in table 1 (entry 4) was employed to find out the catalytic loading in the synthesis of

pyrazolone 2 (Table 4, Entry 2). According to the result obtained, 1% w/w (1.2 mg) (Table 2, entry 3) was found more effective loading for the synthesis of pyrazolone. In order to find out the most effective synthesis of pyrazolone 2 (Table 4, Entry 2) chosen as a model substrate, it was treated with 1.2 mg of Ce-doped-Cu catalyst with various solvents at room temperature (Table 3). The reaction in THF, CH_2Cl_2, $CHCI_3$, Et_2O, EtOAc, DMF and CH_3CN (Table 3, Entries 1-7) was found in the presence of the CH_3CN solvent to give an excellent yield (93%, entries7,8).

A wide variety of aldehydes was applied under optimal reaction conditions to prepare the pyrazolone derivative. The results are summarized in table 4 (entries 1-13). Aldehydes with aromatic possessing both electron-donating and electron-withdrawing groups, aliphatic (Table 4, entry 12,13) heterocyclic (Table 4, entry 11) were employed for pyrazolone formation. Except aliphatic aldehydes, the yields were excellent (Table 4, Entries 1-13).

Compounds Characterization

Entry 2: 1,2-dihydro-4-((2-hydroxynaphthalen-1-yl)(2-nitrophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one, brown solid powder.

Melting point: 276-278°C, **IR (KBr):** 1572(-C=N), 1522(-NO_2), 1712(CO), 3069(-NH), 3200-3500(broad) cm^{-1}(-OH), **H^1NMR :** (500MHz, $CDCl_3$): δ = 1.3 (s, 3H, -CH_3), 2.2 (s, 1H, -NH) ; 4.1(s, 1H ,-CH); 4.4((s, 1H, -OH); 7.0-7.2 (m,Ar-3H); 7.25(d,1H,Ar-H); 7.4 (dd, 3H, Ar-H); 7.65(dd, 3H,Ar-H); 7.9 (d, 2H, Ar-H); 8.1 (d, 2H, Ar-H); 8.3 (d, 1H, Ar-H).

Entry 3: 1,2-dihydro-4-((2-hydroxynaphthalen-1-yl)(3-nitrophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one, orange coloured solid.

Melting point: 280-282°C, **IR (KBr):** 1600(-C=N), 1525(-NO_2), 1703(-CO), 3059(-NH), 3314 cm^{-1}(broad) cm^{-1}(-OH), **H^1NMR :** (500MHz, $CDCl_3$): δ = 1.25 (s, 3H, -CH_3), 2.0 (s, 1H, -NH) ; 4.1(s, 1H ,-CH); 5.2((s, 1H, -OH); 6.9(d,Ar-3H); 7.1(d,1H,Ar-H); 7.25 (dd, 3H, Ar-H); 7.35(dd, 1H,Ar-H); 7.6 (dd, 3H, Ar-H); 7.7 (d, 2H, Ar-H); 8.3 (d, 2H, Ar-H).

Entry 4: 1,2-dihydro-4-((2-hydroxynaphthalen-1-yl)(2-hydroxyphenyl)methyl)-5-methyl-2-phenylpyrazol-3-one-buff colored solid

Melting point: 196-198 °C, **IR (KBr):** 3600 broad (-OH), 1505(-C=N), 1698(-CO), 2921 (-CH), 3259(-NH), **H1NMR :** (500MHz, $CDCl_3$): δ = 1.25 (s, 3H, -CH3), 4.55 (s, 1H, -CH) ; 5.00(s, 1H ,-OH); 6.9-7.1(m,Ar-5H); 7.2(m,3H,Ar-H); 7.4 (m, 3 H,Ar-H); 7.6 (d, 3H, Ar-H); 7.9 (d, 1H, Ar-H); 8.0 (d, 1H, Ar-H); 8.25(d, 2H, Ar-H).

Entry 5: 4-((4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-1,2-dihydro-5-methyl-2-phenylpyrazol-3-one pale yellow coloured solid

Melting point: 234-236 °C, **IR (KBr):** 620 (Ar-Cl), 1598(-C=N), 1703(-CO), 2921 (-CH), 3059(-NH), **H^1NMR :** (500MHz, $CDCl_3$): δ = 1.25 (s, 3H, -CH_3), 2.0 (s, 1H, -NH) ; 4.75(s, 1H ,-CH);5.2((s, 1H, -OH); 7.04(d,Ar-3H); 7.14(d,1H,Ar-H); 7.24 (dd, 2H, Ar-H); 7.28-7.36 (m, 5H,Ar-H); 7.42 (dd, 1H, Ar-H); 7.54 (d, 1H, Ar-H); 7.65 (dd, 2H, Ar-H).

Table 2
Catalytic effect of Ce-doped-Cu in the synthesis of pyrazolone 2 (table no 4-entry 2) in acetonitrile at room temperature.

Entry	Ce/Cu (mg)	Time (min)	Yield (%)[a]
1.	0.4	50	55
2.	0.8	50	60
3.	**1.2**	**15**	**94**
4.	1.6	40	93
5.	2.0	50	93
6.	2.4	60	93

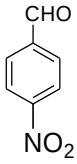
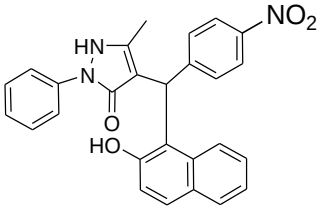
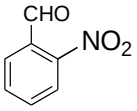
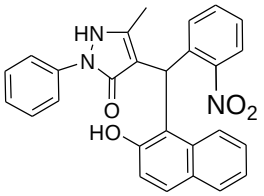
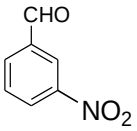
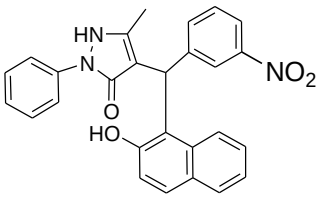
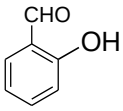
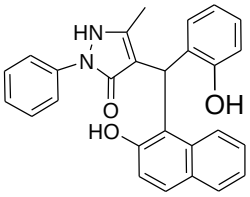
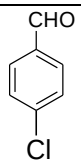
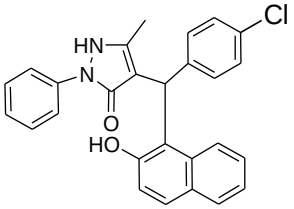
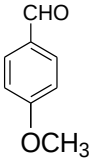
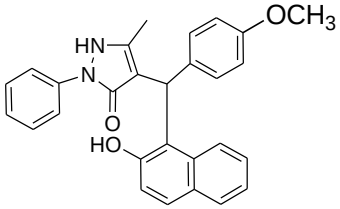
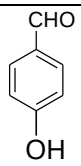
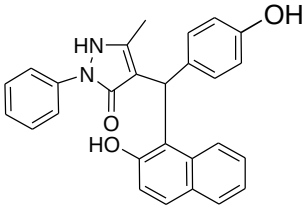
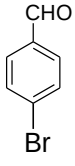
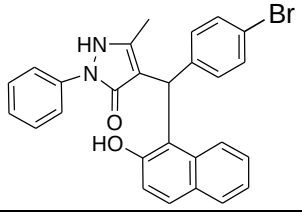
[a] Isolated yield of the corresponding pyrazolone product.

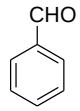
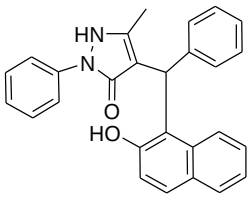
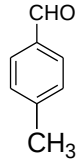
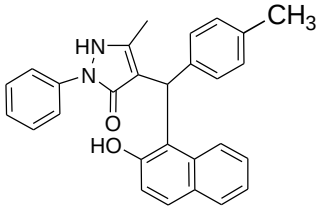
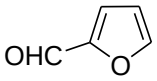
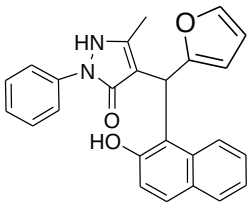
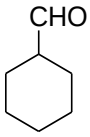
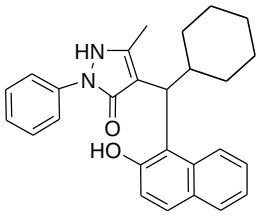
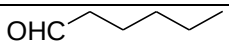
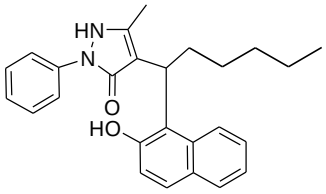
Table 3
Synthesis of pyrazolone 2 (table no 4-entry 2) with different solvents.

Entry	Ce/Cu (mg)	Solvent	Time (min)	Yield (%)
1.	1.2	THF	120	60
2.	1.2	CH_2Cl_2	60	82
3.	1.2	$CHCl_3$	90	70
4.	1.2	Et_2O	120	65
5.	1.2	EtOAc	90	75
6.	1.2	DMF	60	72
7.	1.2	CH_3CN	15	94[b]

[a]Isolated Yield
[b] CH_3CN solvent is more effective.

Table 4
Synthesis of pyrazolone derivatives in the presence of Ce-Doped-Cu nanocatalyst at room temperature with various aldehyde

Entry	Aldehyde	Product	Time (min)	Yield [c]
1			15	93
2[b]			30	94
3[b]			20	86
4[b]			60	82
5[b]			90	75
6			120	68
7[b]			120	78
8			90	70

9			45	85
10			60	70
11			45	88
12			120	40
13			120	30

[a] The substrate 1 mmol was treated with(A+B+C) 1mmol by using 1.2 mg of Ce-doped-Cu in Acetonitrle at room temperature.
[b] All products were identified by their IR and ^{1}H NMR spectra
[c] Isolated yields.

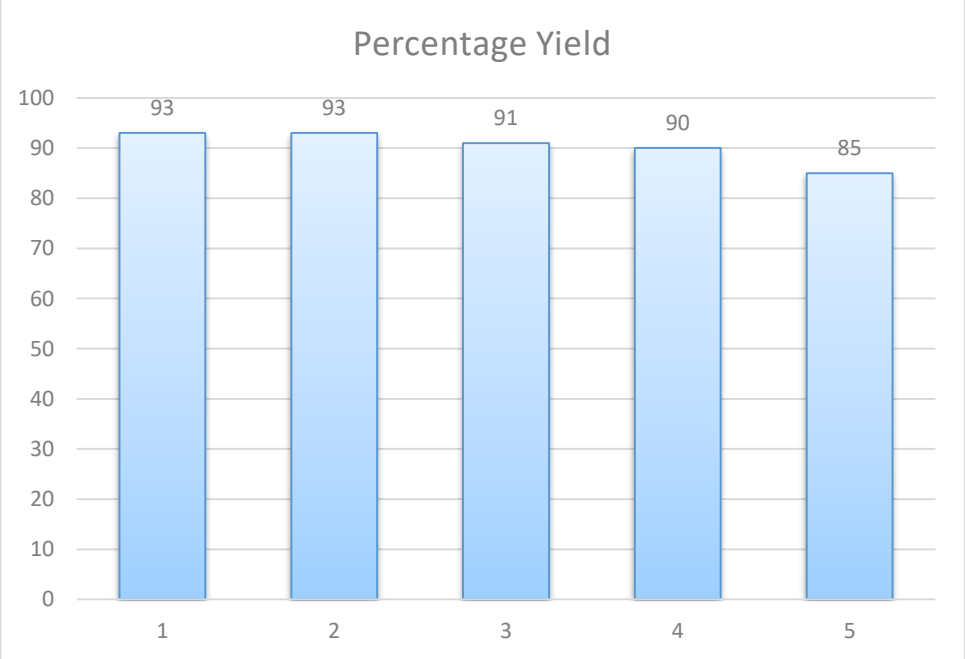


Fig. 6: Recyclability of catalyst

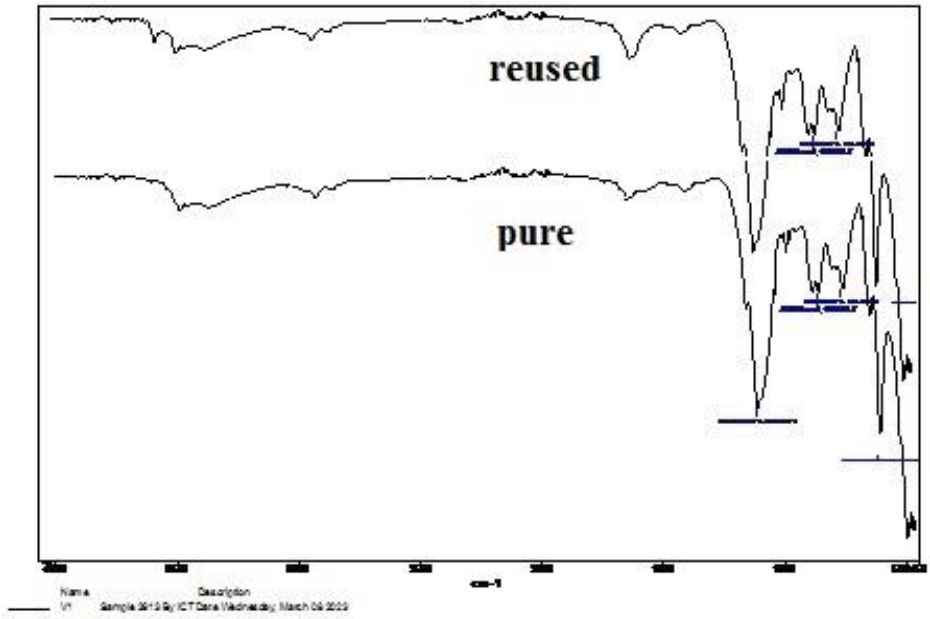
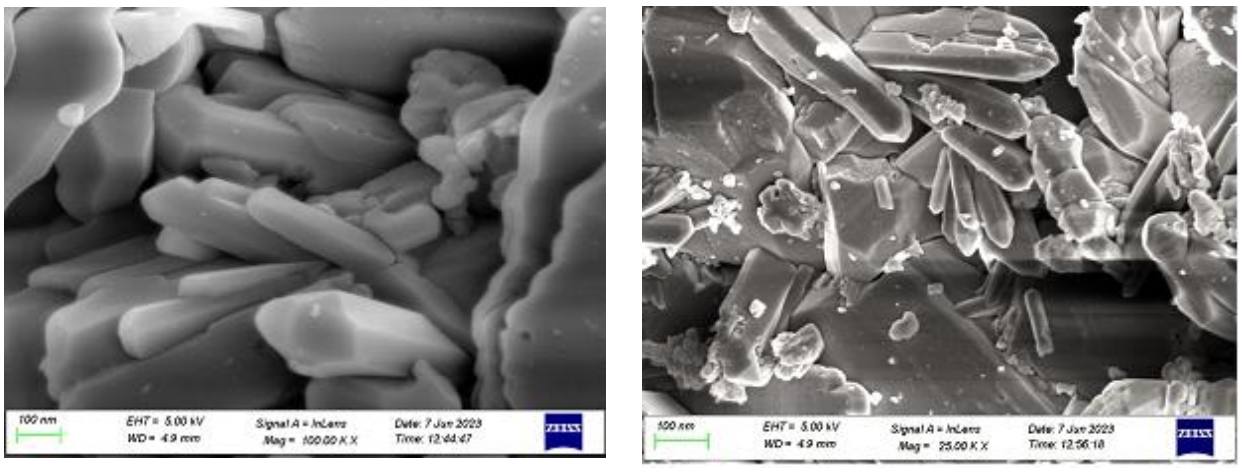


Fig. 7: FTIR of reused and pure catalyst



Pure **reused**

Fig. 8: FE-SEM of pure and recycled catalyst

Entry 7: 1,2-dihydro-4-((2-hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methyl)-5-methyl-2-phenylpyrazol-3-one White colored solid
Melting point: 296-298 °C, **IR (KBr):** 1584(-C=N), 1775(-CO), 2950 (-CH), 3105 (-NH), **H1NMR :** (500MHz, $CDCl_3$): δ = 1.65 (s, 3H, -CH3), 2.1 (s, 1H, -NH) ; 4.8(s, 1H, -CH); 5.0 ((s, 1H, -OH); 6.9-7.8(m,Ar-15H);

Recyclability of catalyst: Ce-doped-Cu nanocatalyst is a heterogeneous catalyst in the reaction mixture, giving easy recovery as in scheme 1. It was observed that the catalyst afforded a product with negligible loss of activity for at least five cycles (Fig. 6).

The recyclability was carried out by simple filtration of the prepared catalyst after the reaction was complete and washed with ethanol twice followed by drying in the oven at 90°C. The catalyst was continued for the next cycle. This we repeated five times where in all cycles, the product formed is in excellent yield. Fig. 7 shows the FTIR and fig. 8 shows FE-SEM spectra of pure and reused catalysts at the time recycling process. FT-IR spectra (fig. 7) and FE-SEM images (Fig. 8) of recovered and pure catalysts do not show any reconstruction of particle morphology.

Conclusion

In conclusion, Ce-doped-Cu nanocatalyst is a highly efficient catalyst for the synthesis of pyrazolone by using various substrates of aldehyde. The advantages include low cost, ease of catalyst handling, the requirement of a very small amount of catalyst, excellent yield, mild reaction conditions and remarkable selectivity of this inexpensive catalyst.

Acknowledgement

The authors acknowledge the support of this work by the Department of Chemistry, C.K. Thakur College New Panvel. Authors are also thankful to retired Prof. Dr. G.A. Meshram of University of Mumbai.

References

1. Akondi A.M., Trivedi R., Bharatam J., Vemulapalli S., Bhargava S., Buddana S. and Prakasham R., Ce/SiO_2 composite as an efficient catalyst for the multicomponent one-pot synthesis of substituted pyrazolones in aqueous media and their antimicrobial activities, *J. Mol. Cat. A. Chem.*, **411**, 325 **(2016)**

2. Costa S., Pisoni D.S., Silva C.B., Petzhold C.L., Russowsky D. and Ceschi M.A., Lewis Acid Promoted Friedländer Condensation Reactions between Anthranilonitrile and Ketones for the Synthesis of Tacrine and its Analogues, *Braz. Chem. Soc.*, **20**, 1448 **(2009)**

3. Heravi M.M., Saeedi M., Beheshtiha Y.S. and Oskooie H.A., One-pot synthesis of benzochromeno-pyrazole derivatives, *Mol. Divers*, **15**, 239 **(2011)**

4. Huang W.B., Jiang J. A., Zhai J., Liu H.W., Cai Q. and Xu L.X., One-pot' synthesis of 4-substituted 1,5-diaryl-1H-pyrazole-3-carboxylates via lithium tert-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction, *Tetrahedron*, **69**, 627 **(2013)**

5. Iizuka M. and Kondo Y., Palladium-Catalyzed Alkynylcarbonylation of Aryl Iodides with the Use of Mo(CO)6 in the Presence of tBu3P Ligand, *Eur. J. Org. Chem.*, **31**, 5180 **(2007)**

6. Karrouchi K. and Radi S., Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review, *Molecules*, **23(1)**, 134 **(2018)**

7. Kramer C.S., Pyrazoles, Privileged scaffolds in medicinal chemistry: Design, synthesis, evaluation, Royal Society of Chemistry **(2016)**

8. Marques M.V., Ruthner M., Fontoura L.A.M. and Russowsky D., Metal Chloride Hydrates as Lewis Acid Catalysts in Multicomponent Synthesis of 2, 4, 5-Triarylimidazoles or 2, 4, 5-Triaryloxazoles, *J. Braz. Chem. Soc.* **23**, 171 **(2012)**

9. Meshram G.A. and Patil V.D., A simple and efficient method for sulfonylation of amines, alcohols and phenols with cupric oxide under mild conditions, *Tetrahedron Lett.*, **50**, 1117 **(2009)**

10. Schwalm C.S., Ceschi M.A. and Russowsky D., Metal Halide Hydrates as Lewis Acid Catalysts for the Conjugated Friedel-Crafts Reactions of Indoles and Activated Olefins, *J. Braz. Chem. Soc.*, **22**, 623 **(2011)**

11. Silveira C.C., Vieira A.S., Braga A.L. and Russowsky D., Stereoselective Mannich-type reaction of chlorotitanium a-phenylseleno esters enolates with aromatic aldimines, *Tetrahedron*, **61**, 9312 **(2005)**

12. Srivastava M., Singh J., Singh S.B., Tiwari K., Pathak K.V. and Singh J., Synthesis of novel fused heterocycle-oxa-aza-phenanthrene and anthracene derivatives via sequential one-pot synthesis in aqueous micellar system, *Green Chem.*, **14**, 901 **(2012)**

13. Wan J.P., Gan S.F., Sun G.L. and Pan Y.J., Novel Regio selectivity: Three-Component Cascade Synthesis of Unsymmetrical 1,4- and 1,2-Dihydropyridines, *J. Org. Chem*, **74**, 2862 **(2009)**.

(Received 10th May 2024, accepted 15th July 2024)