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SOLVENT FREE GREEN MULTICOMPONENT SYNTHESIS OF PYRAZOLE WITH CERIA DOPED COPPER NANO CATALYST

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ABSTRACT :
An efficient, green and facile method for the synthesis of pyrazole derivatives by the reaction of aldehyde, malano nitrile and phenyl hydrazine was developed using Ce-Doped Cu nano catalyst. This reusable nano catalyst efficiently catalyzed the synthesis of Pyrazole derivatives. The eco-friendly, environmentally-benign, multi component solvent free reactions occur at room temp in very short period of time. The catalyst and some selected derivative were characterized by various instrumental techniques including IR,NMR, XRD.

KEY WORDS: Pyrazole, Ceria Dope, Copper Nano, Solvent Free, Green Synthesis.

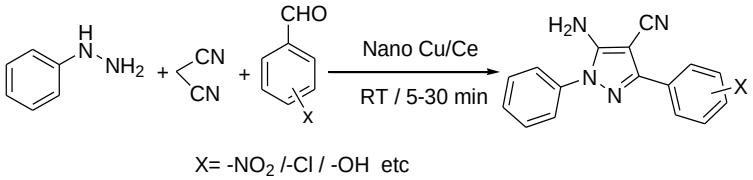
INTRODUCTION

Green chemistry approaches in synthetic heterocyclic chemistry has attracted many researchers in the recent era due to easy handling, environmentally-benign and cost-effective approach. The one pot methods are in great demand for preparation of organic compounds,[i-iii] bioactive medicine[iv], heteromolecule[v] and hetero cyclic combinational chemistry[vi]. The multi component reactions having advantage over the conventional methods like compact reaction, having simple protocol, good yields, inexpensive reactants, time reduction[vii]. In the recent years metal oxides due to the great advantage such recyclable, cost effective and easy workup[viii] are suitable for such reactions.

N- heterocyclic compounds are found promisingly biologically active pharmaceutical and natural products[ix]. Derivative of pyrazole are extremely useful pharmaceutical compound because they exhibits wide range of biological activities such as antibacterial, antiviral, sedative, antifungal, herbicidal, antirhythmic, hypoglycemic, anti-inflamic etc[x]. Many synthetic methods have been reported[xi] like palladium-catalyzed Aakynyl carbonylation of aryl iodides with the use of Mo $(CO)_6$ [xii], 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[xiii]. The development of selective and reusable solid catalyst

for the synthesis of hetero moiety is in great demand[xix-xvii]. However reported approach has limitation like, harsh reaction condition, longer reaction time etc.

In our previous reported work we use a nano CeO_2 catalyst in synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones[xviii], in continuation to that we developed a Ce-doped-Cu nano catalyt that gives general, mild, efficient and solvent free synthesis of pyrazole.



X= -NO_2 /-Cl / -OH etc

Scheme – 1 General Synthesis Of Pyarazole

EXPERIMENITAL:

All AR-Grade chemical by sd fine ltd, loba etc. were used in the experiment. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were obtained on 500 MHz instrument using $CDCl_3$ as solvent. Chemical shifts were reported as **δ** values in parts per million (ppm) relative to the solvent. All reactions were performed in environmental benign. Thin layer chromatography (TLC) was performed on silica coated aluminum plates visualized with ultra violet chamber. All solvents were used without purification and no attempts were made to exclude atmospheric moisture unless indicated otherwise in the following procedures. Before use glassware was dried for at least 1 hours in oven at 90 °C. Catalyst was calcinated in muffle furnace at 500°C made by shimadzu.

GENERAL PROCEDURE:

General Procedure for synthesis of pyrazole derivatives:

A mixture of phenyl hydrazine (1 m mol), Malononitrile (1 m mol), and aromatic aldehyde (1 m mol), Ce-Doped-Cu (1.2 mg) nano catalyst was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The resulting reaction mixture was recrystalised using ethanol where catalyst recovered. The product obtained after the usual work up gave satisfactory spectral data such as IR, ^{1}H-NMR.

Preparation of Ce-doped-Cu nano catalyst

Synthesis of Ce-doped-Cu nano catalyst carried out 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 has taken in minimum amount of de- ionized water .It is heated on hot plate at 80°C in order to get homogenized gel after removal of excess of water which on further heating, gel get swallowed and release brownish gases within 2-3 seconds. At the end powder obtained were calcinated at 500°C in the muffle furnace for 4 hours. The resultant crystalline powder of Ce-doped-Cu nano catalyst has the average particle size 9.8 nm). Nano catalyst were Characterized by XRD and IR.

ANALYTICAL DISCUSSION :

Entry 1: 5-amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile.

- **IR (KBr):** 1334(-NO2), 1532 and 1601 (Aromatic CH), 2100-2200(-CN), 3294(-NH_2 sharp),
- **^{H1}NMR :** (500MHz, CDC_{l3}): δ = 3.55 (s, 2H, -N_{H2}), 6.9(dd,Ar-2H); 7.15(d,2H,Ar-H); 7.35 (dd, 1H, Ar-H); 7.6(d, 2H,Ar-H); 8.2 (d, 2H, Ar-H);

Entry 2: 5-amino-3-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile

- **IR (KBr):** 1342(-NO2), 1528 (Aromatic CH), 2100-2200(-CN), 3250(-NH_2 sharp),

- **H^1NMR :** (500MHz, $CDCl_3$): δ = 3.7 (s, 2H, -NH_2), 6.9(dd,Ar-2H); 7.15(d,2H,Ar-H); 7.3 (dd, 1H, Ar-H); 7.4(dd, 1H,Ar-H); 7.6 (dd, 1H, Ar-H); 7.95 (d, 1H, Ar-H); 8.25 (dd, 1H, Ar-H)

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

- **IR (KBr):** 1342(-NO2), 1528 (Aromatic CH), 2250(-CN), 3350(-NH_2 sharp),
- **H^1NMR :** (500MHz, $CDCl_3$): δ = 1.7 (s, 2H, -OH), δ = 3.7 (s, 2H, -NH_2); 6.9(dd,Ar-2H); 7.15(d,2H,Ar-H); 7.3 (dd, 1H, Ar-H); 7.55(dd, 1H,Ar-H); 7.8 (dd, 1H, Ar-H); 7.8 (d, 1H, Ar-H); 8.45 (dd, 1H, Ar-H)

Characterization of catalyst

The powder XRD pattern of Ce-doped-Cu nano catalyst 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.

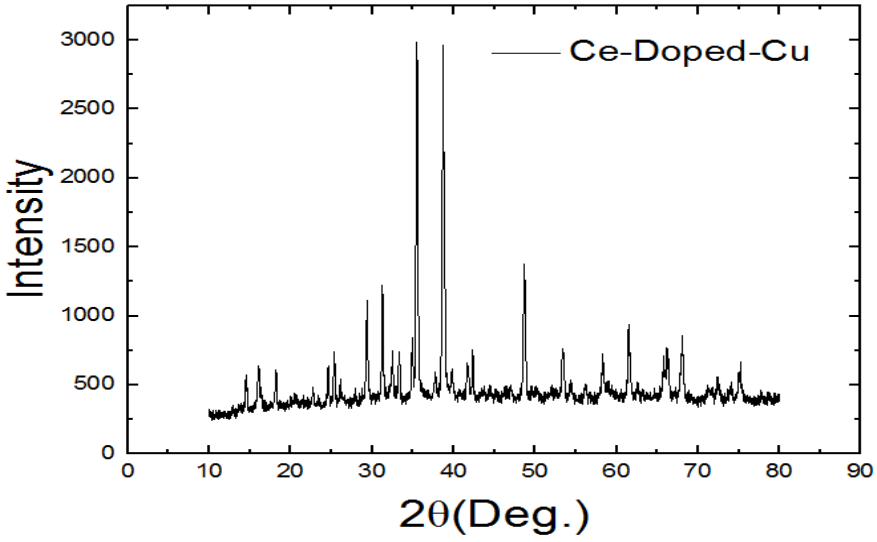


Fig 2. -XRD pattern Of Ce-Doped-Cu Nano Catalyst

FTIR spectra of Ce-doped-Cu Nano catalyst (fig 3) was in the range of 450-4000 cm^{-1} wave number which shows charcterstic peak at 460 cm^{-1} described Ce-O stretching band which show the formation of CeO and peaks in the 600- 700 cm −1 revealed the formation of CuO with the peaks at 3415 cm^{-1} respect to OH of absorbed water

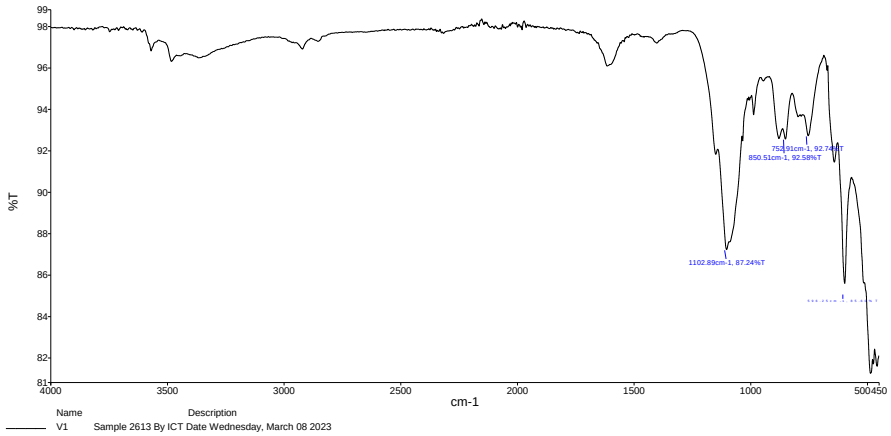


Fig 3-IR Of Ce-Doped-Cu Nano Catalyst

RESULTS AND DISCUSSION:

To get effective combination of dopent (Ce) with Cu nano catalyst for synthesis of pyrazole **1** (table 3, Entry 1) we employed various percentage of ceria metal oxides at room temperature (Table-1). According to the results obtained, 16 % Ce combination was found to be the most efficient catalyst (table 1 entry 4). However, other combination exhibit less significant catalytic properties in the synthesis of pyrazole **1** (table 3,Entry 1).

Table-1: Catalytic effect of dopent (Ce) percentage in pyrazole **1** synthesis (table 3-entry 1) in acetonitrile at room temperature.

Entry	% (w/w) of Ce	Yield (%)[a]
1.	4	70
2.	8	82
3..	12	76
4.	**16**	**95**
5.	20	93
6.	24	90

[a] Isolated yield of the corresponding pyrazole product

The desired percentage combination 16% (w/w) table **1**(entry 4) were employed to find out the catalytic loading in the synthesis of pyrazole **1** (table 3, Entry 1). According to result obtained 1% w/w (1.2 mg) (table 2 entry 3) found more effective loading for synthesis of pyarazole.

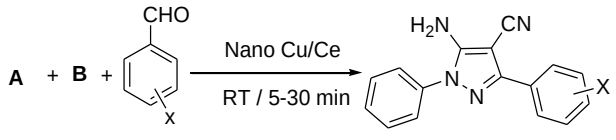
Table-2: Catalytic effect of Ce-doped-Cu in the synthesis of pyrazole **1** (table no 3-entry 1) in acetonitrile at room temperature.

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

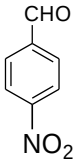
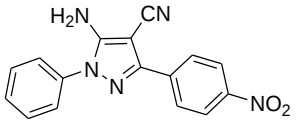
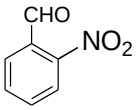
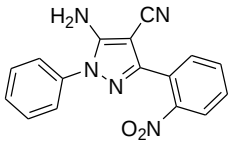
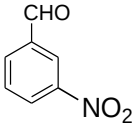
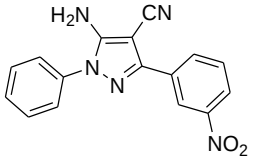
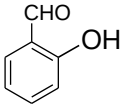
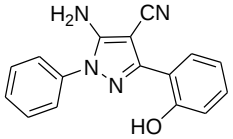
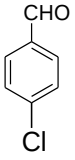
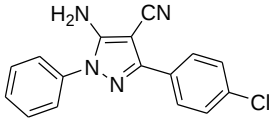
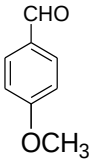
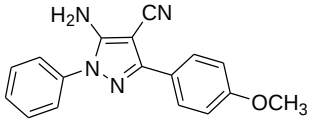
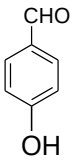
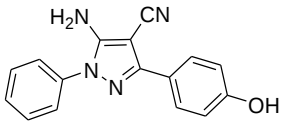
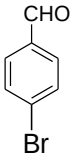
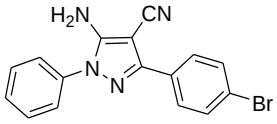
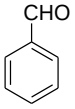
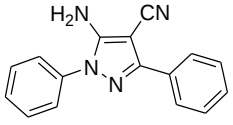
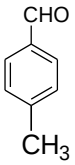
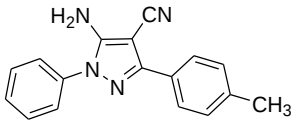
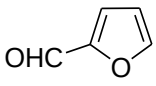
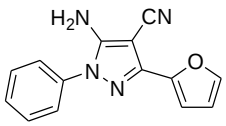
[a] Isolated yield of the corresponding pyrazole product

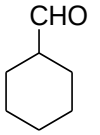
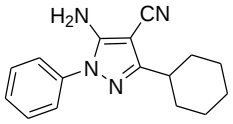
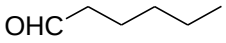
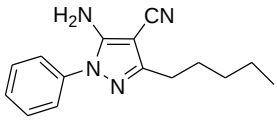
A wide variety of aldehydes were applied under optimal reaction conditions to prepare pyrazole derivative. The results are summarized in Table 3 entry 1-13. Aldehydes with aromatic possessing both electron- donating and electron withdrawing groups, aliphatic (table 3 entry-12,13) heterocyclic (table 3 entry 11)were employed for pyrazole formation. Except aliphatic aldehydes the yields were excellent. (Table 3, entries 1-13).

Table-3. Synthesis of pyrazole derivatives in presence of Ce-Doped-Cu nano catalyst at room temperature with various aldehyde



X= -NO_2 /-Cl / -OH etc
A= phenyl hydrazine
B= malono nitrile

Entry	Aldehyde	product	Time (min)	Yield [c]
1[b]			05	95
2[b]			05	94
3			10	90
4[b]			20	88
5[b]			25	75
6			30	65
7			120	80
8			25	75
9			15	90
10			25	75
11			20	80

12			30	45
13			30	30

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

CONCLUSION:

In conclusion, this manuscript describes a method in which Ce-doped-Cu nano catalyst is highly efficient catalyst for the synthesis of pyrazole, by using various substrate of aldehyde. The advantages include low cost, ease of catalyst handling, requirement of very small amount of cataylyst, excellent yield, Solvent free reaction condition and remarkable selectivity of this commercially available inexpensive catalyst are attractive feature of this method.

Recyclability of catalyst

Ce-doped-Cu nano catalyst is an heterogeneous catalyst in the reaction mixture, giving easy recovery which encouraged to check recyclability of it in scheme 1. It was observed that catalyst afford a product with negligible loss of activity for at least five cycle (table 7 entry 1-7).

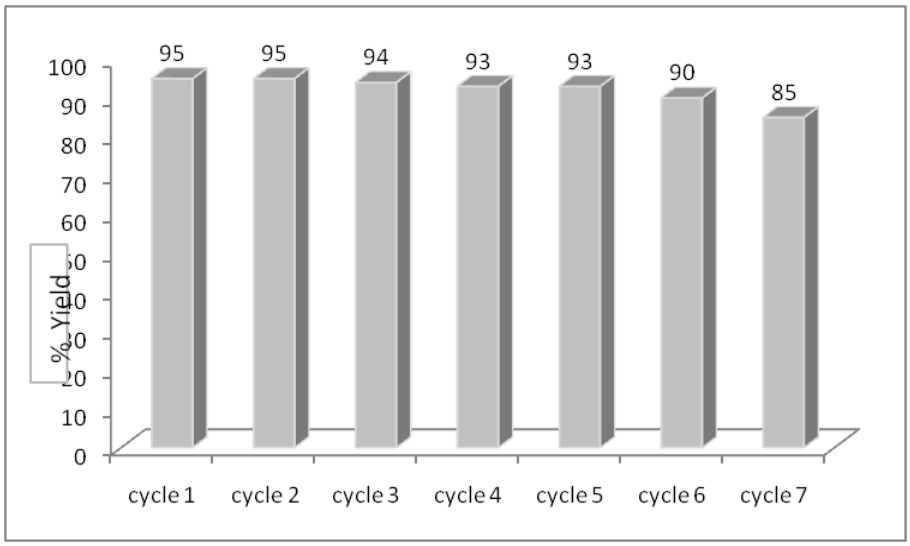


Fig 1 Recylability of catalyst

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