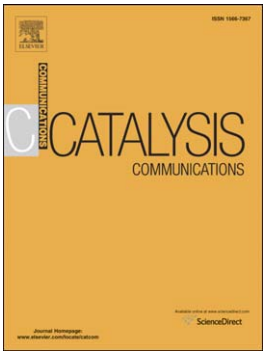

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Synthesis of pyrazole-4-carbonitrile derivatives in aqueous media with CuO/ZrO_2 as recyclable catalyst

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Abstract:

A CuO/ZrO_2 catalysed eco-friendly strategy for the synthesis of pyrazole-4-carbonitrile derivatives in aqueous media in excellent yields (88-92 %) is described. The catalyst was characterised by X-ray diffraction patterns (XRD), Scanning electron microscopy (SEM), Transmission electron microscopy (TEM) and BET surface area analysis. The main benefits of one-pot three component protocol are short reaction times (< 2 h), simple workup procedure, safety and recyclable catalyst. The catalyst is inexpensive, fully recyclable and reusable for over 5 runs, preserving its high activity.

Keywords: Heterogeneous catalysis, Multicomponent reaction, One-pot synthesis, Green Chemistry, CuO/ZrO_2, Reusable catalyst

1. **Introduction:**

Synthetic heterocyclic chemistry using green methods has fascinated many researchers in the recent past due to easy operation, environmental friendly and cost-effective approach. The multicomponent reactions (MCRs) are in the forefront in synthesis of organic [1], agro [2], combinatorial [3], bioactive medicinal [4] and heterocyclic molecules [5], because of the compact reactions, easy procedures and good yields. Advantages of MCRs are wide, including simple protocols, inexpensive reactants and green principles. The additional advantage of MCRs is the reduction in reaction times and scope for green solvent. Thus, such environmentally benign protocols are opportune and well desired.

Many of the conventional protocols for organic synthesis experience constrain such as toxic organic solvents, expensive reagents, tedious workup or prolonged reaction times [6]. In recent years, there is great enthusiasm towards use of heterogeneous catalysts in organic synthesis, due to the inherent advantages such as reusability, low cost, and easy workup [7]. Metal oxides are good candidates for such role, which have proven record as catalysts, supports, and as ion-exchangers. Thermal calcination of these compounds at 500 °C, lead to the formation of acidic/basic mixed metallic oxides with moderate surface area which are prospective candidates as catalysts for various condensation reactions. Relative to conventional linear syntheses, this protocol has benefits including cost effectiveness, atom economy and scope to design the surface properties.

Zirconia (ZrO_2), an acid–based bi-functional catalyst, which is stable in alkaline or acidic solutions [8], has recently emerged as an attractive option as support material for the activation and stabilization of copper. Literature also reports the use of ZrO_2 alone and in combination with other metals in organic synthesis [9]. The crystalline structure of ZrO_2 has been documented as one of the key factors for justification of the structure-activity relationships of Cu-based catalysts [10]. The Cu/ZrO_2 solid material possesses both Bronsted and Lewis acids centers.

Pyrazoles are the important class of heterocyclic compounds that feature in a number of pharmaceutical targets and natural products of medicinal interest. Pyrazole derivatives have exhibited a wide variety of biological activities including antibacterial [11], antifungal [11], antioxidant [11,12], anti HIV [13], anticancer [14], anti-convulsant [15], anti-malarial [16], anti-inflammatory [17] and anti-depressant activities [18]. Literature survey shows several methods reported for synthesis of various pyrazole derivatives and such protocols employed PTSA [19], $Cu(OAC)_2$ [20], $Ti(NMe_2)_2(PyPyr)_2$ [21], LiOH [22], $Sc(OTf)_3$ [23], $Yb(PFO)_3$ [24], $CsF\text{-}Al_2O_3$ [25], Silica chloride [26], I_2 [27], H_2SO_4 [28], (Bim)OH [29], etc as catalysts. Many of these techniques face few or more of the disadvantages such as using toxic reagents, strong acidic or basic conditions, costly reagents and catalysts, strict reaction conditions, tedious steps, and low product yields or long reaction times, which limit their use in practical applications. The importance and prominence of pyrazoles in drug discovery has continually attracted the pursuit for to newer and improved methods [30]. Therefore, a novel protocol with good and inexpensive catalyst demanding short reaction times is well desired.

In continuation of our quest to design environmental friendly protocols for the synthesis of heterocycles giving better yields [31-33], we herein report an efficient one-pot procedure for the synthesis of pyrazole-4-carbonitrile derivatives in excellent yields using Cu/ZrO_2 as a catalyst.

2. Experimental

2.1. *General procedure for the synthesis of pyrazoles*

To equimolar ratios of phenylhydrazine (1 mmol), malononitrile (1 mmol) and substituted aldehyde (1 mmol) were dissolved in water (10 ml) at room temperature (R.T), CuO/ZrO_2 (20 mg) was added as catalyst. Reaction mixture was continuously stirred for 1.5 h at 40 °C (Scheme 1) using a magnetic stirrer. The completion of the reaction was monitored by TLC. The reaction mixture was then filtered, and filtrate was subsequently evaporated under reduced pressure to obtain the crude product. Further, the crude product was purified with 7:3 EtOAc: Hexane solvent mixture to afford pure product (4a-l). The recovered catalyst was subjected for washing with ethanol, dried and reused for up to five cycles.

2.2. Preparation of Catalyst

The Deposition–Precipitation method was used in the preparation of metal oxide supported catalysts [34]. 1.8 g of ZrO_2 was suspended in deionized water (50 mL) by vigorous stirring for 45 min. The pH of the suspension was brought to the desired pH 10 using 0.1 M NaOH and the reaction was run for 2 h with continued stirring. The copper nitrate hydrate ($Cu(NO_3)_2.3H_2O$,) Aldrich, 99.98 % trace metals basis) was dissolved in deionized H_2O and the mixture was left for 1.5 h under stirring separately. The copper nitrate solution was added to the ZrO_2 suspension, while maintaining its basic pH. The reaction mixture was stirred vigorously for 2 h. At 60-70 °C temperature, the obtained precipitate was aged for 60 min in the mother solution. The precipitate was filtered and further washed with deionized water for repetitively followed by overnight drying at 120 °C. The dried sample was calcined in presence of air at 450 °C for 4 h to attain the desired 2% CuO/ZrO_2 catalyst (w/w).

3. Results and Discussion

In the preliminary investigations, reactions were carried out under catalyst-free conditions and employing different catalysts and solvents. In our studies with phenyl hydrazine (1.0 mmol), aromatic aldehyde (1.0 mmol) and malononitrile (1.0 mmol) and water as solvent with no catalyst showed no reaction at R.T. Even after 24 h under reflux conditions, reaction was futile to obtain any product (Table 1, entries 1 & 2). The scope of the different types of catalysts and presence of ionic liquids such as (Bmim)OH, (Bmim)Cl and $(Bmim)BF_4$ on the product yield was investigated, but yields were very low even under reflux conditions (Table 1, entry 3-5). Reaction was performed under reflux conditions using molecular iodine and p-toluenesulphonic acid (PTSA) as catalysts gave 48% and 42% yield respectively (Table 1, entry 6 & 7).

The reactions were repeated using 20 mg of pure CuO, ZrO_2, Mn/ZrO_2 and Cu/ZrO_2 as catalysts under refluxing conditions. Pure CuO, ZrO_2 and Mn/ZrO_2 gave 50%, 54% and 58% yields respectively (Table 1 entry 8-10), while CuO/ZrO_2 gave 85% (Table 1 entry 11). Interestingly, excellent yield of 92% was obtained at 40 °C with CuO/ZrO_2 (Table 1 entry 12) in 1.5 h.

The mixed oxide, a combination of copper and zirconium, displayed excellent catalytic activity towards synthesis of pyrazole derivative in water, relative to other catalyst and solvent conditions. A combination of strong acidic and basic sites provided by Cu and Zr oxides on the catalyst surface and high polarity of water as solvent probably provided the vital conditions for the one-pot MCR, facilitating selectivity towards the product and acceleration of the reaction. Based on the results, optimum dosage of catalyst was assessed by the reaction with different amounts of CuO/ZrO_2. A perusal of the results (Table 1 entry 13-16) suggests that merely 20 mg of CuO/ZrO_2 is sufficient for the optimum reaction yield. The yield of the product continuously increased with increase in catalyst amount from 10 to 20, a further increase in its amount to 30 mg and 40 mg did not contribute significantly to the increase in yield. With 20 mg CuO/ZrO_2, not only the yield of the product was improved, but also increased reaction rate ensuing shorter reaction times (1.5 h).

The efficiency of other solvents relative to water were investigated, water and alcohols gave comparable yields (Table 1, entries 17 & 18), but water had an edge. Non-polar solvents like CH_3CN, toluene and DMF, gave insignificant yields (Table 1, entry 19-21), proving water to be best medium for the reaction. Water is highly polar and dissipates heat faster, which possibly creates necessary conditions for formation of intermediates, and their conversion to final products on the catalyst surface.

Under the chosen conditions, reactions of a range of substituted aldehydes, phenyl hydrazine and malononitrile were investigated to explore the scope and robustness of the protocol. All the reaction products with other details are depicted in Table 2. Interestingly, 4-bromo, 4-trifluoromethyl, 2-chloro, 4-hydroxy, 4-methoxy, 2,5 and 3,4 and 2,4-dihydroxy, aromatic aldehydes with electron withdrawing and electron donating substrates in ortho, meta and para positions of the aromatic ring have also contributed positively to obtain the desired pyrazole-4-carbonitrile derivatives in good to high yields (Table 2). The resultant products were identified and validated by FTIR, ^{1}HNMR and ^{13}CNMR (Electronic Supplementary Information).

3.1. BET Surface Area and Elemental Analysis (BET & ICP)

The BET surface area of CuO/ZrO_2 was confirmed to be 28.1 m^2 g^{-1} by a pore size of 199.8 A° and a pore volume of 0.23 cc g^{-1}. The meso porous nature of the material was established by a type- IV adsorption isotherm (Figure 1).

3.2. Powder X-ray diffractogram (XRD)

The crystal structure of the synthesized calcined CuO/ZrO_2 catalyst was characterized by PXRD spectroscopy, and the resulting patterns are shown in Figure 2. It can be seen that the sample displays the distinctive X-ray diffraction patterns at 2θ = 24.8°, 28.6°, 31.9°, 34.7°, 41.3°, 50.8° and 60.4° of monoclinic ZrO_2 (m-ZrO_2) (JCPDS 37-1484, JCPDS 01-089-9066) crystal phase are predominant for CuO/ZrO_2. In addition to the intensive peaks of ZrO_2, the diffractions at 2θ = 35.5°, 38.8° and 45.7° are detected for CuO/m-ZrO_2, corresponding to crystalline CuO phase (JCPDS 48-1548, JCPDS 05-0661). The reason must be that the Cu loading exceeds the dispersion capacity of CuO on ZrO_2, which is in good agreement the dispersion capacity value of calcined CuO/ZrO_2.

3.3. SEM and ICP-OES Analysis

Figure 3 shows the illustrative SEM morphologies micrograph of the sample copper on zirconia. A lot of large white with irregular shapes are perceived from the low magnification SEM image of CuO/ZrO_2. This micrograph reveals that the aggregative state of the zirconia important particles is with copper. These aggregate in the size range of 0.2 μm. EDS analysis of this catalyst showed that Cu and ZrO_2 are homogenously distributed in the catalyst, and the catalyst ratio is also in agreement with the ICP elemental analysis (Figure 3). The catalyst morphologies as indicated by the SEM image clearly point out the homogeneity in shapes for the sample and high crystallinity.

3.4. TEM Analysis

Figure 4 shows the TEM images of CuO/ZrO_2 catalyst and their particle size distribution. It is observed that the profiles of the catalyst. The magnified shapes of CuO/ZrO_2 sample exhibits irregular mesoporous structures, depicting that catalyst is porous and constructed by metal particles. The interaction between the CuO and the zirconia support seems not very strength since parts of the particles have been separated from the support. The average particle size is calculated to be 12-15 nm.

3.5. Reusability of catalyst

The reusability of the facile heterogeneous catalyst was investigated. After completion of reaction, the catalyst was recovered by filtration, washed with ethanol and dried under vacuum. The recovered catalyst was used repetitively for 5 cycles and only marginal loss in its catalytic activity (< 5%) was observed (Figure 5). The slight loss observed in the catalytic activity after 4^{th} run could be due to the minor losses in recovery process and marginal poisoning of catalyst surface by organic impurities. The SEM images of the fresh catalyst and catalyst material after 5^{th} cycle were compared and only minor differences were observed in morphology, suggesting the intactness of the structure under the operating conditions.

4. Conclusions

In conclusion, we report an environmentally benign and efficient one pot multicomponent green protocol for synthesis of twelve pyrazole-4-carbonitirile derivatives using CuO/ZrO_2 as catalyst in aqueous media in good atom efficiency. This simple and recyclable heterogeneous catalyst, CuO/ZrO_2 shows high catalytic activity for MCR protocol. The current approach deals several advantages such as cost-effectiveness, purity of products, good to high yields, short reaction time, and need of small amount of inexpensive catalyst and environmentally benign green solvent and simple workup. This procedure suggests a promising green method for the synthesis of variety of pyrazole derivatives.

Acknowledgements

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Table 1

Optimization condition for the synthesis of purines by CuO/ZrO_2 catalyst[a]

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)[b]
1	No catalyst	H_2O	R.T	24	--
2	No catalyst	H_2O	Reflux	24	--
3	(Bmim)OH	H_2O	Reflux	12	24
4	(Bmim)Cl	H_2O	Reflux	10	21
5	$(Bmim)BF_4$	H_2O	Reflux	12	28
6	I_2	H_2O	Reflux	8	48
7	PTSA	EtOH	Reflux	10	42
8	CuO (20 mg)	H_2O	Reflux	5	50
9	ZrO_2 (20 mg)	H_2O	Reflux	4	54
10	Mn/ZrO_2 (20 mg)	H_2O	Reflux	3	58
11	CuO/ZrO_2 (20 mg)	H_2O	Reflux	1	85
12	CuO/ZrO_2 (20 mg)	H_2O	40 °C	1.5	92
13	CuO/ZrO_2 (15 mg)	H_2O	40 °C	2	89
14	CuO/ZrO_2 (10 mg)	H_2O	40 °C	2.5	85
15	CuO/ZrO_2 (30 mg)	H_2O	40 °C	1.5	92
16	CuO/ZrO_2 (40 mg)	H_2O	40 °C	1.5	90
17	CuO/ZrO_2 (20 mg)	EtOH	40 °C	2.5	81
18	CuO/ZrO_2 (20 mg)	MeOH	40 °C	3	72
19	CuO/ZrO_2 (20 mg)	CH_3CN	40 °C	3.5	trace
20	CuO/ZrO_2 (20 mg)	Tolune	40 °C	4	trace
21	CuO/ZrO_2 (20 mg)	DMF	40 °C	4	trace

[a]All products were characterised by IR, ^{1}HNMR and ^{13}C NMR spectral analysis.

[b]Isolated yields.

-- No reaction

Table 2
Synthesis of pyrazole derivatives catalyzed by CuO/ZrO_2 catalyst

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	4-Br-Ph	4a	91	163-165	--
2	4-CF_3-Ph	4b	92	201-202	--
3	2-Cl-Ph	4c	90	141‑143	--
4	Ph	4d	92	158-159	159‑160 [27]
5	4-OH-Ph	4e	90	210-211	--
6	4-MeO-Ph	4f	89	106-108	106-108 [23]
7	2-Br-Ph	4g	91	221-223	--
8	3,4-$(OH)_2$-Ph	4h	89	161–162	--
9	2,5-$(OH)_2$-Ph	4i	90	205-206	--
10	anthracen	4j	91	181-182	--
11	2,4-$(OH)_2$-Ph	4k	89	212-213	--
12	2,3-$(OH)_2$-Ph	4l	88	191-193	--

[a]Reaction conditions: phenyl hydrazine (1.0 mmol), aromatic aldehyde (1.0 mmol) and malononitrile (1.0 mmol) and water (10 mL), 40 °C.

[b]All synthesized compounds are identified and their structures were conformed with IR, ^{1}HNMR, ^{13}C NMR spectral data and melting points as compared with literature values.

-- New compounds/no literature available.

Scheme 1: Synthesis of pyrazole-4-carbonitriles derivatives

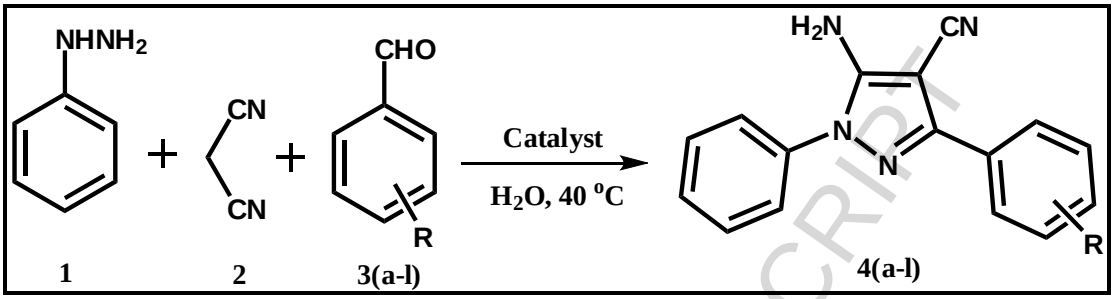


Figure 1: BET surface of CuO/ZrO_2 catalyst

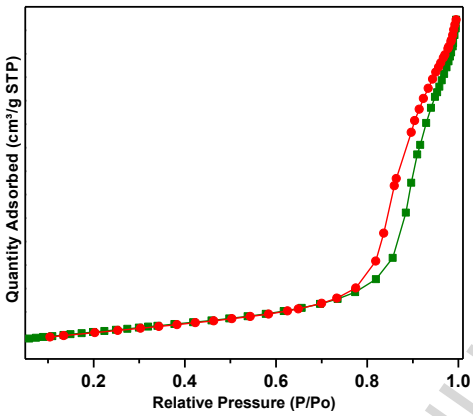


Figure. 2. Powder X-ray diffractogram spectra of CuO/ZrO_2 catalyst

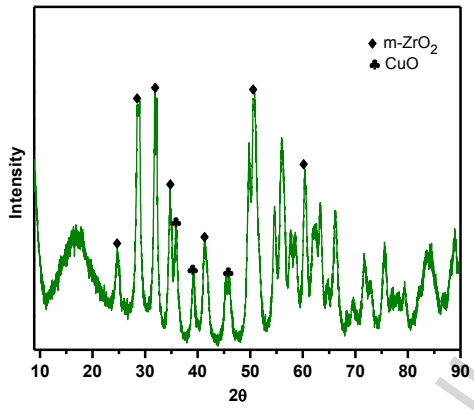


Figure 3. SEM image of CuO/ZrO_2 catalyst

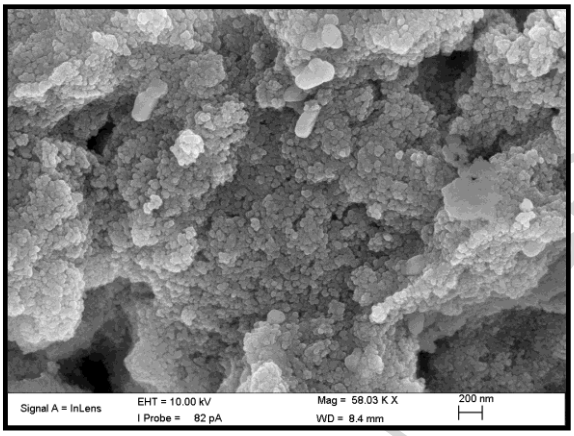


Figure 4. TEM image of CuO/ZrO_2 catalyst

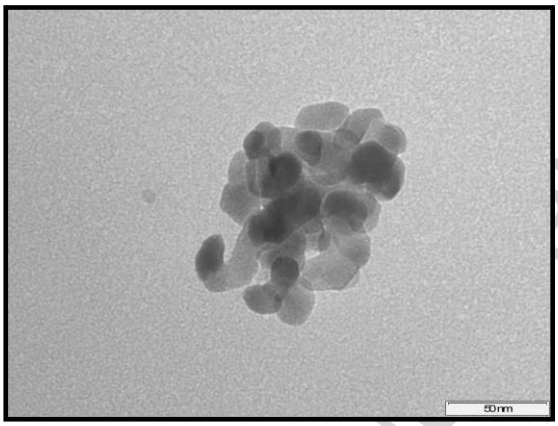
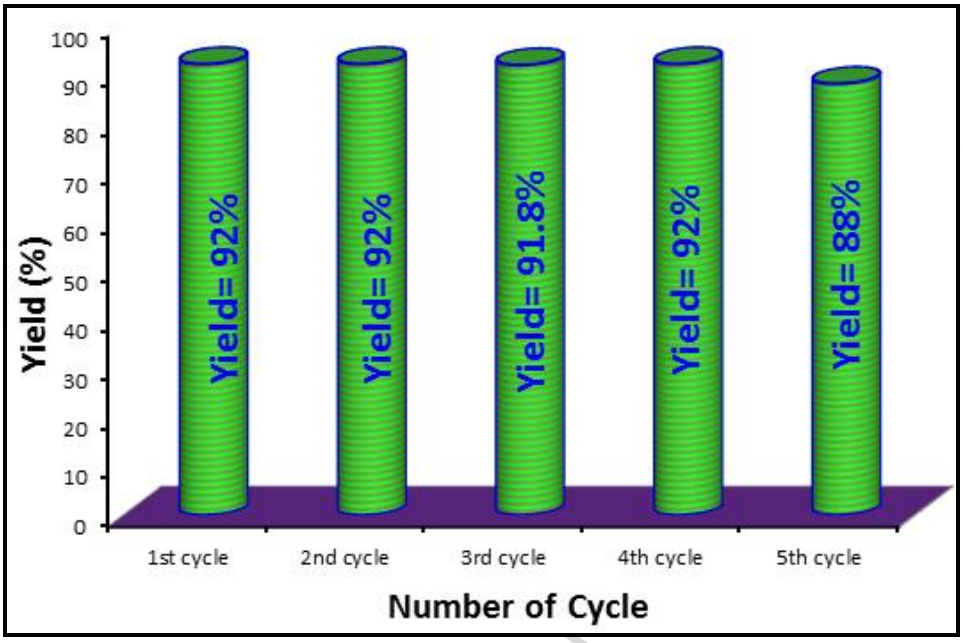


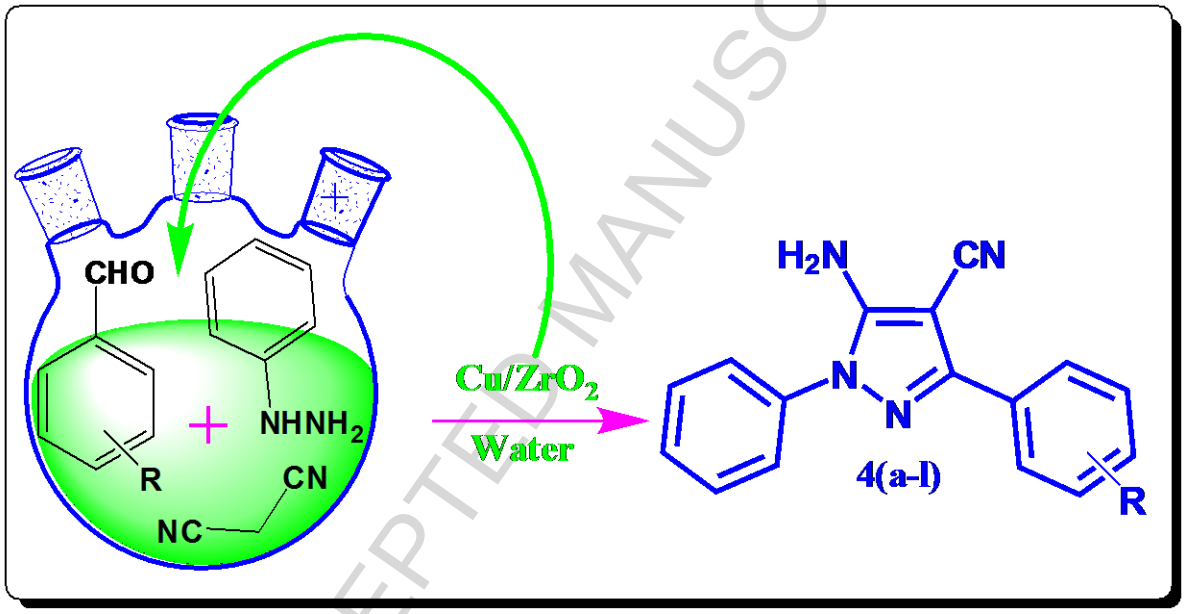
Figure 5. Recyclability of CuO/ZrO_2 catalyst



Synthesis of pyrazole-4-carbonitrile derivatives in aqueous media with CuO/ZrO_2 as recyclable catalyst

Suresh Maddila, Surjyakanta Rana, Ramakanth Pagadala, Shravankumar Kankala, Suryanarayana Maddila and Sreekanth B Jonnalagadda*

Graphical Abstract



Research Highlights:

- One-pot multicomponent synthesis of substituted pyrazoles
- Excellent yields and short reaction times at room temperature.
- Easy recovery and reusability of catalyst
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Research Highlights:

- One-pot multicomponent synthesis of substituted pyrazoles
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- Easy recovery and reusability of catalyst CuO/ZrO_2
- Nontoxic solvent and cost effective reagents