Communication

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

# ZnO: An Ecofriendly, Green Nano-catalyst for the Synthesis of Pyrazole Derivatives under Aqueous Media

Yarabally R. Girish, Kothanahally S. Sharath Kumar, Heggadihalli S. Manasa and Sheena Shashikanth*

*Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, India*

(Received: Apr. 15, 2014; Accepted: Jun. 25, 2014; Published Online: Sept. 12, 2014; DOI: 10.1002/jccs.201400170)

An efficient nano ZnO catalyzed green protocol for the synthesis of pyrazol derivatives by condensation of different substituted phenyl hydrazines/semicarbazide/thiosemicarbazide with 1,3-diketone/ketoester at ambient temperature has been achieved. ZnO nanocatalyst was prepared by low temperature solution combustion method. From the Scherrer method, the crystallite size of ZnO was estimated and found to be in the range of 30-50 nm. The main advantage of this protocol is an excellent yield, short reaction time and easy work-up procedure. The catalyst was found to be reusable up to five catalytic cycles without any appreciable loss in activity of the catalyst.

**Keywords:** Nanocatalyst; ZnO nanoparticles; Heterocyclic compounds; Water; Green synthesis.

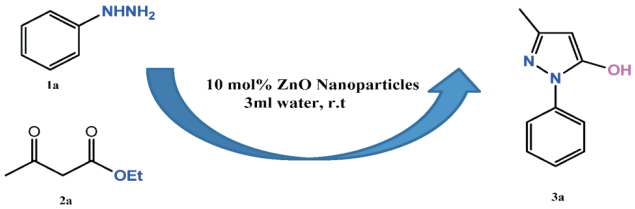
## INTRODUCTION

In recent year, material science has gained much attention for developing environmentally-benign procedures for the synthesis of various heterocyclic compounds.[1] As we know, the properties of metal oxide nanoparticles are very attractive when compared to its bulk counterparts due to their high surface to volume ratio and their active surface atoms[2] Pyrazoles represent an important class of heterocyclic compounds due to their widespread biological activities such as neurodegenerative agents for Alzheimer's disease, anti-tumour, anti-convulsant and anti-microbial agents. They have been used for pain relief and have shown success in the inhibition of the human immune deficiency virus and some other biological activities as well.[3]

Pyrazoles have also received considerable attention because of their widespread applications in the fields of coordination chemistry as ligands,[4] chelators,[5] as precursor for the synthesis of various nitrogen containing heterocycles,[6] in material science as explosives.[7] Because of its diverse pharmaceutical activities, several synthetic efforts have been made to develop this ring. The most common method is one-pot cyclo-condensation of hydrazines with 1,3-diketone.[8] Many heterogeneous catalysts such as $Mg(ClO_4)_2$, $Zn[(L)\ proline]_2$, PTC, p-toluene sulfonic acid (PTSA), $P_2O_5.SiO_2$ have been used for the synthesis of pyrazoles. In addition, microwave irradiation using resins and polymer supported systems[9] has also been developed. In further, few nanoparticles are used to accelerate the cyclocondensation of phenyl hydrazine's and 1,3-diketones to synthesize pyrazole derivatives.[10-12] However, all the above-mentioned methods suffer from one or other disadvantages like tedious workup procedures, difficulty in purification, low yield, harsh reaction conditions and prolonged heating. Hence, a protocol to overcome these difficulties is still in demand.

On the other hand, ZnO nanoparticles have been extensively used in the synthesis of various heterocyclic compounds due to its environmentally friendly nature.[13-16] ZnO is a non-hygroscopic, highly reactive, inexpensive, non-toxic and low processed metal oxide. By inspiring with the high reactivity of ZnO nanoparticles we attempted, ZnO nanoparticles catalysed one-pot two component synthesis of pyrazole derivatives. This process involves condensation between hydrazine (**1a**) and 1,3-diketone (**2a**) under mild reaction conditions (Scheme I) and the results are presented in Table 1.

**Scheme I** Nano ZnO catalyzed synthesis of 3-methyl-1-phenyl-1H-pyrazol-5-ol




## RESULTS AND DISCUSSION

Initially, a model reaction was conducted between

* Corresponding author. E-mail: shashis1956@gmail.com

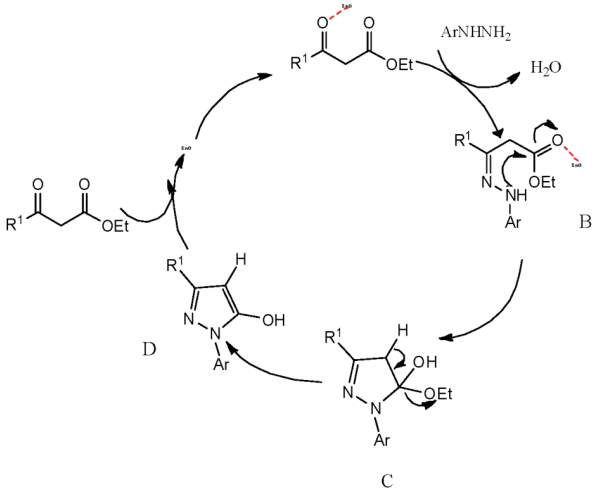
  

Table 1. Synthesis of **3a** under different reaction conditions

| Entry | Catalyst | Amount (mol %) | Time[b] (min) | Yield[c] (%) |
|---|---|---|---|---|
| 1 | Bulk ZnO | 5 | 45 | 50 |
| 2 | Bulk ZnO | 10 | 90 | 52 |
| 3 | $TiO_2$ | 5 | 40 | 30 |
| 4 | Zn:$Al_2O_4$ | 5 | 40 | 45 |
| 5 | $Al_2O_3$ | 5 | 45 | 55 |
| 6 | $Bi_2O_3$ | 5 | 50 | 70 |
| 7 | ZnO | 5 | 25 | 85 |
| 8 | ZnO | 7.5 | 25 | 88 |
| **9** | **ZnO** | **10** | **15** | **95** |
| 10 | ZnO | 15 | 15 | 94 |
| 11 | ZnO | 20 | 15 | 93 |
| 12 | ---- | --- | 60 | 20 |

[a] Reaction conditions: phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), 10 mol% of ZnO nano-catalyst; Solvent: water; r.t. [b] Reaction progress monitored byTLC. [c] Isolated yield.

**Scheme II** Proposed mechanism for the synthesis of pyrazoles




phenyl hydrazine (**1a**) (1 mmol) and ethyl acetoacetate (**2a**) (1 mmol) in water at room temperature using bulk ZnO (5 mol %) for about 25 minutes to synthesize 3-methyl-1-phenyl-1H-pyrazol-5-ol. Thus the reaction between (**1a**) and (**2a**) gave the required product (**3a**) in very low yield (Table 1, Entry 1). Even after using 10 mol% of catalyst and increasing in reaction time (90 min), it doesn't give considerable change in product yield (Table 1, Entry 2). Then, we examined the reaction using ZnO nanoparticles (5 mol %) as catalyst at room temperature. After 25 minutes, the reaction yielded the required product in moderate yield (Table 1, Entry 7). Further increase in molar ratio of the catalyst yielded the desired product in good yield (Table 1, Entry 9) in shorter reaction time. Later, we diverted our interest to explore the different nanocatalyst for the synthesis of pyrazoles, thus the reaction was screened in different nanocatalyst – $TiO_2$, $Al_2O_3$, $Bi_2O_3$, Zn: $Al_2O_4$ gave the desired product in low yield (Table 1, Entry 3-6).

Next, we studied the effect of solvent on reaction. Initially, the reaction was carried out with different solvents such as acetic acid (AcOH), dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), tetrahedronfuran (THF), methanol (MeOH), ethanol (EtOH), 1,4-dioxane and ethyl acetate. When reaction was carried in presence of DMF, DMSO and ethyl acetate, lower yield of the product **3a** was obtained after long time (Table 2, entries 2, 3, 7). In case of acetic acid product yield was high (Table 2, entry 4) at 100 °C. When the reaction was carried out in alcoholic media, the yield was moderate (Table 2, entries 1, 8, 9), where in case of aqueous medium yield as well as reaction time were significantly improved (Table 2, entry 10). ZnO nanoparticles were prepared according to procedure reported by Jagannatha Reddy, A. *et al.*[17]

Aromatic hydrazines containing both electron donating and electron withdrawing groups underwent reaction smoothly. The substituted phenyl hydrazines having electron donating substituents require moderate reaction time (Table 4, entry 2, 9) as donating substituent on aromatic ring increases the nucleophilic character of hydrazine. The thiosemicarbazide (Table 4, entry 12) requires longer reaction time than that of semicarbazide because of presence of electron withdrawing thione group (C=S) in thiosemicarbazide. The shorter reaction time of 15 min with 78% yield was observed for 3-methyl-1-(3-nitrophenyl)-1H-pyrazol-

Table 2. Synthesis of **(3a)** using various solvents

| Entry | Catalyst (Mol %) | Solvent | Time[b] (min) | Yield[c] (%) |
|---|---|---|---|---|
| 1 | 10 | MeOH | 90 | 75 |
| 2 | 10 | DMF | 150 | 55 |
| 3 | 10 | DMSO | 150 | 48 |
| 4 | 10 | AcOH(100 °C) | 30 | 91 |
| 5 | 10 | THF | 120 | 80 |
| 6 | 10 | 1,4-Dioxane | 60 | 87 |
| 7 | 10 | Ethylacetate | 120 | 70 |
| 8 | 10 | EtOH (70 °C) | 30 | 78 |
| 9 | 10 | EtOH | 90 | 85 |
| 10 | 10 | Water | 15 | 95 |

[a] Reaction conditions: phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), 10 mol% of ZnO nano-catalyst; Solvent: water; r.t. [b] Reaction progress monitored by TLC. [c] Isolated yield.

5-ol (Table 4, entry 3), which might be due to the presence of electron withdrawing ($NO_2$) group. This catalytic system also worked well for (4-(trifluoromethyl) phenyl) hydrazine to afford the corresponding products in 94% yield (Table 4, entries 7) within short period of time (10 min) without forming OEt functionality. The nano ZnO was chosen as catalyst because of its inexpensive, biodegradable and easy accessibility. All the synthesized compounds have been characterized by its physical constant, FTIR, $^1$H NMR, and mass spectroscopy and compared with literature.

The crystal structure of the ZnO was also studied by XRD analysis (Fig. 1). The XRD patterns of the ZnO nanoparticles indicate eleven characteristic peaks at 2θ = 31.8, 34.45, 36.15, 47.42, 56, 62.8, 66.4, 67.9, 69.1, 72.5, and 77.1, corresponding to (100), (002), (101), (102), (110), (103), (200), (112), (201), (004) and (202) planes, respectively, as shown in Fig. 1. All diffraction peaks and positions match well with those from the JCPDS card (Joint Committee on Powder Diffraction Standards no. 36–1451) for the hexagonal wurtzite-type structure of ZnO. This shows that the prepared ZnO nanoparticles are pure with a hexagonal wurtzite-type structure and the size of the particles was found to be 30 nm was calculated from the Scherer's equation:

$$d = \frac{0.9\lambda}{\beta \cos\theta}$$

where $d$ is the average grain size of the crystallites, λ, the incident wavelength, θ, the Bragg angle and β, the diffracted full-width at half-maximum (FWHM) in radians caused by the crystallites.

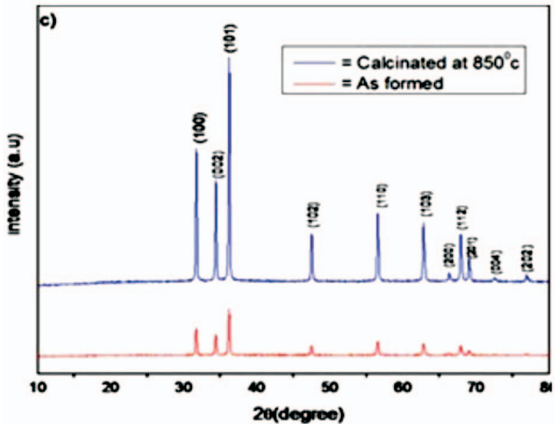



Fig. 1. XRD spectra of nano ZnO prepared by combustion method.

Morphology and characteristics of ZnO nanoparticles were compared by SEM. (Fig. 2). The mean diameter of ZnO is about 30–70 nm with an almost hexagonal shape. It can be observed from the ?gure that nanocatalyst is composed of tiny porous nanoparticles of dimension 10 μm and the particles are uniformly distributed throughout the specimen. From TEM image (Fig. 3), the particle size was found to be 30 nm.

With the optimal multicomponent protocol in hand, we next explored the generality of the protocol by reacting a variety of structurally variable phenyl hydrazine's possessing a wide range of functional groups. Thus phenyl hydrazines bearing various electron donating and electron withdrawing substituent's underwent reaction smoothly and produced respective pyrazole derivatives in good yields (Table 3, Entry 1-10) interestingly reaction of 1,3-diketones with semicarbazide and thiosemicarbazide are also gave the desired product in excellent yield (Table 3, Entry 11 and 12). Most of the synthesized compounds have been characterized by its physical constant, FTIR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy and compared with literature

## CONCLUSIONS

We have developed an efficient, concise, quick and environmentally benign protocol for the synthesis of substituted pyrazole derivatives. The nano ZnO catalyst has high catalytic activity for the generation of a diverse range

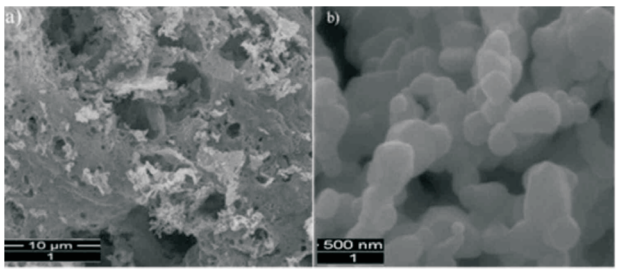



Fig. 2. SEM images of nano ZnO (a) and (b).

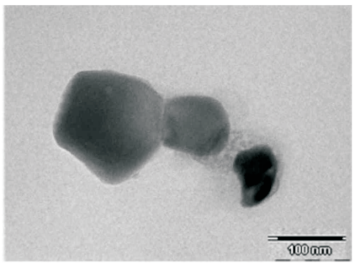
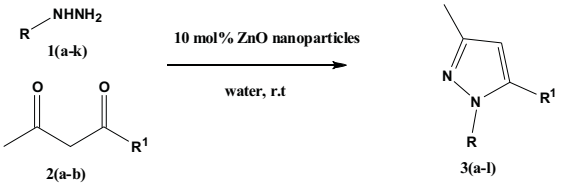



Fig. 3. TEM images of ZnO nanoparticle.

Table 3. Synthesis of pyrazole derivatives (**3a-l**)




| [a]Entry | $R^1$ | $R^2$ | Product | Time /min | Yield / (/%) [b] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ (**1a**) | OEt (**2a**) | **3a** | 15 | 95[18a] |
| 2 | 2-Me$C_6H_5$ (**1b**) | OEt (**2a**) | **3b** | 10 | 93 |
| 3 | 3-$NO_2C_6H_5$ (**1c**) | OEt (**2a**) | **3c** | 15 | 78[18a] |
| 4 | 2,5-di$ClC_6H_5$ (**1d**) | OEt (**2a**) | **3d** | 5 | 85 |
| 5 | 4-$CNC_6H_5$ (**1e**) | OEt (**2a**) | **3e** | 5 | 93[18b] |
| 6 | 4-$FC_6H_5$ (**1f**) | OEt (**2a**) | **3f** | 5 | 93[18c] |
| 7 | 4-$CF_3C_6H_5$ (**1g**) | OEt (**2a**) | **3g** | 10 | 97[18d] |
| 8 | 3-$CF_3C_6H_5$ (**1h**) | OEt (**2a**) | **3h** | 15 | 95 |
| 9 | 4-$OMeC_6H_5$ (**1i**) | Me (**2b**) | **3i** | 10 | 96[18e] |
| 10 | 4-$CNC_6H_5$ (**1e**) | Me (**2b**) | **3j** | 5 | 85 |
| 11 | $NH_2CO$ (**1j**) | OEt (**2a**) | **3k** | 4 | 96[18f] |
| 12 | $NH_2CS$ (**1k**) | OEt (**2a**) | **3l** | 45 | 93[18g] |

[a] Reaction conditions: phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), 10 mol% of ZnO nano-catalyst; Solvent: water; r.t. [a] Reaction progress monitored by TLC. [b] Isolated yield.

of pyrazoles in excellent yields. The experimental simplicity, ease of product isolation, reusability of the catalyst and ready availability of the reagents, wide functional group tolerance are note-worthy features of this protocol. The method is very economical and makes this process very useful.

**Recycling study of the catalyst**

We also investigated reusability of catalyst under water using model phenyl hydrazine **1a** with ethyl acetoacetate **2a** in presence of 10 mol % of nano ZnO. After completion of the reaction, the mixture was dissolved in ethyl acetate (10 mL) and filter off the catalyst . The catalyst was treated with ethanol, acetone, and then finally washing with distilled water. It was then dried in an oven at 80 °C, for 2 h and used for the next catalytic cycle. The catalyst was found to be reusable up to five catalytic cycles without any significant loss in catalytic activity (Table 4).

Table 4. Catalyst recycle studies

| Catalyst recycle | Time[b] (minutes) | Yield[c] (%) |
|---|---|---|
| 1 | 15 | 95 |
| 2 | 15 | 94 |
| 3 | 15 | 92 |
| 4 | 15 | 90 |
| 5 | 20 | 88 |

[a] Reaction conditions: phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol) 10 mol% ZnO Nano-catalyst, 3 mL water. [b] Reaction progress monitored by TLC. [c] Isolated yield.

**ACKNOWLEDGEMENTS**

We are thankful to the UGC-BSR (Order no DV-5/662/RFSMS/2012-13), New Delhi, India for financial support and we are also thankful to SAIF, IITM and SAIF, IITB for their support in carrying out research work regarding the HRMS-TEM analysis.

**REFERENCES**

1. Clark, J. H. *Green Chem*. **1999**, *1*, 1–8; Sheldon, A. R. *Green Chem.* **2005**, *7*, 267–278; Sreedhar, B.; Suresh Kumar, A.; Divya Yada. *Tetrahedron Lett*. **2011**, *52*, 3565–3569.
2. Narayanan, R.; El-Sayed, M. A. *J. Phys. Chem. B* **2005**, *109*, 12663.
3. Rajeshwar, N.; Marcus, P.; Stefanie, L.; Karlheinz, B.; Sabine, K.; Thomas, D.; Sascha, W.; Eckhard, M.; Boris, S. *ChemMedChem* **2008**, *3*, 165-172; Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebbon, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckel, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2767; Kaymakcioglu, B. K.; Rollas, S.; Korcegez, E.; Aricioglu, F. *Eur. J. Pharm. Sci.* **2005**, *26*, 97.
4. Anuradha, M.; Amitabha, S. *Tetrahedron Lett.* **2005**, *46*, 15–18.
5. Vitor, R. F.; Alves, S.; Correia, J. D. G.; Paulo, A.; Santos, I. *J. Organomet. Chem.* **2004**, *689*, 4764–4774.
6. Fawzia, A. Q.; Faisal, M.; Mervat, M. A.; Abeer, A. B. *Molecules* **2009**, *14*, 78-88; Thomas, M, K.; Alexander, P.; Carolin, P.; Jörg, S.; Muhamed, S. *Eur. J. Inorg. Chem.* **2013**, *26*, 4667–4678; Pasupala, R.; Girish, M. G.; Surya, P. T.; Arun, K. S. *J. Mol. Model.* **2011**, *17*, 2475–2484.
7. Tahir, M.; Corey, R. H.; Brian, P.; Nicola, C. *Tetrahedron Lett.* **2004**, *45*, 2137–2139.
8. Mirjalili, B. B. F.; Bamoniri, A.; Amrollahi, M. A.; Emtiazi, H. *Dig. J. Nanomater. Biostruct.* **2010**, *5*, 897-902; Kidwai, M.; Jain, A.; Poddar, R. *J. Organomet. Chem.* **2011**, *696*,

1939-1944; Wen, J.; Fu, Y.; Zhang, R. Y.; Zhang, J.; Chen, S. Y.; Yu, X. Q. *Tetrahedron* **2011**, *67*, 9618-9621; Heravi, M.; Javanmardi, N. O.; Hossein, A.; Baghernejad, B. G.; *Univ. J. Sci.* **2011**, *24*(2), 227; BamoniriI, A.; Mirjalili, B. B. F.; Jafari, A. A.; Abasaltian, F. *Iran. J. Catal.* **2012**, *2*(2), 75-78; Vaddula, B. R.; Varma, R. S.; Leazer, J. *Tetrahedron Lett.* **2013**, *54*, 1538–1541; Donohue, A. C.; Pallich, S.; McCarthy, T. D. *J. Chem. Soc. Perkin Trans.* **2001**, *1*, 2817–2822; Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 397–400.

9. Mamta, S.; Thierry, J.; Julia, J. N.; Frank, G. *Green Chem.* **2012**, *14*, 2193.
10. Dissanayake, A. A.; Odom, A. L. *Chem. Commun.* **2012**, *48*, 440–442.
11. Polshettiwar, V.; Varma, R. S. *Tetrahedron* **2010**, *66*, 1091–1097.
12. Baghernejad, B.; Khorshidi, M. *Bull. Chem. Soc. Ethiop.* **2013**, *27*(2), 309-314.
13. Hosseini-Sarvari, M. *J. Iran. Chem. Soc.* **2011**, *8*, S119-S128.
14. Safaei-Ghomi, J.; Ghasemzadeh, M. A.; Zahedi, S. *J. Mex. Chem. Soc.* **2013**, *57*(1), 1-7.
15. Vinay Kumar, B.; Bhojya Naik, H. S.; Girija, D.; Vijaya Kumar, B. *J. Chem. Sci.* **2011**, *123*, 615–621.
16. Thornburgh, S.; Graupner, P. R.; Cooper, D. H. *J. Heterocycl. Chem.* **2007**, *44*(6), 1389-1393; Shetty, M. R.; Samanth, S. D. *Synth. Commun.* **2012**, *42*(10), 1411-1418; Dandia, A.; Parewa, P.; Gupta, S. L.; Rathore, K. S. *J. Mol. Catal. A: Chem.* **2013**, *373*, 61–71; Chandak, H. S.; Lad, N. P.; Dange, D. S. *Green Chem. Lett. Rev.* **2012**, *5*(2), 135-138.
17. Jagannatha Reddy, A.; Kokila, M. K.; Nagabhushana, H.; Rao, J. L.; Shivakumara, C.; Nagabhushana, B. M.; Chakradhar, R. P. S. *Spectrochim. Acta, Part A*. **2011**, *81* 53–58.