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Research Article

Nano-ZnO Catalyzed Green and Efficient One-Pot Four-Component Synthesis of Pyranopyrazoles

Sunil U. Tekale,[1] Sushma S. Kauthale,[2] Kavita M. Jadhav,[2] and Rajendra P. Pawar[2]

[1] *Department of Chemistry, Shri Muktanand College, Gangapur, Maharashtra 431 109, India*
[2] *Department of Chemistry, Deogiri College, Station Road, Aurangabad, Maharashtra 431 005, India*

Correspondence should be addressed to Rajendra P. Pawar; rppawar@yahoo.com

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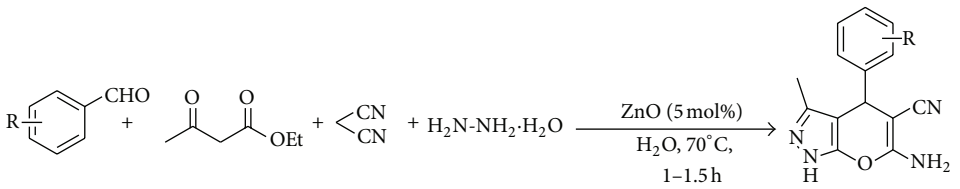
An efficient zinc oxide nanoparticle catalyzed one-pot, four-component synthesis of 6-amino-3-methyl-5-cyano-4-aryl-1,4-dihydropyrano[2,3-c]pyrazoles from aromatic aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in aqueous medium is described. Since water was employed as the reaction medium, it serves as a green route for the synthesis of pyrano[2,3-c]pyrazoles. The advantages associated with the present protocol include nonchromatographic purification technique, use of recyclable heterogeneous nano-ZnO catalyst in aqueous medium, and short reaction time. It combines successfully the synergistic effect of green chemistry with nanocatalysis.

1. Introduction

Multicomponent reactions (MCR), also referred to as the multicomponent assembly processes (MCAP), are the convergent, one-pot reactions of more than two simple precursors. These act as a gateway for providing an easy access to a wide range of functionally novel and complex heterocyclic molecules with high selectivity [1]. Besides routine multistep synthesis, MCRs are superior. In recent years, MCRs came into light over routine multistep synthesis counterparts owing to their atom economy, energy efficiency, lower costs, short reaction time, environmental friendly nature, and simpler purification techniques. Hence nowadays, synthesis of novel heterocyclic compounds by MCR approach has became not only an integral part of pharmaceutical chemistry but also an important tool in the discovery of new potent life-saving drug candidates [2]. Thus the study of multicomponent reactions has attracted tremendous attention of scientific community across the world to develop novel and effective protocols [3].

With the growing concern over environment pollution and related societal health problems, green chemistry concept is emerging as one of the important tools in the development of environmentally benign chemical processes and clean technologies [4] including generation of solvent-free protocols along with replacement of easily volatile organic solvents by water as a green reaction medium [5]. Water is nonhazardous, inexpensive, abundant, and ecofriendly in nature having high boiling point. Furthermore, owing to typical reactivity and selectivity, reactions are preferred in aqueous medium. Reactions in aqueous medium not only possess negative activation volume [6] but also help in controlling exothermic reactions. Hence organic synthesis in aqueous medium is preferred from environmental as well as from economical point of view.

Heterogeneous catalysts are always superior to their homogeneous counterparts in terms of many aspects such as operational simplicity, reusability, environmental compatibility, and high selectivity. In current time along with green chemistry, nanoparticulate heterogeneous solid acid-base catalysts have received notable attention in organic transformations on the ground of their ability to enhance faster rates of organic reactions, high catalytic activity, reusability, and higher yield of products which is due to their ability to afford high particle size-to-volume ratio along with greater surface area. Henceforth utility of these catalysts is gaining significant attention and becomes a more potential thrust area for the synthesis of highly functionalized pharmaceutically significant heterocyclic compounds [7].



Scheme 1: ZnO nanoparticle catalyzed one-pot four-component green synthesis of pyranopyrazoles.

Thus, water-mediated multicomponent reactions using heterogeneous catalysts have become the popular targets for synthetic organic chemists. In present work we have employed water as the clean, environment-friendly reaction medium, rather than the use of organic solvent [8] for the synthesis of 4*H*-pyrano[2,3-c]pyrazoles utilizing zinc oxide nanoparticle catalyzed multicomponent reaction of aromatic aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate.

ZnO is a well-known wide bandgap (Eg ~ 3.3 eV at 300 K) material in the field of electronics and nanotechnology since 1935 (Bunn, 1935). ZnO functions as a heterogeneous catalyst which can be easily separated from the reaction mixture and reused several times. Owing to unique and novel characteristic properties like polar surface, noncorrosiveness, reusability, and ability to generate clean products, nowadays nano-ZnO is extensively recruited as a powerful catalyst for numerous organic transformations by various researchers for exploring its synthetic utility preferably under solvent-free conditions or in aqueous medium [9, 10]. These facts encouraged us to use ZnO nanoparticles for the green synthesis of pyranopyrazoles.

Pyrano[2,3-c]pyrazoles are the medicinally privileged compounds with a wide spectrum of biomedical and pharmaceutical applications [11]. Compound (a) of Figure 1 with pyrano[2,3-c]pyrazole scaffold in its structure has been documented as potential inhibitor of human Chk1 kinase [12]. Furthermore, the biological potential of compound (b) of Figure 1 is better reported in the literature [13]. 4*H*-pyrano[2,3-c]pyrazole derivatives possess significant biological activities such as antiinflammatory, molluscicidal, insecticidal, antitumor, and anticancer properties [14, 15]. They also have applications as pharmaceutical ingredients and biodegradable agrochemicals [16].

On account of these biological activities the synthesis of these compounds has become an interesting area for synthetic organic chemists. These compounds can be synthesized by three-component reaction of 2-pyrazolin-5-ones, malononitrile, and aromatic aldehydes or a four-component reaction of readily available starting materials, namely hydrazine hydrate, ethyl acetoacetate, malononitrile, and aromatic aldehydes.

Khurana et al. [17] reported a three-component approach for the synthesis of pyranopyrazoles using 1-butyl-3-methylimidazolium tetrafluoroborate under sonication bath which required separation of the ionic liquid as an additional task. Nonrecyclable catalyst—triethylbenzylammonium chloride (TEBA)—was used by Shi et al. [18] which required longer reaction time. The three-component synthesis catalyzed by *p*-dodecylbenzenesulfonic acid (DBSA) was

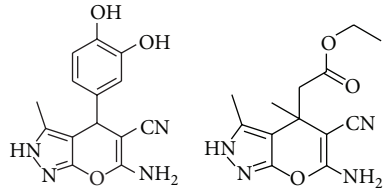


Figure 1: Some biologically potent pyranopyrazoles.

reported by Jin et al. [19]. Four component syntheses were carried out by several researchers using different protocols such as heteropoly acids [20], alumina [21], use of additional microwave or ultrasound irradiation [22, 23], use of toxic base such as piperidine [13], and nonrecoverable molecular iodine [24].

Although the reported methods are effective, many of the existing methodologies suffer from several drawbacks which require comparatively longer time, higher temperature, use of toxic piperazine and piperidine bases, tedious and cumbersome processes in ionic liquid mediated synthesis, use of organic solvents [8] rather than aqueous medium, environment compatibility using toxic and expensive catalysts, lack of recyclability, and so forth. The use of ultrasound or microwave assisted synthesis, although fast, requires additional use of sonicator or microwave oven and may not be suitable for large-scale synthesis. So despite of the available literature for the synthesis of pyranopyrazoles, simple, efficient, and environmentally benign approaches are still demanding. As a part of our ongoing research in the field of developing new routes for the synthesis of various heterocyclic compounds using nanocatalysts [25]; in present work we demonstrated nanoparticles of zinc oxide as an efficient, reusable, heterogeneous catalyst for green and scalable synthesis of 6-amino-3-methyl-5-cyano-4-aryl-1, 4-dihydropyrano[2,3-c]pyrazoles by four-component reaction in aqueous medium (Scheme 1).

2. Result and Discussion

The reaction between hydrazine hydrate, ethyl acetoacetate (EAA), malononitrile, and benzaldehyde was chosen as a model condensation reaction for optimizing the various reaction parameters. Initially, the reaction was tried in presence of 5 mol% of ZnO nanoparticles at room temperature in aqueous medium. But the reaction could not complete even after 4-5 h. When the temperature of the reaction

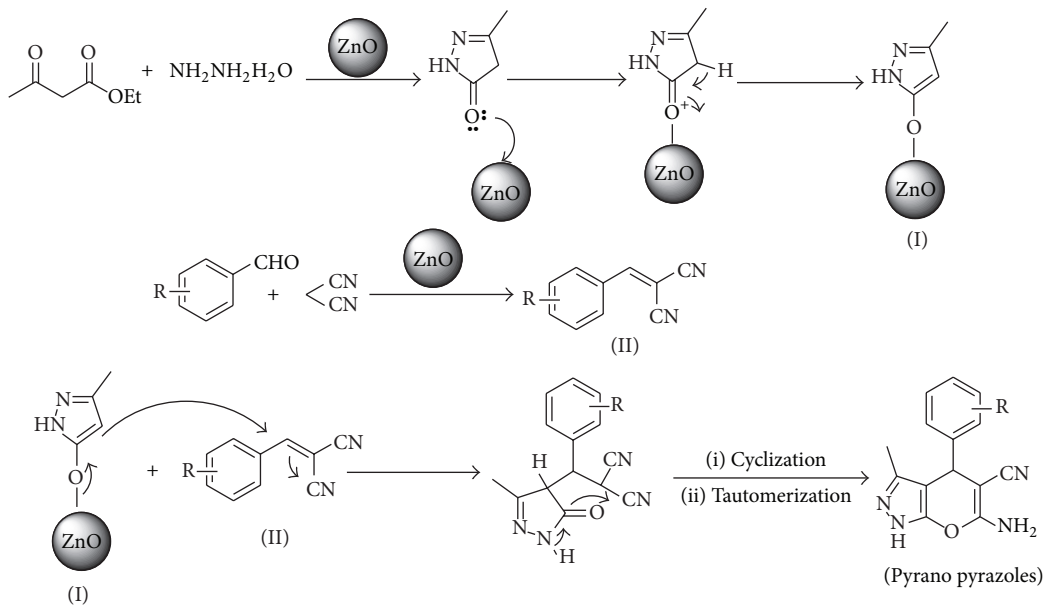


Figure 2: Plausible mechanism for the ZnO nanoparticle catalyzed four-component synthesis of pyranopyrazoles.

was raised to 70°C, TLC showed a drastic change wherein the intermediates were converted into the desired products within 1 h. Further increase in the temperature to 100°C could not enhance yield of the corresponding products significantly (Table 2). Also the effect of several solvents such as DCM, ACN, THF, EtOH, and MeOH under reflux condition did not show any good yields (Table 2). The comparative results showed that Millipore water was observed to be superior as compared to the common organic solvents (Table 2). This suggests that the solvent polarity also contributes a significant role to the synthesis of pyranopyrazoles.

In addition to the above, the effect of catalyst concentration and temperature was also studied which indicated that 5 mol% of the zinc oxide (with 5, 10, 15 mol% of the catalyst in aqueous medium giving 94, 95, 95% of the corresponding product in case of benzaldehyde) at 70°C temperature was sufficient enough to catalyze the reaction. After optimizing the reaction conditions, different aldehydes with electron-donating and electron-withdrawing groups were investigated to check the feasibility of this protocol whose results are tabulated in (Table 1).

Almost all the employed aldehydes resulted in good-to-excellent yield of the corresponding products. Studies revealed that aldehydes having electron-withdrawing substituents reacted faster and gave better yield of the product as compared to the aldehydes with electron-donating substituents. In spectral data the IR spectrum (for entry 1) exhibited sharp bands at 3410, 3356 cm^{-1} (NH_2), 2190 cm^{-1} (CN), supporting the formation of products. Since the product, pyranopyrazole, was insoluble in the aqueous medium, initially it was filtered off along with the catalyst. The residue was washed with hot ethanol and again filtered. The filtrate was allowed to stand at room temperature to get the crystals of product which were subsequently washed with a mixture of (30% EA: hexane) to afford the pure product. Furthermore, the catalyst can be recycled several times without significant loss of its catalytic activity (Table 3).

Thus, this protocol provides an easy access of pure products without using any chromatographic techniques. The products were simply purified by recrystallization from ethanol followed by washing with a mixture of EA: hexane. Comparatively high yield and reduced reaction time can be explained on the basis of large surface area afforded by the catalyst due to smaller particle size (50–100 nm as clearly seen from the TEM images).

The plausible mechanism for ZnO nanoparticle catalyzed synthesis of pyranopyrazoles is depicted in Figure 2. Initially the reaction between ethyl acetoacetate and hydrazine forms the pyrazolone (I). Simultaneously there is formation of arylidene malononitrile (II) by the Knoevenagel condensation between aldehyde and malononitrile. Michael addition of pyrazolone (I) to arylidene malononitrile (II), followed by cyclization and then tautomerization, affords the pyranopyrazole.

3. Conclusion

In summary we have developed ZnO nanoparticle catalyzed efficient, one-pot, four-component coupling reaction of aromatic aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in aqueous medium to access substituted pyranopyrazoles in higher yields within short time. The present protocol has several advantages not only in terms of yield but also applicability for large-scale synthesis using water as the green reaction medium in short reaction time. Operational simplicity, recyclability of the catalyst, and atom economical and environmentally benign nature make it an attractive process. It meets the requirements of clean organic reactions in water as well as the vigorously increasing applications of nanocatalysts in organic synthesis.

Table 1: ZnO nanoparticle catalyzed one-pot four-component synthesis of pyranopyrazoles in aqueous medium.

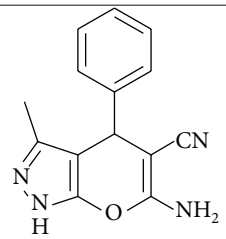
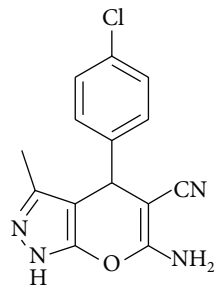
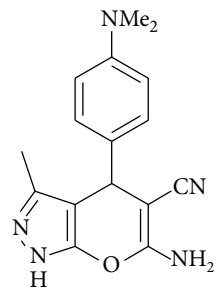
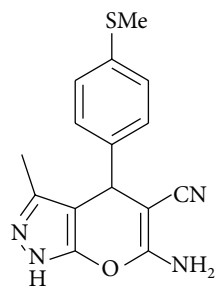
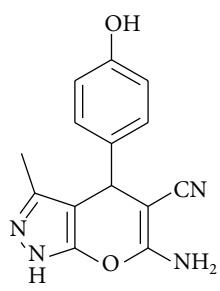
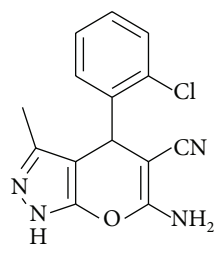
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C)
1	C_6H_5		60	94	243–245 [20]
2	4-Cl–C_6H_4		60	90	233–235 [22]
3	4-NMe_2–C_6H_4		70	86	234-235 [13]
4	4-SMe–C_6H_4		70	88	242–244
5	4-OH–C_6H_4		90	82	222–224 [22]
6	2-Cl–C_6H_4		80	89	244–246 [22]

Table 1: Continued.

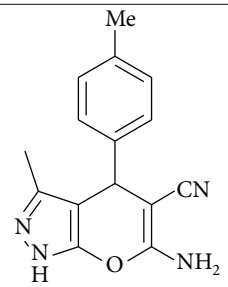
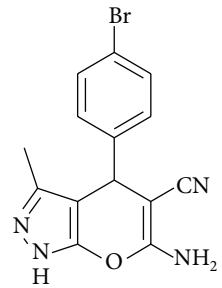
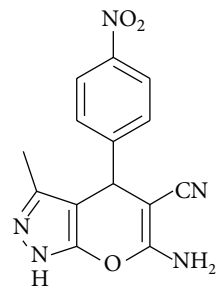
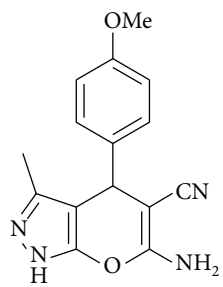
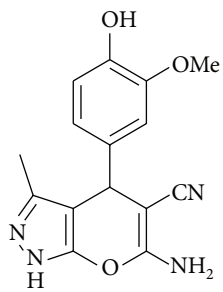
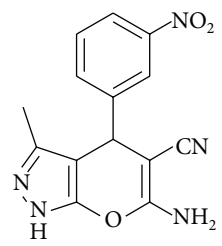
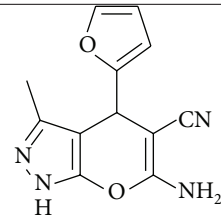
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C)
7	4-Me–C_6H_4		70	90	206-207 [21]
8	4-Br–C_6H_4		65	85	179-180 [23]
9	4-NO_2–C_6H_4		90	87	149–151 [23]
10	4-OMe–C_6H_4		70	90	211-212 [22]
11	3-OMe-4-OH–C_6H_3		80	91	234–236 [21]
12	3-$NO_2C_6H_4$		90	87	214–216 [20]

Table 1: Continued.

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C)
13	2-Furyl		80	86	217–219 [20]

Reactions were tried on aldehyde (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol) in water (1 mL) using ZnO (5 mol%) nanoparticles.

Table 2: Effect of ZnO nanoparticle solvent on the synthesis of pyranopyrazoles.

Entry	Solvent	Temp.	Yield[@] (%)
1	Dichloromethane	Reflux	32
2	Acetonitrile	Reflux	45
3	Tetrahydrofuran	Reflux	52
4	Ethanol	Reflux	67
5	Methanol	Reflux	62
6	Millipore water	r.t.	65
7	Millipore water	70°C	94
8	Millipore water	Reflux	96

[@]Yield obtained with benzaldehyde and 5 mol% amount of ZnO after 60 min.

Table 3: Recycle study of ZnO nanocatalyst.

Run	1	2	3	4
Yield[b] (%)	94	90	87	85

[b]Yield in case of benzaldehyde.

Thus the present protocol helps in generating molecular complexity and developing diversity through the one-pot four-component reactions.

4. Experimental Protocols

All the chemicals required were purchased from Aldrich or SD Fine Chemical companies and used without further purification. Melting points were recorded in capillaries open at one end and were uncorrected. ^{1}H NMR spectra were recorded using DMSO-d_6 solvent on 400 MHz Varian spectrophotometer with TMS as an internal standard, and chemical shifts (δ) are expressed in ppm. Mass spectra were scanned on Shimadzu mass analyzer with EI 70 eV. The catalyst used was Aldrich made. X-ray diffraction pattern was studied on Brucker axe diffractometer (model D8 Advance (German)). TEM images were recorded on the transmission electron microscope instrument (TECNAI G2 20 U-TWIN, FEI, The Netherlands). Infrared spectra were recorded on Bruker Vector 22 FTIR spectrophotometer using KBr discs.

4.1. General Procedure for the Synthesis of Pyranopyrazoles. To a magnetically stirred aqueous solution of ethyl acetoacetate (1 mmol) and hydrazine hydrate (1.5 mmol), aldehyde (1 mmol), malononitrile (1 mmol), and a catalytic amount of ZnO nanoparticles (5 mol%) were successively added. The resulting suspension was stirred and heated at 70°C temperature for appropriate reaction time as specified in (Table 1). The progress of reaction was monitored by TLC (30% EA: hexane). After completion of the reaction as monitored by TLC, the reaction mass was cooled, filtered off, and washed with hot ethanol (5 mL) to separate the product from the catalyst. The ethanol from the filtrate was allowed to evaporate at room temperature to get the crystals of product which were then subsequently washed with a mixture of (30% EA: hexane) to afford the pure products.

The spectral data of principal compounds is represented below.

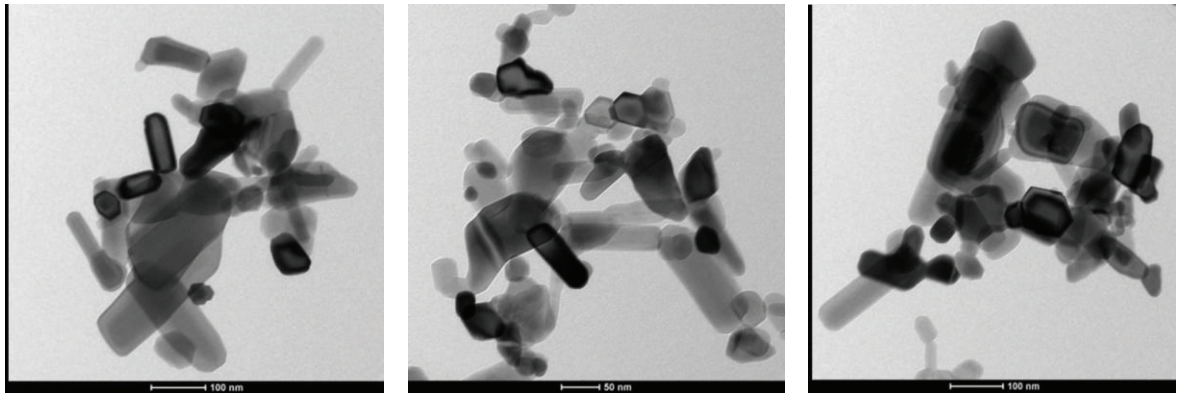
6-Amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (Entry 1, Table 1). White solid, M.P. 243–245°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.10 (s, 1H), 7.10–7.40 (m, 5H), 6.85 (s, br, 2H), 4.60 (s, 1H), 1.78 (s, 3H); IR (KBr) cm^{-1} 3410, 3356, 3167, 2990, 1646, 1596, 1399, 1276, 870; ES-MS *m/z*: 253 (M + 1).

6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 2, Table 1). Off-white solid, M.P. 233–235°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (s, 1H), 7.10–7.40 (m, 4H), 6.95 (s, br, 2H), 4.63 (s, 1H), 1.80 (s, 3H); IR (KBr) cm^{-1} 3478, 3035, 2985, 2193, 1647, 1596, 1398, 1284, 870; ES-MS *m/z*: 287 (M + 1).

6-Amino-4-(4-N,N-dimethylaminophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 3, Table 1). Yellow solid, M.P. 234-235°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.10 (s, 1H), 6.70–7.15 (m, 4H); 6.55 (s, br, 2H), 4.40 (s, 1H); 2.85 (s, 6H), 1.78 (s, 3H); IR (KBr) cm^{-1} 3385, 3172, 2957, 2189, 1644, 1601, 1397, 1279, 868; ES-MS *m/z*: 296 (M + 1).

6-Amino-4-(4-thiomethylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 4, Table 1). Pale yellow solid, M.P. 242–244°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.10 (s, 1H), 7.10–7.35 (m, 4H), 6.95 (s, br, 2H), 4.58 (s, 1H), 2.47 (s, 3H), 1.80 (s, 3H); IR (KBr) cm^{-1} 3482, 3035, 2985, 2190, 1597, 1391, 1279, 851; ES-MS *m/z*: 299 (M + 1).

4.2. Morphology and Structural Investigations of ZnO Nanoparticles. The morphology and structural investigations of the catalyst were studied with XRD, TEM, and FTIR analyses.



(a) (b) (c)

Figure 3: TEM images of the nano-ZnO.

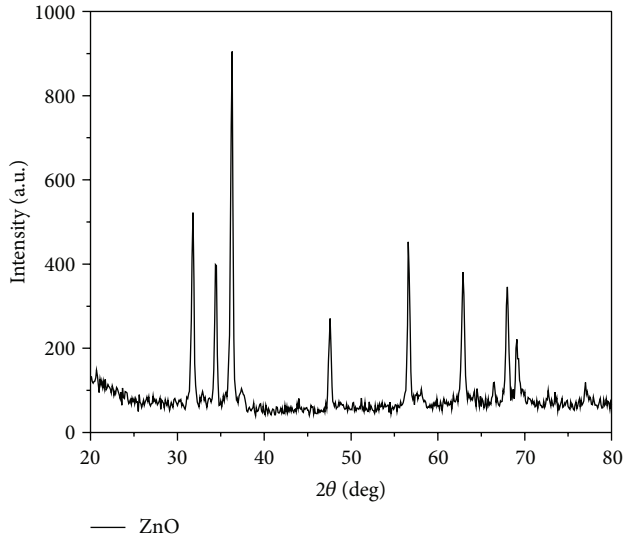


Figure 4: XRD of nano-ZnO.

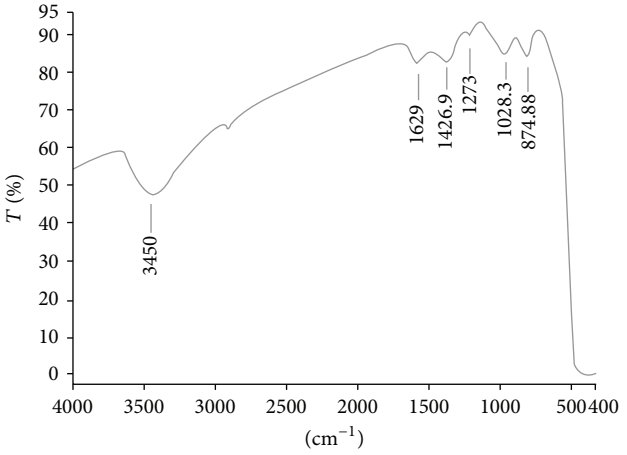


Figure 5: FTIR spectrum of nano-ZnO.

4.2.1. TEM. The images in Figure 3 indicate that the particle size of the crystalline ZnO nanoparticles is in the range of 50–100 nm. This small particle size of the nanocrystalline ZnO provides large surface area to the catalyst and assists for enhancing the rate of product formation.

4.2.2. XRD. XRD studies of nano-ZnO showed a characteristic pattern as shown in Figure 4. Diffraction peaks present at 2θ values of 32.08, 34.74, 36.64, 48.04, 57.04, 63.22, 68.28, and 69.24 correspond to (100), (002), (101), (102), (110), (103), (200), and (201) planes, respectively. The strongest peak at $2\theta = 36.64$ belongs to the (101) plane. No impurity peaks were detected. It indicates good crystalline-nature the catalyst.

4.2.3. FTIR. FTIR spectrum was recorded on a Shimadzu 8400s spectrophotometer from samples in KBr pellets. Normally the IR spectra of ZnO sample particles are influenced by morphology and the particle size. Figure 5 illustrates the FTIR spectrum of the ZnO particles.

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