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Highly Efficient Zinc Oxide Nanoparticles Catalyzed Green Synthesis of 1,5-Benzodiazepines under Solvent-Free Path

YUHAO ZHAO[1], XUEJIE YU[2], MANPREET SAINI[3], YANXU MA[4,*] and RAJESH K. SINGH[3,*]

[1]School of Traditional Chinese Medicine, Capital Medical University, 100069 Beijing, P.R. China
[2]Beijing University of Chinese Medicine, 100029 Beijing, P.R. China
[3]Department of Pharmaceutical Chemistry, Shivalik College of Pharmacy, Nangal-140 126, India
[4]Department of Orthopedics, Beijing Traditional Chinese Medicine Hospital, Capital Medical University, Beijing 100010, P.R. China

*Corresponding authors: E-mail: rksingh244@gmail.com; yanxumabjtcm@126.com

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An efficient and simple environment-friendly method for the preparation of substituted 1,5-benzodiazepines as biologically interesting compounds under heterogenous catalyst is described. The one-pot multicomponent condensation of *o*-phenylene-diamine and substituted ketones catalyzed by zinc oxide nanoparticles (ZnO NPs) under microwave under solvent-free condition has been developed. The present protocol provides a green and improved pathway for the synthesis of 1,5-benzodiazepines in terms of excellent yields, short reaction times and reusability of catalyst.

Keywords: 1,5-Benzodiazepines, Zinc oxide nanoparticles, Heterogenous catalyst.

INTRODUCTION

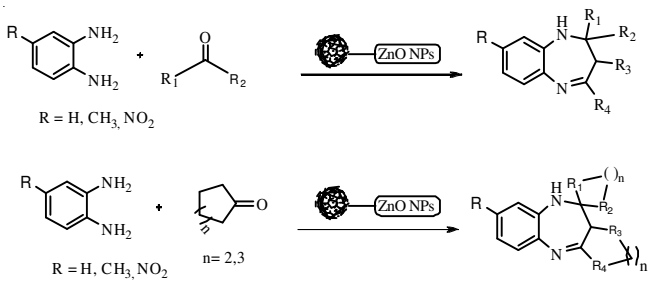
Multicomponent coupling reaction (MCR) is one of the important and powerful green chemistry tools for the synthesis of wide varieties of biologically active medicinal compounds[1,2]. Another important aspect of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. Some natural active constituents extracted from herbs such as polygala, platycladi seed and cortex albiziae have sedative effects, but the extracting process costs great energy and fund, and so an advanced synthesis is needed. Development of such multicomponent coupling reaction strategies under solvent-free condition has been of considerable interest, as they provide simple and rapid access to a large number of organic molecules through a sustainable path.

Benzodiazepines are widely used class of bioactive compounds that show interesting features, making them attractive targets for multicomponent coupling reactions. Among different types of the benzodiazepine class, 1,5-benzodiazepines are of particular interest as they belong to privileged medicinal scaffolds serving for the generation of medicinal compounds having pronounced central nervous system (CNS), antiinflammatory, antifeedant, antibacterial and analgesic activities[3-5]. The current interest in 1,5-benzodiazepine derivatives arise from their potential application in the treatment of cancer, viral infection (on-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular diseases[6]. Many of the methods reported for the synthesis of these compounds[7-9] are associated with the minor limitations like tedious work up procedure, the necessity of neutralization of strong acidic media, producing undesired washes, long reaction times, unsatisfactory yields, require separation of the catalyst from the product and formation of side products.

Catalyst has played a vital role in the success of the chemical industry[10]. The use of transition-metal nanoparticles in catalysis is decisive as they mimic metal surface activation and catalysis at the nanoscale and thereby bring selectivity and efficiency to heterogeneous catalysis[11]. Among transition-metal nanoparticles, zinc oxide nanoparticles (ZnO NPs) have been of considerable interest because of the role of ZnO in solar cells, catalysts, antibacterial materials, gas sensors, luminescent materials, and photocatalyst[12]. The recent literature survey reveals that ZnO nanoparticles as a heterogeneous catalyst has received considerable attention because it is inexpensive, nontoxic and environment-friendly properties[13-17].

In continuation of our previous studies on exploration of various methods and catalysts in organic transformations[18], herein, we report a highly efficient, green and solvent-free protocol for the one-pot multi-component synthesis of 1,5-benzodiazepines using ZnO nanoparticles (**Scheme-I**). It is noteworthy that this work has none of the above-mentioned drawbacks at all. To the best of our knowledge, there is no report available in the literature describing the use of ZnO

nanoparticles as catalysts for the synthesis of 1,5-benzodiazepines. The effectiveness of the process was studied by comparing the results obtained with and without catalyst under normal conditions.



Scheme-I: Chemical reaction for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines using zinc oxide nanoparticles

EXPERIMENTAL

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance spectra were obtained using Brucker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using potassium bromide pellets (in cm^{-1}). Elemental analyses for C, H, and N were performed on Perkin-Elmer 2400 CHN elemental analyzer. X-ray diffraction of nanoparticles were obtained using X-ray diffractometer, Panlytical X' pert Pro and (CuK_α) radiations were used. TEM images were obtained from Transmission Electron Microscope, Hitachi H-7500 with 0.204 nm resolution and 6,00,000X magnification. Reactions were monitored and the homogeneity of the products was checked by TLC, which were prepared with silica gel G and activated at 110 °C for 0.5 h. The plates were developed by exposure to iodine vapours. Anhydrous sodium sulphate was used as a drying agent.

Synthesis of ZnO nanoparticles: Zinc oxide nanoparticles are prepared according to the literature method with some modifications[19]. Zinc acetate (9.10 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) were combined by grinding in a mortar for 1 h at room temperature. The formed $ZnC_2O_4.2H_2O$ nanoparticles were subjected to microwave irradiation at 150 W microwave power for 20 min to produced ZnO nanoparticles under thermal decomposition conditions (yield: 75 %).

General procedure for the preparation of 2,3-dihydro-1*H*-1,5-benzodiazepines: *o*-Phenylenediamine (1 mmole) and ZnO nanoparticles (20 mol % or 0.2 mmole) were crushed in mortar and pestle to a fine powder and transferred to a china dish and various ketone (2.2 mmole) was added. The reaction mixture was heated on oil bath for 40-60 min with occasional stirring. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and ethyl acetate was added. The catalyst was insoluble in ethyl acetate and it could therefore be separated by a simple filtration. The filtrate was collected, dried and residue was recrystallized from ethanol or subjected to column chromatography to get the pure products.

2,3-Dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-benzodiazepine: (entry 1) IR (KBr, ν_{max}, cm^{-1}): 3277 (*sec* N-H), 3061 (aromatic C-H), 2972 (aliphatic C-H), 1559 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.8 (s, 3H, $-CH_3$), δ 3.1 (d, 1H, -CH), δ 3.2 (d, 1H, -CH), δ 6.8-7.7 (m, 14H, ArH); Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; found: C, 84.60; H, 6.42; N, 8.94.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine: (entry 3) IR (KBr, ν_{max}, cm^{-1}): 3292 (NH), 2955 (aromatic CH), 1632 (alkene C=C), 1474 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 6H, $-C(CH_3)_2$), δ 2.2 (s, 2H, $-CH_2$), δ 2.4 (s, 3H, $-CH_3$), δ 6.7-7.2 (m, 4H, ArH); Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; found: C, 76.51; H, 8.52; N, 14.92.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[*e*][1,4] diazepine: (entry 6) IR (KBr, ν_{max}, cm^{-1}): 3328 (*sec*. NH), 3060 (aromatic CH), 2923 (alkene CH), 2852 (alkane CH), 1617 (imine C=N), 1493 (aromatic C=C). ^{1}H NMR ($CDCl_3$): δ 1.5-2.4 (m, 21H, $-CH_2$, -NH), δ 2.6 (m, 2H, $-CH_2$), δ 2.8 (m, 1H, -CH), δ 6.6-7.4 (m, 4H, ArH); Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45; found: C, 81.15; H, 9.56; N, 9.54.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine: (entry 7) IR (KBr, ν_{max}, cm^{-1}): 3454 (*sec*. NH), 2924 (aromatic CH), 2854 (alkane CH), 1437 (aromatic C=C), 1237 (C-N), 946 (1,2,4-substituted oop); ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 6H, $-CH_3$), δ 1.35 (s, 3H, $-CH_3$), δ 2.3 (m, 5H, $-CH_3$, -CH, -CH), δ 6.5 (s, 1H, ArH), δ 6.79 (d, 1H, J = 7.4, ArH), δ 7.0 (d, 1H, J = 8.7, ArH); Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.17; H, 8.97; N, 13.85; found: C, 77.22; H, 8.91; N, 13.93.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1*H*-dibenzo[*b*,*e*][1,4] diazepine: (entry 9) IR (KBr, ν_{max}, cm^{-1}): 3351 (*sec*. NH), 2931 (alkene CH), 2857 (alkane CH), 1633 (imine C=N), 1484 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.7-2.5 (m, 18H, $-CH_2$), δ 3.0 (s, 3H, $-CH_3$), δ 3 (t, 1H,-CH), δ 7.3-7.9 (m, 3H, ArH); Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; found: C, 80.86; H, 9.34; N, 9.98.

2,2,4-Trimethyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine: (entry 11) IR (KBr, ν_{max}, cm^{-1}): 3280, 1645, 1600. ^{1}H NMR ($CDCl_3$), δ ppm: δ 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.18 (s, 1H), 8.0-8.10 (m, 1H), 8.5-8.9 (m, 1H); Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.01 %; found: C, 61.85; H, 6.66; N, 18.12 %.

RESULTS AND DISCUSSION

Initially we studied the influence of ZnO nanoparticles for the synthesis of 1,5-benzodiazepine using *o*-phenylenediammine and acetophenone as a model reaction and varying the amount of ZnO nanoparticles by simple optimization study (Table-1). The catalyst quantity was optimized to 20 mol % of ZnO nanoparticles and excellent results (93 % yields) were achieved. Similarly, another 1,5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones in 85-93 % yields (Table-2). It seems that high surface area and better dispersion of nanoparticles in the reaction mixture are reasons for better activities of ZnO nanoparticles. The catalytic activity of ZnO nanoparticles was evident when no product was obtained in the absence of the catalyst.

TABLE-1
OPTIMIZATION OF CONCENTRATION OF ZINC OXIDE NANOPARTICLES FOR THE SYNTHESIS OF 2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINES UNDER SOLVENT-FREE CONDITION[a].

Entry	Amount of catalyst mol (%)	Time (min)	Yield[b] (%)
1	5.0	60	78
2	10.0	60	83
3	15.0	60	88
4[c]	20.0	60	93, 90, 85, 85
5	25.0	60	93

[a]Reaction conditions: *o*-phenylenediammine, acetophenone and catalyst; [b]Isolated yields; [c]Catalyst was recycled three times

To examine the reusability, the catalyst was recovered by filtration from the reaction mixture after dilution with ethyl acetate, washed with methanol, dried at 100 °C for 5 h and reused as such for the model reaction using ZnO nanoparticles (20 %) under optimized conditions (up to three cycles). It was observed that the yields of the product remained comparable in these experiments (Table 1, entry 4) which established the recyclability and reusability of the catalyst without any significant loss of activity.

In order to determine the catalytic behavior of ZnO nanoparticles, the possible mechanism of the reaction is shown in **Scheme-II**. To the best of our knowledge, ZnO nanoparticles catalyzed the reaction by the activations of both reactants through both Lewis acids (Zn^{2+}) and basic sites (O^{2-}). At one place, ZnO nanoparticles initiated electrophilic activation of the carbonyl groups of ketones by coordinated to oxygen through Lewis acid sites (Zn^{2+}) making them susceptible to nucleophilic attack by amines (activated by Lewis basic sites (O^{2-}) giving the intermediate diimine A. A 1,3-hydrogen shift of the attached methyl group then occurs to form an isomeric enamine B, which cyclize to afford seven membered ring with the generation of catalyst.

The XRD pattern of ZnO nanoparticles is shown in Fig. 1. The particle size was calculated from X-ray diffraction images of ZnO nanoparticles using Scherrer formula as follows:

$$d = \frac{K\lambda}{\beta \text{Cos}\,\theta}$$

where d is the average particle size perpendicular to the reflecting planes, K is a grain shape dependent constant (0.9), λ is the X-ray wavelength, β is the full width at half maximum (FWHM), and θ is the diffraction angle. The average size of ZnO nanoparticles obtained from the XRD is about 40 nm, using the Scherrer formula.

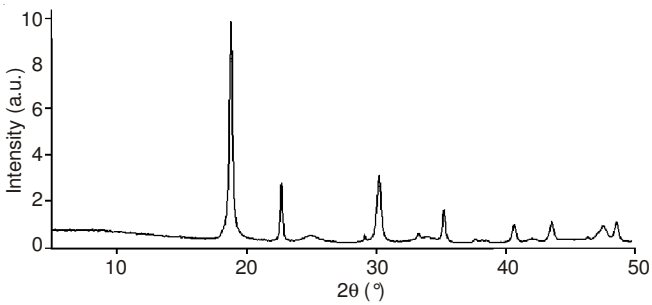
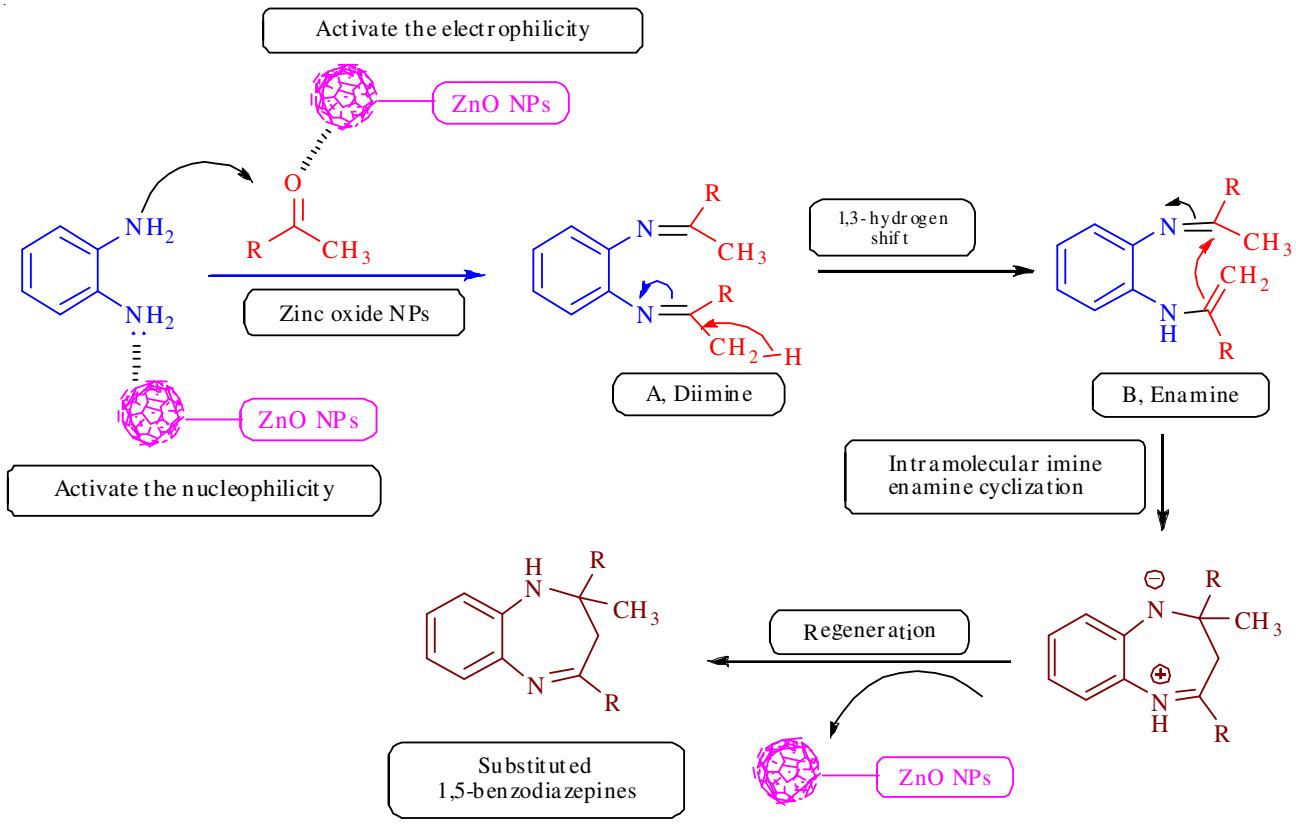


Fig. 1. XRD Pattern of ZnO nanoparticles

The TEM image of ZnO nanoparticles is shown in Fig. 2. As can be seen, the sample has a nanocrystalline structure with a spherical shape that were gained from zinc acetate and



Scheme-II: Proposed mechanism and possible intermediates

TABLE-2
CONDENSATION OF *o*-PHENYLENEDIAMINE WITH VARIOUS KETONES CATALYZED BY ZINC OXIDE NANOPARTICLES

Entry	R	R_1	R_2	R_3	R_4	Yield (%)	Time (min)	m.p. (°C)	m.p.^{lit} (°C)
1	H	C_6H_5	CH_3	H	C_6H_5	93	60	149-150	151-152[10]
2	H	$CH_3C_6H_5$	CH_3	H	$CH_3C_6H_5$	89	50	97-99	98-99[6]
3	H	CH_3	CH_3	H	CH_3	90	40	138-139	137-139[10]
4	H	CH_3	C_2H_5	H	CH_3	85	45	137-139	137-138[10]
5	H	$-(CH_2)_5-$		$-(CH_2)_4-$		88	40	137-138	138-139[11]
6	H	$-(CH_2)_6-$		$-(CH_2)_5-$		87	45	133-134	136-139[11]
7	CH_3	CH_3	CH_3	H	CH_3	90	50	126-128	127-128[11]
8	CH_3	C_6H_5	CH_3	H	C_6H_5	88	60	91-92	92-93[12]
9	CH_3	$-(CH_2)_5-$		$-(CH_2)_4-$		92	60	140-142	142-143[12]
10	CH_3	$-(CH_2)_6-$		$-(CH_2)_5-$		88	55	121-122	124-125[12]
11	NO_2	CH_3	CH_3	H	CH_3	92	45	115-117	114-116

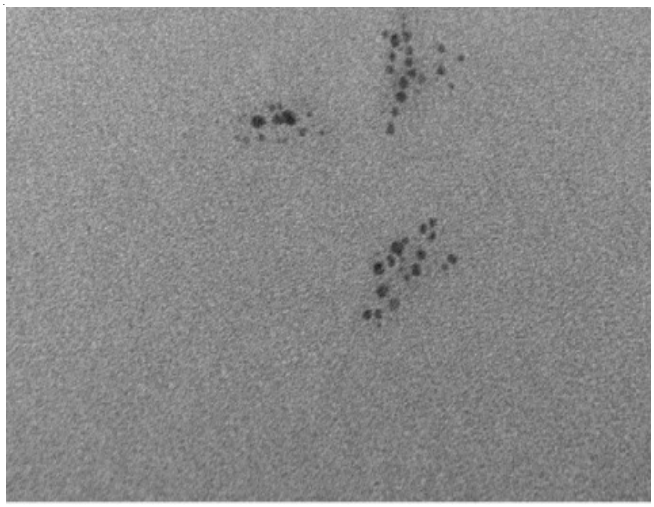


Fig. 2. TEM image of ZnO nanoparticles

oxalic acid with a particle size of about 40 nm under solution-free mechanochemical conditions.

Conclusion

We have reported an efficient, inexpensive, non-hazardous ecofriendly procedure using a catalytic amount of ZnO nanoparticles under neat conditions. This method has several advantages, including high yield of products, short reaction time and easy experimental work-up. The reactivated catalyst can be reused for three consecutive cycles without any significant loss in catalytic activity.

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