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ARTICLE TYPE

# ZnS nanoparticles as efficient recyclable heterogeneous catalyst for one-pot synthesis of 4-substituted-1,5-benzodiazepines

**Hossein Naeimi*, Hossein Foroughi**

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An efficient and novel method was developed for the synthesis of 4-substituted-1,5-benzodiazepine derivatives via one-pot three-component catalytic reaction. The *o*-phenylenediamine and dimedone were reacted with aldehyde derivatives in the presence of ZnS nanoparticles as heterogeneous catalyst under thermal condition. The reaction was completed in high to excellent products yield and short reaction times. Simplicity of operation, high yields, easy work-up, accessible catalyst and purification of products through crystallization method (non-chromatographic) are the key advantages of this work.

## Introduction

The multi component reactions (MCRs), which have obtained significant attention during the past few years, do not occur through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions [1a-f]. MCRs are processes in which at least three different simple substrates react in one-pot to give the target materials [2a-b]. Although, MCRs have great contribution in conversant synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [3a-b]. Simplicity, greater efficiency, atom economy and generation of molecular complexity with diversity in one-pot transformations are some advantages of these reactions [4a-b].

1,5-Benzodiazepines are some of the important heterocyclic compounds from the view point of biological activities [5a-d]. Some examples are diazepam and chlorodiazepoxide that act as anti anxiety drugs [5d]. Also, clozapines from the piperidinyl dibenzodiazepine in schizophrenia drugs, as well as the platelet activating factor inhibitor apafant and the muscarinic receptor (M1) antagonist pirenzepines. Modifications in the structure of these heterocycles have been made and the anxiolytic effect of benzodiazepines (clobazam) has been described. Benzodiazepine compounds shows extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity. Many undesirable side effects have been associated with the use of benzodiazepines [6a-c].

Some types of scientist groups are studying for development of benzodiazepine derivatives [7-9]. Some ways for the synthesis of these compounds have been verified in the literature via the condensation of one equivalent of *o*-phenylenediamine with various aldehydes in the presence of wide variety catalysts.

*Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, 87317, I.R. Iran; Tel./Fax: 98-3155912388/ 98-3155912397, Email: naeimi@kashanu.ac.ir*

The $Yb(OTf)_3$ in $CH_2Cl_2$ as solvent [7a], $SiO_2$ under $N_2$ atmosphere [7b], amorphous mesoporous iron alumino phosphate (FeAlP-550) catalyst under solvent-free condition [7c] and $Fe_3O_4$ nanoparticles in ethanol solvent [7d] are some of previous works. Moreover, the synthesis of 4-substituted-1,5-benzodiazepine derivatives have been carried out by three-component condensation of *o*-phenylenediamine, dimedone and aldehyde derivatives in various conditions such as; acetic acid in ethanol using reflux [8a-b], oxalic acid in water [8c], acetic acid in toluene [8d], $H_2SO_4$ in water [8e] and HCl in ethanol [8f]. In addition, they can also be synthesized by the cycloaddition reaction of 2,2-dihydroxy-1-phenylethanone, *o*-phenylenediamine and dimedone derivatives [9a], condensation of 2-formyl benzoic acid, *o*-phenylenediamine and tetronic acid in water under microwave irradiation as hetero-Cope rearrangement [9b].

In 2009 Gowan and co-workers [9c] were synthesized benzodiazepine derivatives by using acylchlorid. Also, Schimer and co-workers [9d-e] were reported a reaction between 4-substituted-1,5-benzodiazepines and acyl chlorid derivatives by $Et_3N$ as catalyst in THF at -43 °C. So far, the derivatives of 1,5-benzodiazepines affected a important role in medicinal chemistry [10a] by serving as anti-inflammatory [10b], antibacterial [10c], antidepressant [10d], hypnotic [10e], anticoagulant [10f], antiepileptic agents [11a-b], analgesic [11c], Hepatitis C Virus (HCV) NS5B inhibitors [9c] and HIV-1 protease inhibiting [9d-e] (Fig. 1).

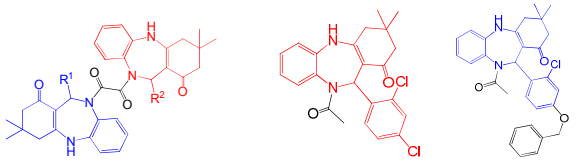

**Fig. 1** HCV NS5B inhibitors

Nanoparticles (NPs) have drawn considerable interest in recent years because of their special properties such as increased activity for using as catalyst, a large surface to volume ratio, unique

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optical and electrical properties as compared to those of the bulk materials [12a-b]. NPs referred to much interest in different organic reactions provide its cost effectiveness, experimental simplicity and ease of handling [13a-e]. ZnS nanoparticles ($NP_S$) have been intensively investigated because of their efficient heterogeneous catalyst, low Curie temperature and high coercively [14a-c]. In recent decades, semiconductor nanostructured materials have attracted of interest due to their unique properties which are different from the bulk materials [15a-f]. The one dimensional ZnS nanostructures like nanoparticles, nanorods and nanowires have been synthesized by important methods such as electrochemical deposition, laser ablation, solvothermal method, microwave irradiation, epitaxy, sonochemical method and etc [16a-i].

In continuation of our work toward preparation of ZnS NPs [17], herein, we report a simple, mild and facile MCR one-pot synthesis of 4-substituted-1,5-benzodiazepine in high yields with high purity, using ZnS nanoparticles as a heterogeneous catalyst in ethanol under thermal conditions. The developing of MCRs and improving known multicomponent reactions are a wide of considerable route interest. This green procedure has many obvious advantages compared to those reported in the previous literatures [1-4], including avoiding the usage of harmful catalysts, easy workup of the reaction, excellent yields and simplicity of the methodology.

## Experimental

### General information

All of the reagents were purchased from Merck, Aldrich, CDH and Fluka and used without further purification. Fourier transform infrared (FT-IR) spectra were obtained as KBr pellets on a Perkin–Elmer 781 spectrophotometer. Ultraviolet (UV-Vis) spectra were obtained in $CDCl_3$ solvents on a Perkin–Elmer 550 S spectrophotometer. Nuclear magnetic resonance ($^1$H NMR and $^{13}$C NMR) were recorded in DMSO and $CDCl_3$ solvents on a Bruker DRX-400 spectrometer with tetramethylsilane (TMS) as internal reference. Micro wave irradiation (M.W) obtained from a SAMSUNG Model GE4020W. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (CuK, radiation, k= 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° (2Ø). Electron Dispersive X-Rey (EDX) of nanoparticles was performed on a Zeiss ∑ 1 GMA vp. Photoluminescence (PL) spectra were obtained on the Avantes Avaspec-2048 spectrophotometer. Scanning electron microscope (SEM) of nanoparticles was performed on a KYKY EM-3200. Transmission electron microscope (TEM) of nanoparticles was performed on a LEO AB-912. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Electron Ionization Mass (EI- MASS) spectra were recorded on Agilent Technology (HP) 5973 instrument at an ionization potential of 70 eV. Melting points (M.P) obtained with a Thermo Scientific 9300. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

### General procedure for preparation of ZnS nanoparticles

In a typical procedure for preparation of ZnS NPs, 1 mmol of $Zn(OAc)_2$ $2H_2O$ and 1 mmol of thioacetamide (TAA) were added into 20 ml ethylene glycol in a 50 ml round-bottomed flask at room temperature. The solution was heated to 110 $^oC$ by microwave and kept the temperature for 5 min with stirring. After this time, the solution was naturally cooled to room temperature. The white products were separated, washed with absolute ethanol (3×10 mL) and dried at 60 $^oC$ for 3 h [12-16].

The prepared ZnS NPs was confirmed and characterized by FT-IR, XRD, PL, SEM and TEM. The FT-IR spectra (Fig. 2) of ZnS NPs showed very low absorption bands at 478, 1050 and 1415 $cm^{-1}$ which were assigned to the fundamental stretching and bending vibrations of ZnS band corresponding to sulphides. A broad intense absorption between 3000 and 3700 $cm^{-1}$ is observed due to O–H vibration of water molecules as characterized by its bending vibration at 1627 $cm^{-1}$ [12-16].

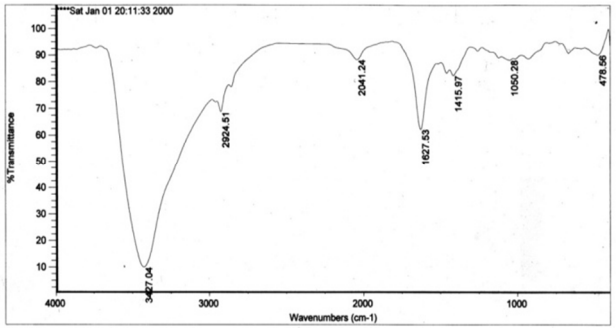


**Fig. 2** The FT-IR Spectum of ZnS NPs catalyst

The X-ray diffraction patterns of ZnS nanoparticles are shown in Fig. 3. The position and relative intensities of all peaks confirm well with standard XRD pattern of ZnS nanoparticles indicating retention of the crystalline cubic spinel structure during of NPs. The average NPs core diameter was calculated to be 6 nm from the XRD results by Scherrer's equation, $D= k\lambda/\beta\cos\theta$ where k is a constant (generally considered as 0.94), $\lambda$ is the wavelength of Cu Ka (1.54A°), $\beta$ is the corrected diffraction line full-width at half-maximum (FWHM), and $\theta$ is Bragg's angle.

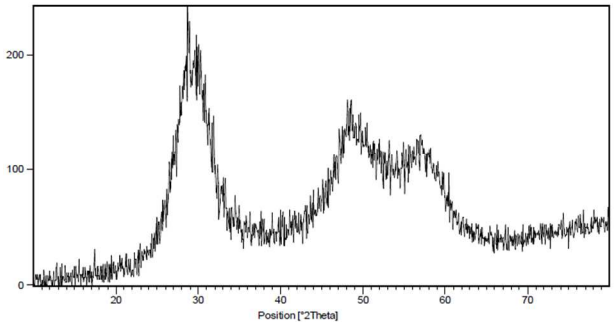


**Fig. 3** XRD spectrum of ZnS nanoparticles

The Photoluminescence (PL) properties of the synthesized ZnS NPs were studied at room temperature with a wavelength of 307 nm as shown in Fig. 4 [12-16]. The indicated spectrum is similar to that previously reported for photoluminescence (band gap) of undoped ZnS NPs.

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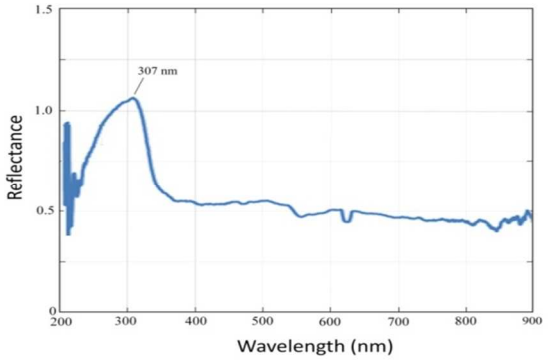


**Fig. 4** PL spectrum of ZnS nanoparticles

The chemical composition of the product was further examined with energy dispersive X-ray spectrometry (EDX). As can be shown in Fig. 5, the purity of nanoparticles was confirmed by strong peaks of Zn and S in spectrum. A relatively weak O peak in the spectrum probably originates from unavoidable surface-adsorption of oxygen on to the spheres from exposure to air during sample processing [12-16].

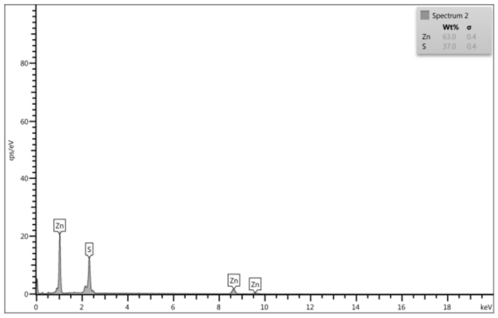

**Fig. 5** The EDX spectrum of ZnS NPs catalyst

Also, the morphology of prepared nanoparticles was studied by SEM (Fig. 6) and TEM (Fig. 7) analysis shows the typical images for ZnS nanoparticles prepared under microwave irradiation with zinc salt and thioacetamide [12-16]. As can be determined, the ZnS nanoparticles are assembled into about 20-30 nm spherical structure.

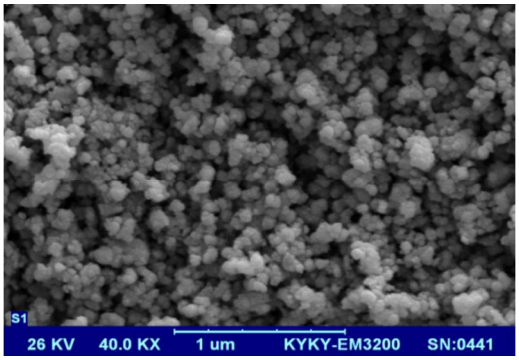


**Fig. 6** SEM image of ZnS nanoparticles

**General procedure for synthesis of 4-substituted-1,5-benzodiazepine**

In a 50 mL round bottom flask, dimedone (1 mmol), *o*-phenylenediamine (1 mmol) and selected aromatic aldehydes (1 mmol) were taken in the presence of 10 mol% (0.01g) ZnS nanoparticles in ethanol (5 mL). Then, the reaction mixture was stirred at 80 $^{o}$C for the stipulated period of time. The progress of the reaction was monitored by thin layer chromatography (TLC) (ethyl acetate:petroleum ether 1:1). After completion of the reaction, the mixture was cooled to room temperature and then centrifuged to separate the catalyst. The reaction mixture was concentrated on a rotary evaporator under reduced pressure. After the solvent was evaporated, the oily mixture was crystallized from methanol and water (6:5) to afford the product. The residue was purified by recrystallization from ethanol. They were characterized by comparison of their physical and spectral data with those of authentic samples.

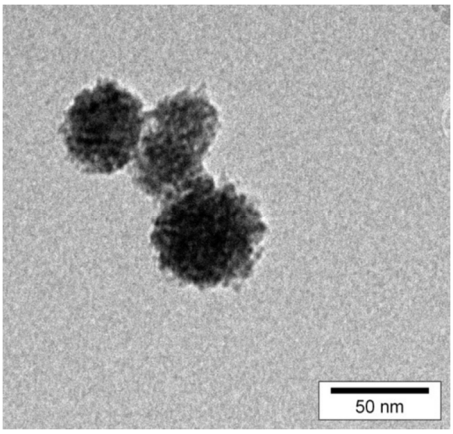


**Fig. 7** TEM image of ZnS nanoparticles

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3a):*** pale green solid, m.p.= 246-248 $^{o}$C, m.p.= 250-252 $^{o}$C [18a]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 360 nm; IR (KBr)/ υ ($cm^{-1}$): 3296, 3237, 3057, 2955, 1584, 1384, 1530, 1329, 1424, 1277; $^{1}$H NMR (DMSO+$CDCl_3$, 400 MHz)/ δ ppm: 1.03(s, 3H, $CH_3$-), 1.08(s, 3H, $CH_3$-), 2.11 (A.B q, 2H, J=16 Hz, $CH_2$), 2.56(s, 2H, -$CH_2$-C=O), 5.71(s, 1H, N-H), 6.08(s, 1H , C-H), 6.47-6.57(m, 3H, Ar-), 6.89(d, 1H, J=8 Hz, Ar-), 6.95(t, 1H, J=8 Hz Ar-), 7.0-7.1(m, 3H, Ar-), 8.15(d, 1H, J=4 Hz, Ar-), 8.69(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 27.95, 29.06, 32.21, 44.74, 50.05, 56.49, 110.68, 119.87, 120.44, 121.01, 122.98, 126.11, 127.7, 127.98, 131.49, 138.84, 145.1, 155.12, 192.52; Anal. Calcd. For $C_{21}H_{22}N_2O$: C 79.21, H 6.96, N 8.80, Found C 79.24, H 6.98, N 8.84; EI-MASS (m/z, %): 318($M^+$, 26), 241(100), 149(52), 83(45), 77(34), 57(85), 55(62).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3b):*** yellow solid, m.p.= 280-281 $^{o}$C (decomp), m.p.= 274-275 $^{o}$C [18b]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$=348 nm; IR (KBr)/ υ ($cm^{-1}$): 3355, 3279, 3181, 2955, 1591, 1381, 1511, 1339, 1425, 1275; $^{1}$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 0.99(s, 3H, $CH_3$-), 1.06(s, 3H, $CH_3$-), 2.14(A.B q, 2H, J=16 Hz, $CH_2$-), 2.53(s, 2H, -$CH_2$-C=O), 5.64(s, 1H, N-H), 5.87(s, 1H, C-H), 6.43(d, 1H, J=6.4 Hz, Ar-), 6.55-6.61(m, 2H, Ar-), 6.9(d, 1H, J=6.4Hz, Ar-), 7.21(d, 2H, J=8.8Hz, Ar-), 7.84(d, 2H, J=8.8 Hz, Ar-), 8.58(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.09, 28.80, 32.20, 44.82, 49.93, 56.63, 109.44, 120.52, 120.75, 121.09, 123.08, 123.43, 128.57, 131.39, 138.03, 146.05, 153.05, 155.05, 192.85; Anal. Calcd. For $C_{21}H_{21}N_3O_3$: C 69.41, H

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5.82, N 11.56, Found C 69.45, H 5.85, N 11.59; EI-MASS (m/z, %): 397($M^+$, 29), 241(100), 149(66), 83(51), 77(32), 57(39), 55(47).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1 one(3c):*** orange solid, m.p.= 230-232 °C (decomp), m.p.= 115-117 °C (decomp) [18a]; $R_f$ = 0.281 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 346 nm; IR (KBr)/ υ ($cm^{-1}$): 3378, 3303, 3069, 2957, 1591, 1381, 1528, 1332, 1473, 1279; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 0.95(s, 3H, $CH_3$-), 1.05(s, 3H, $CH_3$-), 2.01(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.58(s, 2H, -$CH_2$-C=O), 5.04(s, 1H, N-H), 6.01(s, 1H, C-H), 6.32(d, 1H, J=8 Hz, Ar-), 6.58(t, 1H , J=8 Hz, Ar-), 6.67(t, 1H, J=8 Hz, Ar-), 6.79(d, 1H, J=8 Hz, Ar-), 7.04(d, 1H, J=8 Hz, Ar-), 7.14-7.2(m, 2H, Ar-), 7.74(d, 1H, J=8 Hz, Ar-),8.91(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.11, 28.82, 32.22, 44.87, 49.91, 56.62, 109.46, 120.53, 120.78, 121.07, 123.1, 123.46, 126.14, 128.56, 128.59, 131.38, 138.06, 146.03, 153.08, 155.08, 192.89; Anal. Calcd. For $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56, Found C 69.46, H 5.85, N 11.60; EI-MASS (m/z, %): 363($M^+$, 26), 241(100), 149(55), 83(36), 77(42), 57(49), 55(62).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3d):*** pale yellow solid, m.p.= 195-197 °C, m.p.= 161-168 °C [18c]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 348 nm; IR (KBr)/ υ ($cm^{-1}$): 3375, 3328, 3049, 2959, 1589, 1383, 1529, 1345, 1431, 1277; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.05(s, 3H, $CH_3$-), 1.09(s, 3H, $CH_3$-), 2.14(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.58(s, 2H, -$CH_2$-C=O), 5.81(s, 1H, N-H), 6.20(s, 1H, C-H), 6.50 (d, 1H, J=5.2 Hz, Ar-), 6.51-6.6(m, 2H, Ar-), 6.9(d, 1H, J=7.2 Hz, Ar-), 7.29(t, 1H, J=8.0 Hz, Ar-), 7.45(d, 1H, J=8.0 Hz, Ar-), 7.81(d, 1H, J=9.2 Hz, Ar-), 7.98(s, 1H, Ar-), 8.79(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.1, 28.81, 32.24, 44.86, 49.93, 56.64, 109.47, 120.56, 120.76, 121.06, 123.11, 123.47, 126.16, 128.49, 128.56, 131.39, 138.09, 146.05, 153.1, 155.09, 192.86; Anal. Calcd. For $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56, Found C 69.45, H 5.86, N 11.57; EI-MASS (m/z, %): 363($M^+$, 30), 241(100), 149(38), 83(40), 77(41), 57(39), 55(58).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-chloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3e):*** pale green solid, m.p.= 235-237 °C, m.p.= 235-237 °C [18a]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 344 nm; IR (KBr)/ υ ($cm^{-1}$): 3301, 3238, 3054, 2956, 1587, 1381, 1532, 1329, 1426, 1278; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.0(s, 3H, $CH_3$-), 1.06(s, 3H, $CH_3$-), 2.11(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.52(s, 2H, -$CH_2$-C=O), 5.73(s, 1H, N-H), 5.78(s, 1H, C-H), 6.45 (d, 1H, J=8.2 Hz, Ar-), 6.55(m, 2H, Ar-), 6.88(d, 1H, J=8.2 Hz, Ar-), 6.98(d, 2H, J=8.4 Hz, Ar-), 7.01(d, 1H, J=8.4 Hz, Ar-), 8.61(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.17, 28.69, 32.24, 44.84, 49.90, 56.43, 109.38, 120.62, 120.72, 121.05, 123.11, 123.28, 128.36, 131.45, 138.06, 146.08, 150.02, 152.06, 192.81; Anal. Calcd. For $C_{21}H_{21}ClN_2O$: C 71.48, H 6.0, N 7.94, Found C 71.53, H 6.5, N 7.98; EI-MASS (m/z, %): 362($M^+$, 33), 354(M+2$^+$, 11), 241(100), 149(57), 83(35), 77(28), 57(68), 55(53).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-chloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3f):*** white solid, m.p.= 239-240 °C (decomp), m.p.= 233-235 °C (decomp) [18a]; $R_f$ = 0.281 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 348 nm; IR (KBr)/ υ ($cm^{-1}$): 3292, 3235, 3062, 2959, 1589, 1382, 1515, 1314, 1422, 1278; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.02(s, 3H, $CH_3$-), 1.07(s, 3H, $CH_3$-), 2.09(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.57(s, 2H, -$CH_2$-C=O), 5.07(s, 1H, N-H), 6.01(s, 1H, C-H), 6.33 (d, 1H, J=7.2 Hz, Ar-), 6.44-6.62(m, 2H, Ar-), 6.7(d, 1H, J=7.6 Hz, Ar-), 6.82(d, 1H, J=7.6 Hz, Ar-), 6.85-7.0(m, 2H, Ar-), 7.20(d, J=7.6 Hz, 1H, Ar-), 8.77(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.17, 28.72, 32.26, 44.84, 49.88, 56.42, 109.32, 120.61, 120.66, 121.12, 123.13, 123.42, 126.11, 128.53, 128.62, 131.42, 138.04, 146.06, 149.55, 151.06, 192.82; Anal. Calcd. For $C_{21}H_{21}ClN_2O$: C 71.48, H 6.0, N 7.94, Found C 71.54, H 6.6, N 7.99; EI-MASS (m/z, %): 352($M^+$, 36), 354(M+2$^+$, 12), 241(100), 149(52), 83(49), 77(33), 57(42), 55(51).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2,3-dichloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3g):*** pale green solid, m.p.= 256-258 °C (decomp); $R_f$ = 0.281 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$=348 nm; IR (KBr)/ υ ($cm^{-1}$): 3379, 3301, 3060, 2958, 1589, 1380, 1532, 1332, 1423, 1289; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.01(s, 3H, $CH_3$-), 1.07(s, 3H, $CH_3$-), 2.12(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.56(s, 2H, -$CH_2$-C=O), 4.96(s, 1H, N-H), 6.07(s, 1H, C-H), 6.30(d, , 1H, J=7.6 Hz, Ar-), 6.53-6.60(m, 2H, Ar-), 6.62(d, , 1H, J=7.2 Hz, Ar-), 6.75(t, 1H, J=8 Hz, Ar-), 6.91(d, 1H, J=7.6 Hz, Ar-), 7.08(d, 1H, J=7.6 Hz, Ar-), 8.64(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 28.14, 28.67, 32.23, 44.81, 49.92, 56.29, 109.10, 120.68, 121.08, 121.35, 123.65, 126.13, 126.84, 128.83, 131.71, 132.05, 132.57, 137.33, 143.52, 156.12, 192.90; Anal. Calcd. For $C_{21}H_{20}Cl_2N_2O$: C 65.12, H 5.20, N 7.23 Found C 65.15, H 5.24, N 7.26; EI-MASS (m/z, %): 386($M^+$, 24), 388(M+2$^+$, 14), 390(M+4$^+$, 4), 351(52), 241(100), 149(25), 83(34), 77(24), 69(52), 57(43), 55(54).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2,4-dichloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin 1-one(3h):*** pale green solid, m.p.= 230-232 °C (decomp), m.p = 252 °C [18d]; $R_f$ = 0.281 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 347 nm; IR (KBr)/ υ ($cm^{-1}$): 3303, 3241, 3055, 2957, 1590, 1382, 1533, 1330, 1468, 1278; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.02(s, 3H, $CH_3$-), 1.07(s, 3H, $CH_3$-), 2.11(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.57(s, 2H, -$CH_2$-C=O), 4.99(s, 1H, N-H), 5.99(s, 1H, C-H), 6.34 (d, 1H, J=7.6 Hz, Ar-), 6.56-6.63(m, 2H, Ar-), 6.65(d, 1H, J=8.4 Hz, Ar-), 6.79(d, 1H, J=8.0 Hz, Ar-), 6.92(d, 1H, J=7.2 Hz, Ar-), 7.22(s, 1H, Ar-), 8.74(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.16, 28.69, 32.26, 44.78, 49.93, 56.31, 109.12, 120.72, 121.06, 121.37, 123.68, 126.15, 126.88, 128.87, 131.68, 132.04, 132.59, 137.38, 149.57, 156.18, 192.92; Anal. Calcd. For $C_{21}H_{20}Cl_2N_2O$: C 65.12, H 5.20, N 7.23, Found C 65.16, H 5.25, N 7.28; EI-MASS (m/z, %): 386($M^+$, 26), 388(M+2$^+$, 16), 390(M+4$^+$, 6), 241(100), 149(66), 83(57), 77(30), 57(65), 55(45).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-chloro-3-nitro)phenyl]-1H-dibenzo[b,e][1,4] diazepin-1-one(3i):*** pale yellow solid, m.p.= 196-197 °C; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$=348 nm; IR (KBr)/ υ ($cm^{-1}$): 3305, 3240, 3039, 2958, 1600, 1381, 1532, 1339, 1426, 1276; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.02(s, 3H, $CH_3$-), 1.07(s, 3H, $CH_3$-), 2.13(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.54(s, 2H, -$CH_2$-C=O), 5.77(s, 1H, N-H), 6.08(s, 1H, C-H), 6.50(d, 1H, J=8 Hz, Ar-), 6.59(m, 2H, Ar-), 6.91(d, 1H, J=8 Hz, Ar-), 7.24-7.29(m,

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2H, Ar-), 7.68(s, 1H, Ar-), 8.74(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 28.04, 28.75, 32.19, 44.69, 49.84, 56.02, 109.07, 120.75, 120.85, 121.18, 123.36, 123.63, 124.85, 131.21, 131.44, 132.66, 138.04, 146.18, 147.33, 155.94, 192.9; Anal. Calcd. For $C_{21}H_{20}ClN_3O_3$: C 63.40, H 5.07, N 10.56, Found C 63.46, H 5.13, N 10.64; EI-MASS (m/z, %): 397($M^+$, 21), 399($M+2^+$, 4), 241(100), 149(47), 83(47), 77(27), 69(81), 57(91), 55(67).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-methyl)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3j):*** pale green solid, m.p.=224-226 °C, m.p.= 157-158 °C (decomp) [18e]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 361 nm; IR (KBr)/ υ ($cm^{-1}$): 3307, 3245, 3050, 2959, 1595, 1380, 1538, 1327, 1471, 1276; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.01(s, 3H, $CH_3$-), 1.07(s, 3H, $CH_3$-), 2.01 (A.Bq, 2H, J=16 Hz, $CH_2$-),2.01(s, 3H, Me-), 2.52(s, 2H, -$CH_2$-C=O), 5.69(s, 1H, N-H), 5.69(s, 1H, C-H), 6.45 (d, 1H, J=7.6 Hz, Ar-),6.5-6.6 (m, 2H, Ar-),6.81 (d, 2H, J=7.6 Hz, Ar-), 6.86(d, 1H, J=8.04 Hz, Ar-), 6.92(d, J=7.6 Hz, 2H, Ar-), 8.53(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 27.85, 29.16, 32.23, 44.71, 50.09, 55.07, 56.51, 110.69, 119.86, 120.47, 121.07, 122.96, 126.35, 127.58, 127.94, 131.53, 138.87, 145.11, 155.14, 192.56; Anal. Calcd. For $C_{22}H_{24}N_2O$: C 79.48, H 7.28, N 8.43, Found C 79.53, H 7.35, N 8.49; EI-MASS (m/z, %): 332($M^+$, 43), 241(100), 149(55), 83(39), 77(41), 57(77), 55(46).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-methoxy)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3k):*** pale cream solid, m.p.=229-231 °C, m.p.=203-205 °C [18b]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 364 nm; IR (KBr)/ υ ($cm^{-1}$): 3301, 3238, 3015, 2956, 1587, 1382, 1535, 1327, 1426, 1279; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.01(s, 3H, $CH_3$-), 1.06(s, 3H, $CH_3$-), 2.10(s, 3H, Me-), 2.10(s, 1H, C-H), 2.11(A.Bq, 2H, J=16 Hz, $CH_2$-),2.52(s, 2H, -$CH_2$-C=O), 5.7(s, 1H, N-H), 6.45 (d, 1H, J=7.6 Hz, Ar-),6.5-6.58 (m, 2H, Ar-),6.81 (d, 2H, J=8Hz, Ar-), 6.87(d, 1H, J=8.4 Hz, Ar-), 6.91(d, J=8 Hz, 2H, Ar-), 8.55(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 27.82, 29.19, 32.23, 44.75, 50.04, 54.11, 56.42, 110.67, 111.46, 113.56, 119.93, 120.41, 121.05, 123.06, 128.89, 131.46, 138.89, 146.66, 155.21, 192.08; Anal. Calcd. For $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04, Found C 75.86, H 6.97, N 8.07; EI-MASS (m/z, %): 348($M^+$, 67), 241(100), 149(36), 83(35), 77(42), 57(43), 55(52).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-methoxy)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3l):*** pale cream solid, m.p.=217-218 °C (decomp), m.p.=213-215 °C (decomp) [18a]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 361 nm; IR (KBr)/ υ ($cm^{-1}$): 3369, 3306, 3063, 2955, 1599, 1384, 1534, 1327, 1425, 1236; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.07(s, 3H, $CH_3$-), 1.08(s, 3H, $CH_3$-), 2.12(A.Bq, 2H, J=16 Hz, $CH_2$-),2.57(s, 2H, -$CH_2$-C=O) 3.89(s, 3H, Me-), 5.0(s, 1H, N-H), 5.95(s, 1H, C-H), 6.28 (d, 1H, J=7.6 Hz, Ar-),6.45-6.55 (m, 3H, Ar-),6.58 (d, 1H, J=7.6Hz, Ar-), 6.75(d, 1H, J=8.4 Hz, Ar-), 6.86(d, J=7.6 Hz, 1H, Ar-), 6.94(t, 1H, J=8Hz, Ar-), 8.59(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm)**:** 27.95, 29.08, 32.32, 44.77, 50.05, 54.79, 56.43, 110.75, 111.47, 113.56, 119.89, 120.06, 120.40, 121.05, 123.06, 128.85, 131.47, 138.86, 146.65, 155.26, 159.24, 192.65; Anal. Calcd. For $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04, Found C 75.9, H 6.98, N 8.10; EI-MASS (m/z, %): 348($M^+$, 42), 241(100), 149(52), 83(61), 77(27), 57(85), 55(72).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-methoxy)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3m):*** pale green solid, m.p.= 225-227 °C, $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 364 nm; IR (KBr)/ υ ($cm^{-1}$): 3326, 3278, 3050, 2954, 1586, 1382, 1538, 1332, 1497, 1274; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.01(s, 3H, $CH_3$-), 1.06(s, 3H, $CH_3$-), 2.12(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.52(s, 2H, -$CH_2$-C=O), 3.55(s, 3H, Me-), 5.64(s, 1H, N-H), 5.72(s, 1H, C-H), 6.44-6.48(m, 2H, Ar-), 6.53-6.57(m, 2H, Ar-), 6.60(s, 1H, Ar-), 6.62(d, 1H, J=8 Hz, Ar-), 6.86(d, 1H, J= 7.6 Hz, Ar-), 6.91(t, 1H, J=8 Hz, Ar-), 8.53(s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 27.81, 29.18, 32.21, 44.72, 50.02, 54.99, 56.41, 110.64, 111.44, 113.54, 119.91, 120.08, 120.43, 121.03, 123.03, 128.87, 131.44, 138.87, 146.63, 155.24, 159.25, 192.60; Anal. Calcd. For $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04, Found C 75.86, H 6.97, N 8.07; EI-MASS (m/z, %): 348($M^+$, 72), 241(100), 149(45), 83(31), 77(37), 69(34), 57(35), 55(42).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-hydroxy)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one(3n):*** pale cream solid, m.p.=201-202 °C, m.p.=164-166 °C [18b]; $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 360 nm; IR (KBr)/ υ ($cm^{-1}$): 3622, 3302, 3238, 3100, 2957, 1599, 1384, 1528, 1328,1424,1276; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.06(s, 3H, $CH_3$-), 1.08(s, 3H, $CH_3$-), 2.13(A.Bq, 2H, J=16 Hz, $CH_2$-),2.56(s, 2H, -$CH_2$-C=O), 5.18(s, 1H, N-H), 5.93(s, 1H, C-H), 6.35 (t, 2H, J=7.2 Hz, Ar), 6.38(d, 1H, J=6.8 Hz, Ar-), 6.50-6.55 (m, 3H, Ar-),6.66 (d, 1H, J=8Hz, Ar-), 6.76(t, 1H, J=7.2 Hz, Ar-), 6.86(d, J=7.2 Hz, 1H, Ar-), 8.53(s, 1H, N-H), 9.35(s, 1H, O-H); $^{13}$C NMR ($CDCl_3$, 100 MHz)/ δ (ppm)**:** 28.04, 29.05, 32.22, 44.71, 50.11, 56.39, 110.89, 113.22, 115.08, 118.65, 119.77, 120.43, 120.96, 122.97, 128.71, 131.47, 138.95, 146.62, 155.07, 157.26, 192.55; Anal. Calcd. For $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.38, Found C 75.47, H 6.68, N 8.43; EI-MASS (m/z, %): 348($M^+$, 23), 241(100), 149(47), 83(35), 77(46), 57(40), 55(48).

***3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-hydroxy)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (3o):*** pale green solid, m.p.= 287-289 °C (decomp), $R_f$ = 0.125 (1:1 Ethylacetate/ n-Hexane); UV-VIS: $\lambda_{max}$= 348 nm; IR (KBr)/ υ ($cm^{-1}$): 3447, 3307, 3048, 2927, 1585, 1386, 1519, 1332, 1425, 1275; $^1$H NMR (DMSO+$CDCl_3$, 400MHz)/ δ (ppm): 1.03(s, 3H, $CH_3$-), 1.08(s, 3H, $CH_3$-), 2.11(A.Bq, 2H, J=16 Hz, $CH_2$-), 2.54(s, 2H, -$CH_2$-C=O), 5.60(s, 1H, N-H), 5.94(s, 1H, C-H), 6.37(d, 1H, J=7.6 Hz, Ar-), 6.48-6.57(m, 5H, Ar-), 6.82(t, 1H, J=7.6 Hz, Ar-), 6.89(d, 1H, J=7.6 Hz, Ar-), 8.64(s, 1H, N-H), 8.90(s, 1H, O-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 28.02, 29.09, 32.20, 44.74, 50.07, 56.36, 110.86, 113.19, 115.05, 118.60, 119.75, 120.39, 120.98, 122.94, 128.74, 131.43, 138.93, 146.59, 155.04, 157.21, 192.50; Anal. Calcd. For $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.38, Found C 75.46, H 6.66, N 8.42; EI-MASS (m/z, %): 334($M^+$, 34), 241(100), 149(61), 83(57), 77(25), 69(84), 57(90), 55(72).

***2,3,4,5,10,11-hexahydro-11-[phenyl]-1H-dibenzo[b,e][1,4] diazepin-1-one (3p):*** orange solid, m.p.= 213-216 °C, IR (KBr)/ υ ($cm^{-1}$): 3307, 3245, 3030, 2930, 1530, 1364, 1020, 1008; $^1$H NMR (DMSO+$CDCl_3$, 400 MHz)/ δ ppm: 1.11 (m, 2H, $CH_2$), 2.24 (m, 2H, $CH_2$), 2.48 (m, 2H, -$CH_2$-C=O), 5.84 (s, 1H, N-H),

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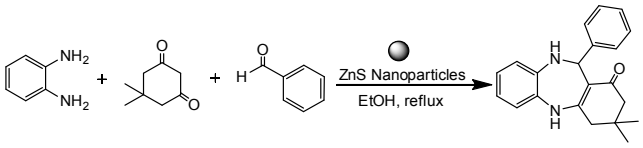
6.10 (s, 1H , C-H), 6.62-6.78 (m, 3H, Ar-), 6.95 (d, 1H, J=8 Hz, Ar-), 7.07 (t, 1H, J=8 Hz Ar-), 7.18-7.27 (m, 3H, Ar-), 8.20 (d, 1H, J=4 Hz, Ar-), 8.82 (s, 1H, N-H); $^{13}$C NMR (DMSO+$CDCl_3$, 100 MHz)/ δ (ppm): 30.25, 45.21, 50.48, 55.18, 108.84, 117.69, 122.30, 120.40, 124.67, 127.94, 128.04, 129.41, 131.64, 139.07, 146.45, 157.40, 195.74.

## Results and discussion

In this work, a simple energy, eco-friendly and convenient method for the synthesis of 4-substituted-1,5-benzodiazepine using ZnS nanoparticles as new catalyst was described. Initially, in order to optimize the reaction conditions, it is considered to represent the reaction of dimedone, *o*-phenylenediamine and benzaldehyde in equal ratio to afford the benzodiazepine**s** under various reaction conditions for an appropriate time (**Scheme 1**).




**Scheme 1** Synthesis of 4-substituted-1,5-benzodiazepine under thermal conditions

Choice of a solvent is also very important factor for MCRs. The reaction was occurred in both aprotic and protic solvents such as; EtOH, MeOH, $H_2O$, $CH_3CN$, $CHCl_3$ and n-Hexane. But none of the above solvents was found to be effective than ethanol for this reaction (Table 1). Nevertheless, the reaction at 25 $^oC$ did not give the desired product and the starting material was completely recovered, whereas, at 50 $^oC$ only trace of the desired product was identified by TLC. It was found that the ethanol was a selected solvent for the reaction using ZnS NPs as heterogeneous catalyst at 80 $^oC$, the desired product was obtained in excellent yield (Table 1, entry 16). The obtained results from the reaction to determine the optimum amount of catalyst are presented in Table 2. As can be seen from this Table, the best results were obtained by using 10 mol % (0.01g) of ZnS NPs as catalyst in the reaction of dimedone (1 mmol), *o*-phenylenediamine (1 mmol) and *p*-Cl-benzaldehyde (1 mmol) (Table 2, entry 4).

**Table 1** Optimization of reaction condition[a]

| Entry | Catalyst | Solvent | Time (min) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $MeSO_3H$ | EtOH | 50 | 65 |
| 2 | $CF_3COOH$ | EtOH | 45 | 70 |
| 3 | CuI | EtOH | 16 | 55 |
| 4 | $Fe_3O_4$ | EtOH | 16 | 55 |
| 5 | MgO | EtOH | 13 | 25 |
| 6 | ZnO | EtOH | 16 | 50 |
| 7 | ZnS | EtOH | 14 | 55 |
| 8 | Zn $(CH_3COO)_2$. $2H_2O$ | EtOH | 15 | 35 |
| 9 | None | EtOH | 40 | 40 |
| 10 | ZnS NPs[c] | None | 14 | 30 |
| 11 | ZnS NPs | n-Hexane | 15 | 20 |
| 12 | ZnS NPs | $CHCl_3$ | 13 | 40 |
| 13 | ZnS NPs | $H_2O$ | 18 | 65 |
| 14 | ZnS NPs | $CH_3CN$ | 11 | 75 |
| 15 | ZnS NPs | MeOH | 9 | 80 |
| 16 | ZnS NPs | EtOH | 10 | 85 |

[a]All the reactions were carried out using 10% mol of catalyst, 1mmol of o-phenylenediamine, 1 mmol of dimedone and 1 mmol of p-Cl-benzealdehyde in solvent (5.0 mL). [b]Isolated yields; [c]ZnS NPs (10 % mol)

In generality and development of this protocol, the reaction of *o*-phenylenediamine, dimedone with various aryl aldehydes was carried out in according to the general experimental procedure. In all of the cases, the corresponding benzodiazepines were obtained in high to excellent yields and short reaction times. The obtained similar products are summarized in Table 3. Furthermore, It was also examined a wide variety of aldehydes (both aromatic and aliphatic) with various substituents to establish the catalytic importance of ZnS nanoparticles for this reaction. A wide range of *ortho*, *meta* and *para* substituted aromatic aldehydes undergo this one-pot multicomponent reaction with dimedone and *o*-phenylenediamine toward benzodiazepines in excellent yields. In all of entries, it was observed the almost same performance of catalyst for this cyclo-condensation toward synthesis of the desired products (Table 2). While, the aliphatic aldehydes gave the corresponding 4-substituted-1,5-benzodiazepine in lower yield (20–30%) than aromatic aldehydes (73–94%) (Table 3). Reaction profile is very clean and no side reaction products were formed. All of the synthesized 4-substituted-1,5-benzodiazepines have been characterized on the basis of elemental and spectral studies.

**Table 2** Optimization of catalyst amount in the reaction[a]

| Entry | Catalyst (g) | Time (min) | Yield[b] (%) |
|---|---|---|---|
| 1 | None | 40 | 40 |
| 2 | 0.005 | 18 | 65 |
| 3 | 0.008 | 15 | 75 |
| 4 | 0.01 | 10 | 85 |
| 5 | 0.013 | 10 | 85 |
| 6 | 0.015 | 10 | 85 |

[a] The reaction is using a different amount of catalyst, 1 mmol of dimedone, 1mmol of o-phenylene diamine and 1 mmol of p-Cl-benzealdehyde in ethanol (5.0 mL). [b]Isolated yields.

The possibility of recycling of the catalyst was examined through the reaction of *o*-phenylenediamine, dimedone and 4-chlorobenzaldehyde catalyzed by ZnS NPs under optimized conditions. Upon completion of the reaction, the catalyst was centrifuged, filtered and washed several times with ethyl acetate. Also the recycled catalyst was saved for the next reaction. The recycled catalyst could be reused five times without any decrease in catalytic activity so that the yields were ranged from 85-75 % (Fig. 8).


**Fig. 8** Reusability of ZnS NPs

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**Table 3** Synthesis of 4-substituted-1,5-benzodiazepine (**3a-o**) catalyzed by ZnS nanoparticles in ethanol under thermal condition[a]

| Entry | Aldehyde | Product | Time (min) | Yield (%)[b] | Mp.(°C) Found (Lit.[b]) |
|---|---|---|---|---|---|
| 1 | | 3a | 12 | 78 | 246-248 (250-252) |
| 2 | | 3b | 8 | 94 | 280-281[c] (274-275) |
| 3 | | 3c | 10 | 91 | 230-232[c] (115-117[c]) |
| 4 | | 3d | 9 | 92 | 195-197 (161-168) |
| 5 | | 3e | 10 | 85 | 235-237 (235-237) |
| 6 | | 3f | 11 | 82 | 239-240[c] (233-235[c]) |
| 7 | | 3g | 10 | 83 | 256-258[c] |
| 8 | | 3h | 9 | 88 | 230-232[c] (252) |
| 9 | | 3i | 10 | 73 | 196-197 |
| 10 | | 3j | 13 | 83 | 224-226 (157-158[c]) |
| 11 | | 3k | 15 | 76 | 229-231 (203-205) |
| 12 | | 3l | 13 | 76 | 217-218[c] (213-215[c]) |
| 13 | | 3m | 14 | 82 | 225-227 |
| 14 | | 3n | 14 | 73 | 201-202 (164-166) |
| 15 | | 3o | 13 | 81 | 287-289[c] |
| 16[d] | | 3p | 12 | 88 | 213-216 |

[a] Reaction condition: o-phenylenediamine (1mmol), aldehyde (1mmol), dimedone (1mmol), ZnS nanoparticles 10% mol (0.01 g); [b] Yields of isolated pure product; [c] Decomposition point; [d] Reaction condition: *o*-phenylenediamine (1mmol), benzaldehyde (1mmol), 1,3-cyclohexadione (1mmol), ZnS nanoparticles 10% mol (0.01 g)

In order to ascertain the effect of reaction cycles on the catalyst, TEM analysis on the used catalyst after five subsequent runs was provided and shown in Fig. 9. Compared to the TEM of catalyst after and before (Fig 7) used in the reaction, was indicated that the reaction cycles not affected on the morphology and dimension of nanaparticles.

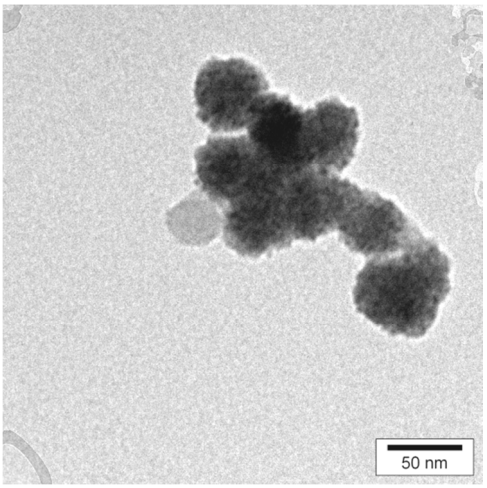


**Fig. 9** TEM image of ZnS nanoparticles after five subsequent runs

The structure of the obtained products was confirmed by FT-IR, $^{1}$H NMR, $^{13}$C NMR and EI-MASS spectroscopic data. The FT-IR spectrum of the **3i** exhibit a broad band at 3305 and 3240 cm$^{-1}$ related to amine protons (2 NH groups). The bands at 3039 and

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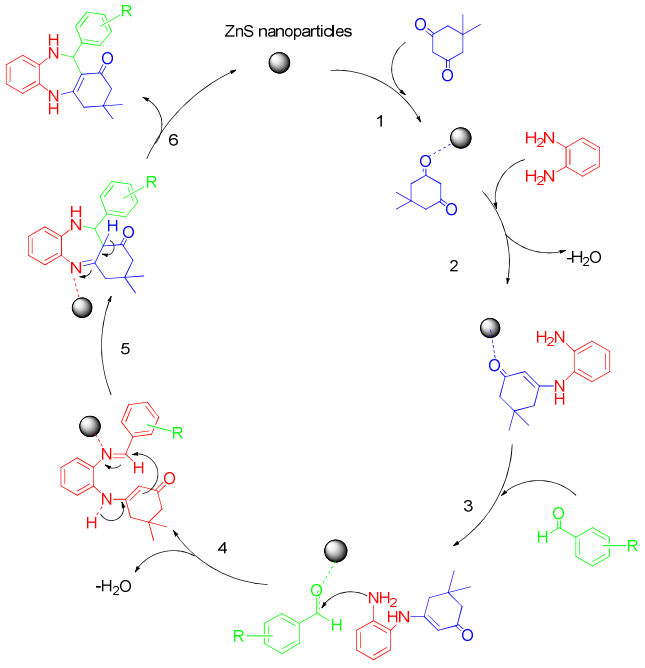
2958 $cm^{-1}$ confirm the presence of CH, $CH_2$, $CH_3$ groups, strong bands at 1600 and 1381 $cm^{-1}$ related to the general carbonyl groups (C=O stretching). Moreover, strong bands at 1532 and 1339 $cm^{-1}$ confirm the presence of C-N stretching, a band at 1426 $cm^{-1}$ is related to the C=C stretching and a strong band at 1276 $cm^{-1}$ confirms the presence of C-O bond stretching. In addition, the $^1$H NMR spectrum of compound **3i** exhibited two singlet bands for two methyl groups at δ = 1.02 ppm and δ = 1.07 ppm. Also, a AB quartet signal at δ = 2.13 ppm with *J*=16 Hz for $CH_2$ protons, a signal at δ = 2.54 ppm for $CH_2$-C=O protons, a signal at δ = 5.77 ppm for NH proton, a signal at δ = 6.08 ppm for CH proton, aromatic protons at δ = 6.50-7.68 ppm and a signal at δ = 8.74 ppm for NH proton are presented in this spectrum. Also, the $^{13}$C NMR spectrum of compound **3i** was shown distinct 21 carbon atoms in agreement with proposed structure. Finally, the mass spectrum of product 3i was displayed molecular ion peak at the appropriate m/z value [18a].

The formation of 4-substituted-1,5-benzodiazepine from *o*-phenylenediamine, dimedone and aldehyde in the presence of ZnS nanoparticles as efficient catalyst can be explained. It was proposed a mechanism for the ZnS nanoparticles catalyzed one pot synthesis of 4-substituted-1,5-benzodiazepine. As can be shown in **Scheme 2,** the desired product was formed in this reaction catalyzed by ZnS nanoparticles as following various steps (Scheme 2). The role of ZnS nanoparticles comes in steps 2 and 3 where it catalyze the Michael type coupling of dimedone with *o*-phenylenediamine and intermediate A with aldehyde. Also, it catalyze the Knoevenagel type in step 5 for seven-membered ring cyclization, finally, give 4-substituted-1,5-benzodiazepine as final product (Scheme 2).




**Scheme 2** Proposed mechanism for ZnS NPs catalyzed 4-substituted-1,5-benzodiazepine synthesis

## Conclusion

In the present work, we were described using ZnS nanoparticles as a reusable, readily available, inexpensive and efficient catalyst for the one-pot synthesis of 4-substituted-1,5-benzodiazepines. These compounds were prepared through treatment of *o*-phenylenediamine and dimedone with various aromatic aldehydes under thermal conditions at 80 °C. Simplicity of operation, high yields, easy work-up, available catalyst, short reaction time, and purification of compounds by crystallization method (non-chromatographic) are the key advantages of this work. We hope this method expand to others synthetic methods for medicinal chemistry.

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## Graphical abstract

# ZnS nanoparticles as efficient recyclable heterogeneous catalyst for one-pot synthesis of 4-substituted-1,5-benzodiazepines

Hossein Naeimi* and Hossein Foroughi

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, 87317, I.R. Iran; Tel. No.: +98-361-5912388; Fax No.: +98-361-5912397;

E-mail: naeimi@kashanu.ac.ir