



Greener and efficient synthesis of Benzodiazepines using mixed Ferrite under solvent free condition

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Abstract

The Ferrite material $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ was synthesized by the sol-gel auto combustion method and characterized by its TG and DTA. The crystallographic structures were studied by XRD. Morphology and structure of the powder samples were studied by SEM and TEM. The synthesis of benzodiazepines via one-pot two-component condensation reaction of o-phenylene diamine and ketones carried by using synthesized ferrite as a recyclable catalyst. This synthetic approach eliminates the use of hazardous organic solvents with the important benefit of easy separation and reusability of the catalyst without compromising the yield or purity

Keywords: ferrite, benzodiazepine, green catalyst, solvent free synthesis

Introduction

Recently, metal nanoparticles have received much attention in the field of organic synthesis. Metal nanoparticles are much more reactive than the bulk because of their higher surface to volume ratio recently; metal nanoparticles have received much attention in the field of organic synthesis. Metal nanoparticles are much more reactive than the bulk because of their higher surface to volume ratio ^[1]. Benzodiazepines derivatives are an important class of pharmacologically active compounds and their synthesis has been receiving great importance in the field of pharmaceutical chemistry owing to their application as anticonvulsant, anti-inflammatory, analgesic, hypnotic, and sedative agents and to their hypnotic activity ^[2-7]. The derivatives of 1, 5-benzodiazepines are also used as dyes for acrylic fibers in photography ^[8]. In addition, benzodiazepines are the useful precursors for the synthesis of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines ^[9-12]. Benzodiazepines are generally synthesized by the condensation of o-phenylenediamine with α , β -unsaturated carbonyl compounds, α -haloketones, or with ketones ^[13] using acidic catalysts which are critical to enhance the condensation process. Different reagents such as BF_3 -etherate, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, lead nitrate, L-proline, acetic acid under microwave conditions, molecular iodine, and ionic liquids have also been used for the synthesis of benzodiazepines ^[14-24]. Unfortunately, many of these catalysts suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious workup procedure. These factors stimulate the search for a better catalyst, which should offer a high activity for the synthesis of 1, 5-benzodiazepines under mild reaction conditions. In recent years much attention has been paid to the utilization of magnetic metal oxides nanoparticles as heterogeneous and easily recycled catalysts for various organic reactions. Magnetite nanoparticles have been immobilized on different catalyst supports, because of easily retrievable and reusable heterogeneous catalyst they are still have high demand. Iron oxide nanoparticles catalyst is that they can be easily

separated using an external magnet, which achieves a simple separation of catalyst without filtration. In this context, we have described use of magnetic metal oxides nanoparticles as heterogeneous and easily recycled catalysts for the synthesis of 1, 5-benzodiazepine using $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ as catalyst through a condensation reaction between ortho phenylene diamine and ketones under solvent free condition. The effect of catalyst and the catalyst concentration on the above process has been investigated in detail.

Material and method

A. Synthesis and Characterization of Catalyst

$Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ was synthesized by the sol-gel auto-combustion method from analytical reagent grade Zinc nitrate, Nickel nitrate, copper nitrate, zinc nitrate, and iron nitrate as starting material using citric acid as fuel. TG and DTA of precursor were carried on SDT Q600 V20.9 Build 20 instrument in air atmosphere. The crystallographic structure was studied by X-ray powder diffraction with by Phillips X-ray diffractometer (Model 3710). Morphology and structure of the powder sample was studied on JEOL-JSM-5600N Scanning Electron Microscope (SEM) and on Philips (model CM 200). Transmission Electron Microscope (TEM). Melting point of synthesized benzimidazole was determined in capillary tubes and is uncorrected. Column chromatography employed silica gel of 60-120mesh. XRD pattern of the $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ spinels ferrite confirmed the formation of cubic spinel structure of single phase ferrites without additional peaks corresponding to any other phases. The observed crystallite size is 30.3 nm also confirmed by TEM. It is observed from the SEM images that the prepared samples are amorphous and porous in nature. The particles were well distributed and slightly agglomerated. The agglomeration is the indication of high reactivity of the prepared sample with the heat treatment and it may also be come from the magneto static interaction between particles.

The synthesized $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ was then applied as a reusable catalyst in a condensation reaction which intern will

produce biologically important heterocyclic compounds such as benzodiazepine and their derivatives.

The model condensation reaction between *o*-phenylenediamine (1mmol) and aceto phenone (2.2 mmol) in presence of $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ was carried out under solvent free condition (Scheme 1).

The reaction was carried out in various solvents, like water, THF, acetonitrile, ethanol and toluene. Significant improvement was achieved in ethanol and acetonitrile, but the best result was observed under solvent free condition. However the reaction did not proceed in water medium which might be due to poor solubility of the starting materials.

B. Experimental

All the reagents (AR Grade) were purchased from SD Fine Chem Limited (India) and Thomas Baker (India) and were used directly without any further purification. The characterization of the products was done by comparing their physical constants with the literature values and by recording spectra. All the melting points were recorded on digital melting point apparatus and are uncorrected. IR spectra were recorded in KBr on Bruker FT-IR (Alpha-P). ¹H spectra were measured at ambient temperatures using CDCl₃ as the solvent on a 400 MHz BRUKER AVANCE DRX-500 instrument. Progress of reaction was monitored by TLC.

General procedure for the synthesis of benzothiazepines

the catalyst $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ (10 mol %) was added to a mixture of *o*-phenylenediamine (1 mmol) and acetophenone (2.2 mmol) and heated at 70°C under solvent free condition. Progress of reaction, was monitored by TLC, the reaction mixture was cooled to room temperature and dissolved in 10 mL ethyl acetate. The catalyst was then separated by external magnetic field. The separated catalyst was washed with ethyl acetate and dried. Then it was used for another set of reaction under similar condition. The reaction mixture was then washed with water (3x5 mL), and dried over anhydrous Na₂SO₄. The reaction mass was concentrated under vacuum and the pure product was obtained by purification through column chromatography using ethyl acetate–hexane as eluent.

Reaction Scheme

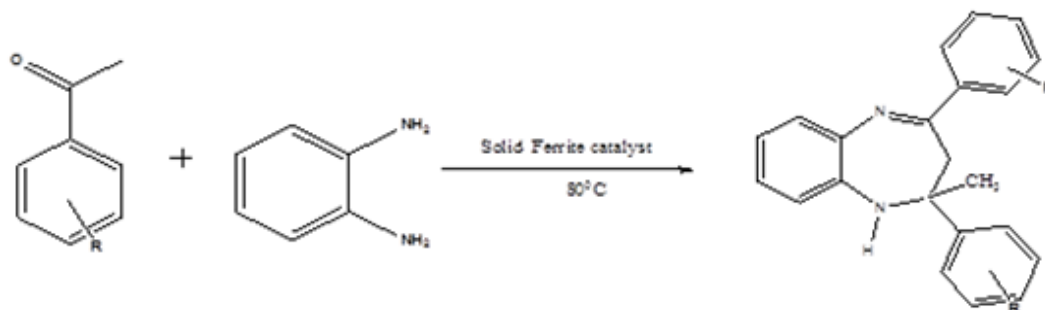


Fig 1

Result and Discussion

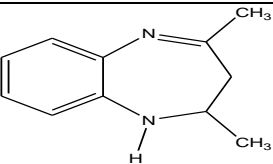
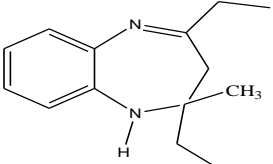
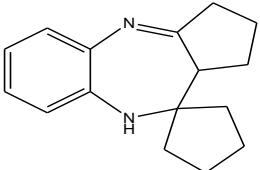
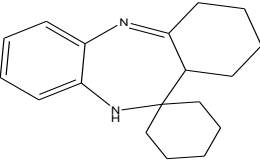
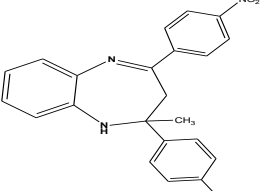
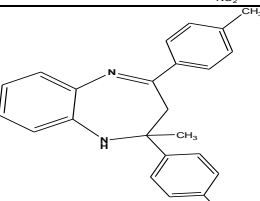
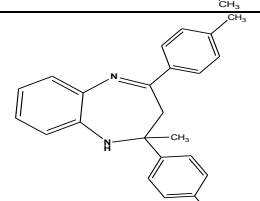
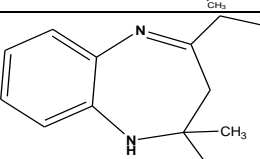
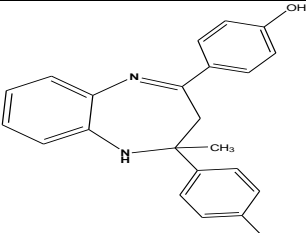
The catalyst $Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_2O_4$ was prepared and characterized by different techniques such as XRD, SEM and TEM thus confirmed its structure. The synthesized catalyst was then applied as a reusable catalyst in a condensation reaction like heterocyclic compounds such as benzodiazepine and their derivatives. The amount of catalyst concentration for the model reaction was scanned. Firstly, the condensation reaction of *o*-phenylenediamine (1mmol) and acetophenone (2.2 mmol) was carried out in absence of catalyst, very less conversion was observed (22%). The reaction was then studied with various mol% of the catalyst (2–16 mol %). It was found that the product yield proportionally increased with catalyst concentration. Maximum yield was obtained by using 10 mol% of the catalyst. Further increase in the catalyst concentration (12 mol% and 14 mol %), the yield of the product did not improve. So 10 mol% is the optimum catalyst concentration in this reaction. We have carried out the said condensation reaction of *o*-phenylenediamine and acetophenone in presence of above said catalyst (10 mol %) under solvent free condition at 80°C (Scheme 1). The reaction went to completion within 15 min yielding a solid pale white product in high yield (89%). The structure of the compound was established by analytical and spectroscopic methods (detailed is given in table-1).

Spectral discussion: The significant peak of IR at 3331 (N-H Str.), 1637 (C=N), 1590 (Ar) clearly confirms the formation of product. The presence of peaks in ¹H NMR at 3.4 (brs, 1H), 3.08(d, J=13.2 Hz, 1H) and 2.92 (d, J=13.2Hz, 1H) also indicates the formation of benzodiazepine.

Effect of temperature: The effect of temperature on the product yield was also studied. The reaction was carried out at room temperature but no desired product was obtained only starting materials were recovered after 1 h. with increase in the temperature, yield of the desired product

Increases and maximum yield was achieved at 70°C. Initially the catalyst facilitated the reaction between diamine and ketones and generates intermediate. The intermediate this undergoes intramolecular cyclization followed by hydride shift to furnish the benzodiazepine [25-26].

Table 1: Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe₂O₄ Catalyzed Synthesis of 1, 5-Benzodiazepines under Solvent Free Conditions

Entry	Ketone	Products	Yield (%)	M.P.(°C)
a	Acetone		82	142-144
b	Ethyl methyl ketone		87	135-136
c	Cyclopentanone		86	135-137
d	Cyclohexanone		84	136-138
e	p-nitro acetophenone		88	136-138
f	Acetophenone		92	148-150
g	p-methyl acetophenone		89	139-140
h	Diethyl ketone		84	144-146
i	p-hydroxy acetophenone		88	148-150

Conclusion

In conclusion, we have developed a new efficient and ecofriendly method for the synthesis of benzodiazepine derivatives. This method has great advantages because workout procedure is easy, short reaction time, reaction mild reaction conditions and in excellent yield, solvent free and catalyst can be separated by external magnetic yield and reused for several runs.

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