Greener and Efficient Synthesis of Benzodiazepines Using Mixed Ferrite under Solvent Free Condition

Suryawansi Venkat S.
Department of Chemistry, P. G. and Research Centre, Shri Chhatrapati Shivaji College, Omerga 413 606
Dist. Osmanabad, Maharashtra, INDIA

Corresponding Author: vssurya11@gmail.com

ABSTRACT
The Ferrite material Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_{2}O_{4} was synthesized via sol-gel auto-combustion method and characterized by its TG and DTA. The crystallographic structures were studied by XRD. Shape, size and structure of the powder samples were confirmed by SEM and TEM analysis. 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 advantage of ease separation process and repeat use of the catalyst without affecting the yield as well as purity.

Keywords-- Ferrite, Benzodiazepine, Green Catalyst, Solvent free synthesis

I. INTRODUCTION
Recently ferrite nanochemistry has received much focus on the field of organic transformation. Metallic nanocatalyst is much more reactive and beneficial than the bulk because of their great surface to volume ratio. Recently, nanomaterials prepared from metal have received much focus in the field of organic catalysis.[1] Benzodiazepines derivatives are an important class of pharmacologically valuable compounds and their various methods of synthesis has been receiving great scopes in the field of medicinal chemistry pertaining to their various applications such as anticonvulsant, anti-inflammatory, analgesic, hypnotic, and sedative agents and to their hypnotic activity [2–7]. The various new derivatives of 1,5-benzodiazepines are also used in dye industry.[8] In addition, benzodiazepines are the useful scaffold for the other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines [9–12]. Benzodiazepines are commonly synthesized by the cyclocondensation of o-phenylenediamine with αβ-unsaturated carbonyl compounds(chalcones), α-haloketones, or with ketones [13] using various acidic catalysts which are critical to transformation into suitable product. Different reagents such as boron trifluoride-etherate, polyphosphoric acid, sodium borohydride,MgO/POCl_{3},Yb(OTf)_{3},Ga(OTf)_{3},Pb(NO_{3})_{2},L-proline,CH_{3}COOH under microwave irradiation, molecular I_{2}, and various greener solvents have also been used for the synthesis of benzodiazepines [14–24]. But literature reports shows that majority of these catalysts have one or more limitations, such as longer reaction time, generation of several biproducts, severe reaction conditions, low yields, and tedious workup. These drawbacks motivates to search for a better catalyst, which should offer a good activity in all respect for the synthesis of 1,5-benzodiazepines derivatives under mild reaction conditions. In recent years many of the researchers has focused on utilization of magnetic metal oxides nanoparticles as heterogeneous and easily recycled catalysts for various organic reactions. Magnetic 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 catalysts for the synthesis of 1,5-benzodiazepine using Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_{2}O_{4} as best catalyst through a condensation reaction between ortho phenylene diamine and ketones under solvent free condition. The catalyst effect and its effect of concentration for the above process have been studied.

II. MATERIAL AND METHOD
A) Synthesis and Characterization of catalyst
Zn_{0.6}Ni_{0.2}Cu_{0.2}Fe_{2}O_{4} was synthesized by was synthesized by the sol-gel auto-combustion method for which we have used analytical reagent grade Zinc nitrate, Nickel nitrate, copper 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 XRD 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 60-120 mesh.
XRD pattern of the Zn$_{0.6}$Ni$_{0.2}$Cu$_{0.2}$Fe$_2$O$_4$ 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 clearly 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$_2$O$_4$ was then used as a reusable catalyst for a condensation reaction which intern will be useful for the synthesis of biologically important heterocyclic compounds such as benzodiazepine and their derivatives. The model reaction between o-phenylenediamine (1mmol) and acetophenone (2.2 mmol) was performed under solvent free condition (Scheme -1). The reaction was also carried out in various solvents, like H$_2$O, THF, CH$_3$CN, ethanol and toluene. Significant improvement in yield was observed in ethanol and acetonitrile, but the best result was recorded under solvent free condition. However due to poor solubility of the starting materials the reaction did not proceed in water medium.

**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). $^1$H NMR at ambient temperatures using CDCl$_3$ 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$_2$O$_4$ (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 for appropriate time (12-18 min). Progress of reaction was checked by TLC; the whole reaction mixture was cooled to room temperature and dissolved in 10 mL ethyl acetate. The catalyst was then separated by simply on applying external magnetic field. The separated catalyst was washed with ethyl acetate and dried and it was used for another set of reaction under same condition. The reaction mixture was then washed with water (3x5ml) and well dried over anhydrous sodium sulphate. The reaction mass was concentrated under vacuum and the pure product was obtained by purification through column chromatogram using ethyl acetate–hexane as eluent.

**III. RESULT AND DISCUSSION**

The catalyst Zn$_{0.6}$Ni$_{0.2}$Cu$_{0.2}$Fe$_2$O$_4$ was prepared and characterized by different techniques such as XRD, SEM and TEM thus confirmed its structure. The synthesized catalyst was then tried as a reusable catalyst in a condensation reaction like heterocyclic compounds such as benzodiazepine and their derivatives. The quantity 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 by using various mol% of the catalyst (2 mol-% to 16 mol-%). It was observed that the yield of the product was increased with increase in catalyst concentration. Maximum yield was obtained by using 10 mol % of the catalyst. Further by increasing the catalyst concentration (12 mol-% and 14 mol-%), the yield of the product did not improve. So we kept 10 mol% optimum catalyst concentrations for all cases in this reaction. We have carried out the said cyclization 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 has been completed within 15 min yielding a solid white product in high yield (89%). The structures of all synthesized compound was confirmed 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 observed peaks in $^1$H NMR at 3.4 (broad s, H Str), 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 observed. The reaction was performed at room temperature but no desired product was obtained, 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 diamin and ketones and generates intermediate. The intermediate further undergoes intramolecular cyclization and followed by hydride shift to furnish the benzodiazepine[25-26].

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**Reaction Scheme**

![Reaction Scheme Diagram](image_url)

| Entry | Ketone                | Products | Yield (%) | M.P(°C) |
|-------|-----------------------|----------|-----------|---------|
| a     | Acetone               | ![Product Image](image_url) | 82        | 142-144 |
| b     | Ethyl methyl ketone   | ![Product Image](image_url) | 87        | 135-136 |
| c     | Cyclopentanone        | ![Product Image](image_url) | 86        | 135-137 |
| d     | Cyclohexanone         | ![Product Image](image_url) | 84        | 136-138 |
| e     | p-nitro acetophenone  | ![Product Image](image_url) | 88        | 136-138 |

Table 1: Zn0.6Ni0.2Cu0.2Fe2O4 promoted synthesis of 1, 5-benzodiazepines under solvent free conditions
IV. CONCLUSION

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

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