

Green Multicomponent Synthesis of Benzodiazepines in the Presence of CuFe_2O_4 as an Efficient Magnetically Recyclable Nanocatalyst under Solvent-Free Ball-Milling Conditions at Room Temperature

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In this work, an efficient and green procedure for the synthesis of various substituted 1,5-benzodiazepine derivatives *via* a one-pot three-component catalytic reaction is described. The reaction was conducted between *o*-phenylenediamine, dimedone and aldehyde derivatives in the presence of CuFe_2O_4 nanoparticles as a magnetic heterogeneous nanocatalyst under ball-milling conditions at room temperature. High yields of the products, short reaction times, simplicity of operation, mild reaction conditions, non-toxicity, easy work-up and purification of the products through crystallization method (chromatography-free) and recyclability of the catalyst are added advantages of this work.

Keywords: Multicomponent reactions, Benzodiazepine, Magnetic heterogeneous nanocatalyst, CuFe_2O_4

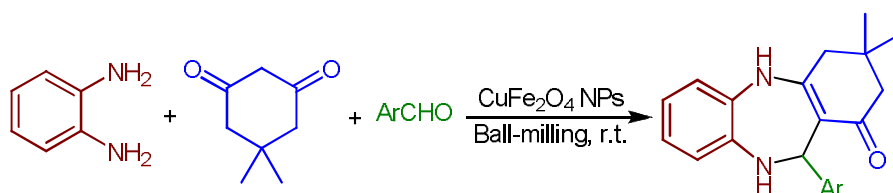
INTRODUCTION

Multicomponent reactions (MCRs) as an important organic synthesis strategy are one-pot processes in which three or more accessible substrate react to produce a more complex molecule that essentially includes most or all atoms of the starting materials. MCRs possess remarkable advantages such as high atom-economy, simplicity, structural diversity and shortness of the synthetic pathway in comparison to conventional bimolecular. Recently, much attention has been paid to MCRs for producing various biologically active compounds with diverse pharmacological activities [1]. Benzodiazepines are nitrogen-containing heterocyclic compounds which have attracted significant attention due to their various medicinal, biological and pharmaceutical activities such as anticonvulsant, anti-anxiety, antitumor, psychosis, hypnotic, antipyretic, anti-inflammatory and as dyes for

acrylic fibers [2,3]. Because of the significant features of these heterocyclic scaffolds, many protocols were developed to more efficient synthesis of benzodiazepine derivatives. Generally, the synthesis of benzodiazepine derivatives is carried out in an acid-catalyzed one-pot two-component manner between *o*-phenylenediamines (OPDAs) with α,β -unsaturated carbonyl compounds, β -haloketones, β -aminoketones and ketones or terminal alkynes [4]. Various catalytic systems have been developed for the two-component synthesis of benzodiazepines, which include organic acids, trichlorotriazine (TCT) [5], silica sulfuric acid (SSA) [6], $\text{Yb}(\text{OTf})_3$ [7], $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [8], NaBH_4 [9], ceric ammonium nitrate (CAN) [10], $\text{Sn}(\text{HPO}_4)_2 \cdot \text{H}_2\text{O}$ [11], MgO/POCl_3 [12], aerogel supported ionic liquid phase (ASILP) [13], AcOH under microwave conditions [14], *N*-bromo succinimide (NBS) [15] and $\text{Sc}(\text{OTf})_3$ [16].

Heterogeneous catalysts, a very important class of catalysts, are frequently utilized in the chemical industry [17]. These catalysts have received considerable interest due

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Scheme 1. Three-component synthesis of benzodiazepines

to high reactivity, low toxicity, operational simplicity, non-corrosive nature and reusability [18]. Magnetic nanoparticles (MNPs) have attracted much attention in organic synthesis as heterogeneous catalysts. Among all MNPs, copper ferrite magnetic nanocatalysts have attracted much attention in many organic reactions and transformations due to their easy preparation, large surface area ratio and facile separation *via* magnetic force as well as low toxicity [19-21].

In the recent years, ball milling as an effective and green technique in organic synthesis has received much interest due to the lack of high temperature treatment and high yields production. Noteworthy, in this method, kinetic colliding balls are applied, and there is no need for solvent. The reagents are placed in a vial with these grinding balls which is shaken at high speeds, and chemical reactions were occurred by mechanical process to produce the aim products [22,23].

Herein, we have focused our attention on a three-component reaction between OPDA, dimedone and various aldehydes in the presence of CuFe_2O_4 nanoparticles (NPs) as an efficient heterogeneous nanocatalyst under ball-milling conditions at room temperature for the preparation of benzodiazepine derivatives (Scheme 1).

EXPERIMENTAL

GENERAL

All chemicals and reagents were purchased from Merck, Fluka and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer by the method of KBr pellet. The ^1H NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500

MHz.

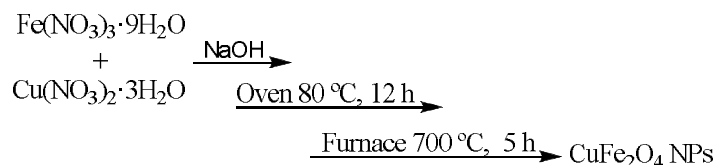
All the products were known compounds and were identified by comparison of their spectroscopic and analytical data with those authentic samples.

Preparation of CuFe_2O_4 Nanoparticles

CuFe_2O_4 NPs were prepared by thermal decomposition of $\text{Cu}(\text{NO}_3)_2$ and $\text{Fe}(\text{NO}_3)_3$ in water in the presence of sodium hydroxide. Briefly, to a solution of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (3.3 g, 8.2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (1 g, 4.1 mmol) in 75 ml of distilled water, 3 g (75 mmol) of NaOH dissolved in 15 ml of water was added at room temperature over a period of 10 min, during which a reddish-black precipitate was formed. Then, the reaction mixture was warmed to 90 °C and stirred. After 2 h, it was cooled to room temperature and the synthesized magnetic NPs were separated by an external magnet. After that, it was washed with water and dried in an air oven overnight at 80 °C. Finally, the catalyst was ground in a mortar and pestle and kept in a furnace at 700 °C for 5 h (step up temperature 20 °C min^{-1}) and then cooled to room temperature slowly; 820 mg of magnetic CuFe_2O_4 NPs were obtained.

General Procedure for the Synthesis of 4-Substituted-1,5-benzodiazepine Derivatives 4a-n

The mixture of OPDA (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol) and aromatic aldehydes (1 mmol) were ball-milled at 28 Hz for 25-46 min in the presence of CuFe_2O_4 (0.046 g). When the reaction was complete, the reaction mixture was solubilized in EtOH and magnetic catalyst was removed from the reaction by a strong magnet. The solution retaining product was placed in the refrigerator to obtain pure crystalline products in good-to-high yields.

Scheme 2. Preparation of CuFe₂O₄ NPs

All the products were known compounds identified by characterization of their melting points (as indicated in Table 3) by comparison with those authentic literature samples and also in some cases their FT-IR, ¹H and ¹³C NMR spectral data.

Selected Spectral Data for 3,3-Dimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (4a)

Yellow crystals. IR (KBr) (ν_{max} , cm^{-1}): 3353, 3278, 2954, 1508, 1380, 1345. ¹H NMR (500 MHz, DMSO-*d*₆): δ_{H} (ppm): 1.20 (3H, s, CH₃), 1.80 (3H, s, CH₃), 2.49 (2H, s, CH₂), 2.61 (2H, s, CH₂), 5.77 (1H, d, *J* = 9 Hz, CH), 6.36 (1H, d, *J* = 9 Hz, NH), 6.52 (1H, m, CH), 6.62 (2H, m, CH), 6.96 (1H, m, CH), 7.32 (2H, d, *J* = 14 Hz, CH), 8.00 (2H, d, *J* = 14 Hz, CH), 8.93 (1H, s, NH).

RESULTS AND DISCUSSION

In this work, we have synthesized CuFe₂O₄ NPs *via* thermal decomposition of Cu(NO₃)₂ and Fe(NO₃)₃ in the presence of sodium hydroxide. After that, the synthesized magnetic NPs were separated by an external magnet and washed with water and dried in an air oven overnight at 80 °C. Finally, the catalyst was ground in a mortar and pestle and kept in a furnace at 700 °C to produce CuFe₂O₄ NPs (Scheme 2). Moreover, we continued this study by subjecting 5,5-dimethylcyclohexane-1,3-dione and OPDA to react with aromatic aldehydes in the presence of 10% mmol of CuFe₂O₄ NPs under ball-milling for condition optimization. The mixture was introduced into a stainless steel jar (10 ml). The reaction vessel was closed and fixed on the vibration arms of a ball-milling apparatus, along with two stainless balls of 7.0 mm diameter, using a second parallel jar to equilibrate the system. Then, both vessels were vibrated vigorously at

a frequency of 28 Hz at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, a physical magnetic filtration of the catalyst and after that an aqueous workup afforded compound 4a-n in high yield.

As indicated in Table 1, the reaction of OPDA, 3-nitrobenzaldehyde and 5,5-dimethylcyclohexane-1,3-dione was also carried out in the presence of various amount of the nanocatalyst.

We have prepared copper ferrite NPs as described by Baghbanian *et al.* [24]; and characterized them by powder X-ray diffraction (XRD), EDX with elemental analysis and FT-IR analyses.

The synthesized CuFe₂O₄ NPs were analyzed by powder X-ray diffractometry (XRD) to identify the crystalline phase. Figure 1 shows the XRD patterns of CuFe₂O₄ NPs and recycled CuFe₂O₄ NPs after 4 runs. It was found that there is no significant changes in the crystalline structure of CuFe₂O₄ NPs after several runs.

The surface morphology of CuFe₂O₄ was investigated by SEM, as shown in Fig. 2. As seen in this figure, the nanocatalyst has nearly spherical shape and uniform size with an average size of 50.98 ± 11.85 nm. As a result, SEM image can confirm the nanosized structure and morphology of this catalyst. The result of the EDX analysis of the CuFe₂O₄ NPs is illustrated in Fig. 3. It confirms the presence of copper, oxygen and iron elements in the nanocatalyst. In the FT-IR spectrum of CuFe₂O₄ NPs, there are two characteristic peaks at 400 and 600 cm^{-1} related to iron oxide and copper oxide, respectively (Fig. S4).

Catalytic Application of CuFe₂O₄ in the Synthesis of 4-Substituted-1,5-benzodiazepine Derivatives 4a-n

According to the results summarized in Table 1, the

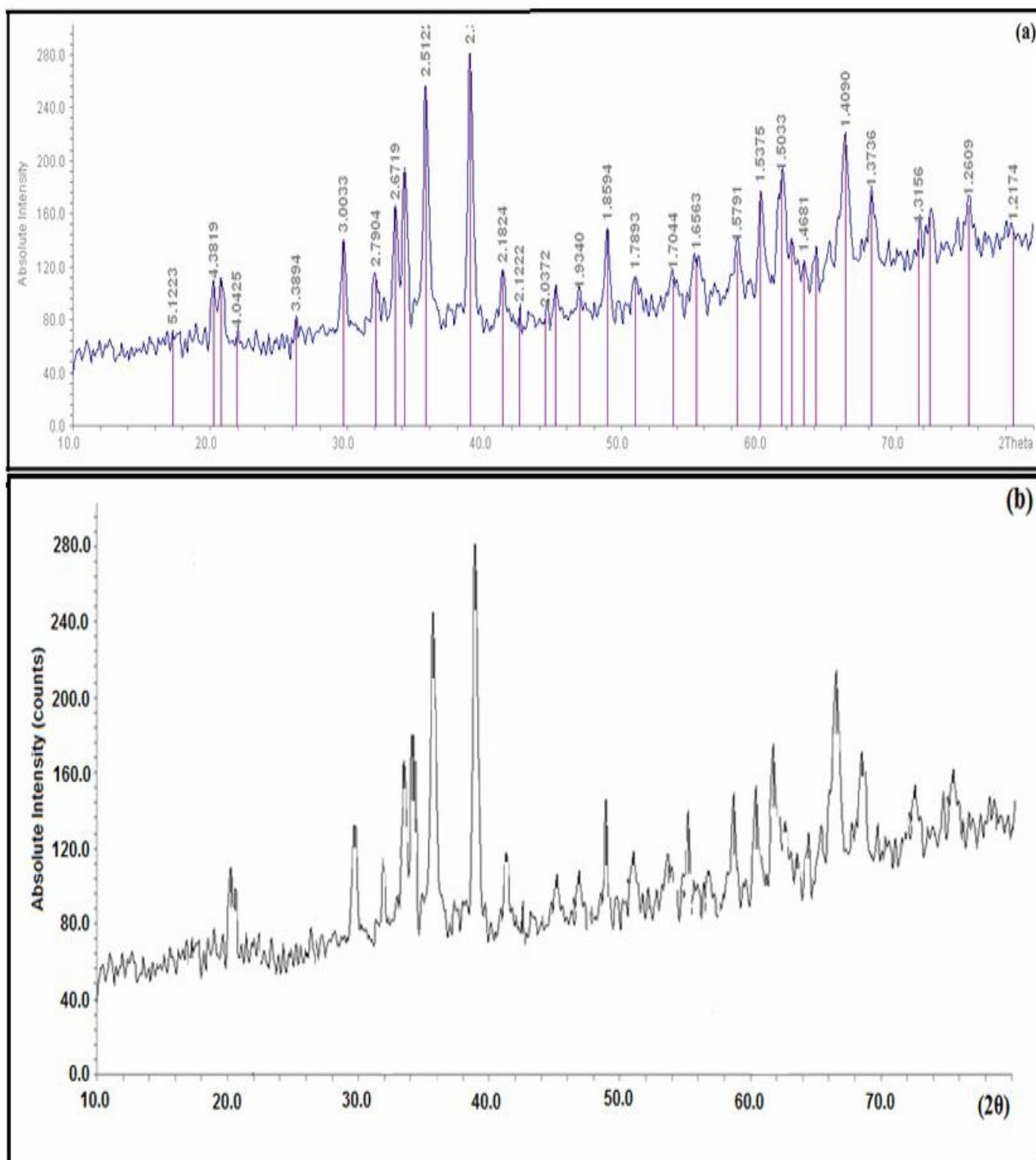


Fig. 1. XRD patterns of (a) CuFe₂O₄ NPs and (b) recycled CuFe₂O₄ NPs.

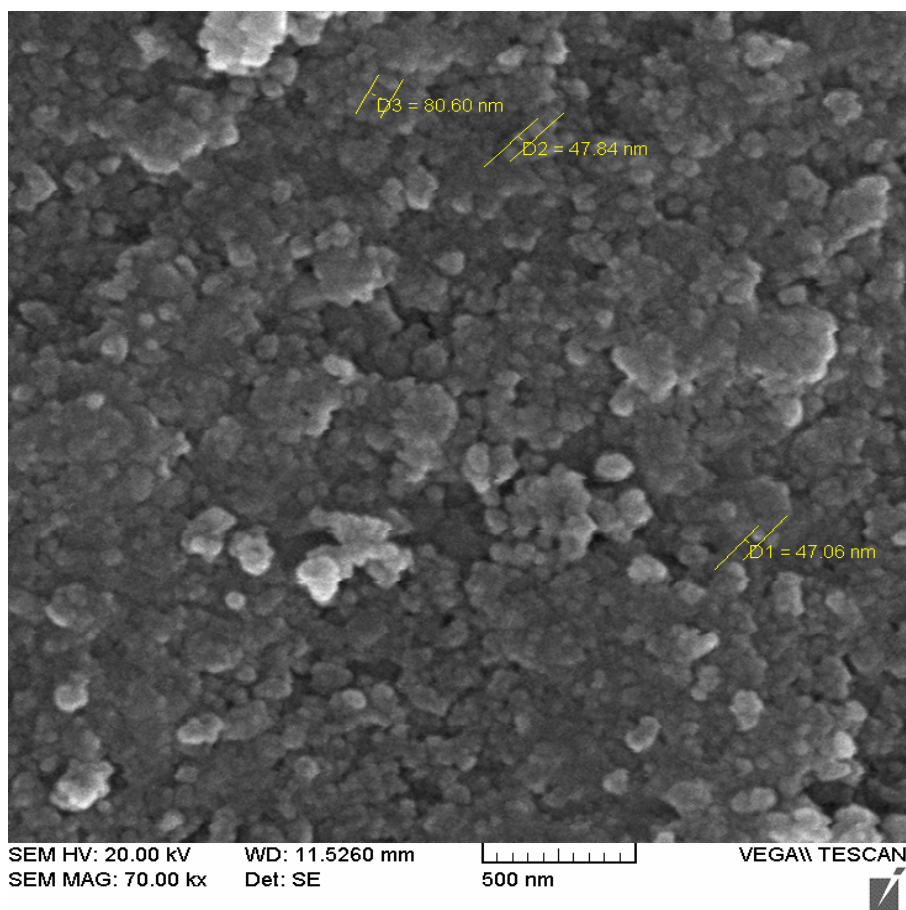


Fig. 2. SEM image of CuFe_2O_4 NPs.

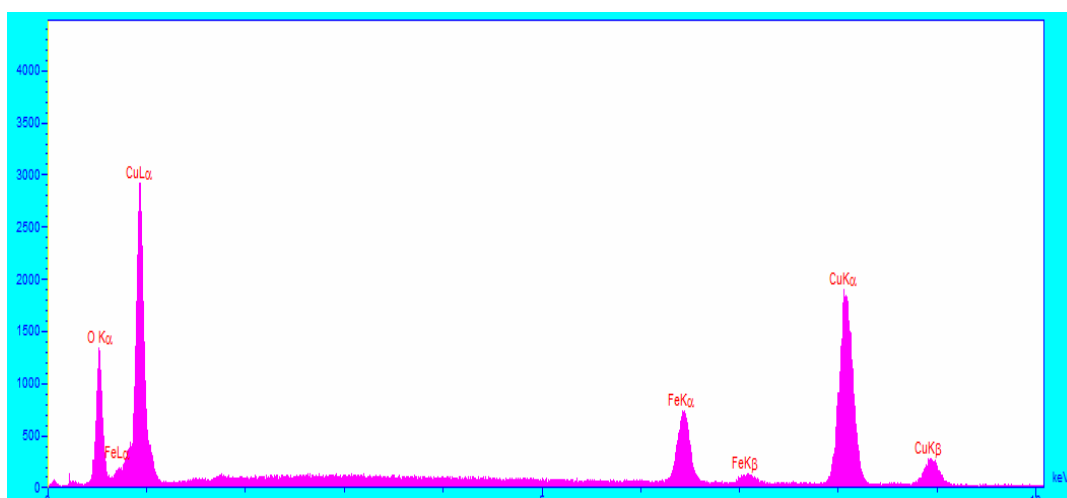


Fig. 3. EDX analysis of CuFe_2O_4 NPs.

Table 1. Screening the amount of CuFe₂O₄ Nanocatalyst on the Model Reaction

Entry	Amount of catalyst (g)	Time (min)	Yield (%) ^a
1	0.004	25	20
2	0.023	25	82
3	0.046	25	98
4	0.069	25	90
5	-	40	trace

^aIsolated yields.**Table 2.** Comparison of the Effect of some Catalysts with CuFe₂O₄ NPs on the Model Reaction

Entry	Catalyst	Solvent	Temp. (°C)	Time (min)	Yield (%) ^a	Ref.
1	MeSO ₃ H	EtOH	Reflux	50	65	[1]
2	Nano-Fe ₃ O ₄	EtOH	Reflux	16	55	[1]
3	ZnS NPs	EtOH	Reflux	60	51	[1]
4	Fe ₃ O ₄ @chitosan	EtOH	r.t.	120	91	[25]
5	CuFe ₂ O ₄ NPs	Solvent-free	Reflux	25	91	This work

^aIsolated yields.

optimal results for the model reaction of OPDA (1 mmol), 4-chlorobenzaldehyde (1 mmol), and 5,5-dimethylcyclohexane-1,3-dione (1 mmol) are obtained under ball-milling conditions at room temperature. It is illustrated that using 0.046 g of the CuFe₂O₄ NPs is sufficient to complete the reaction after 25 min in 98% yield to give 4d.

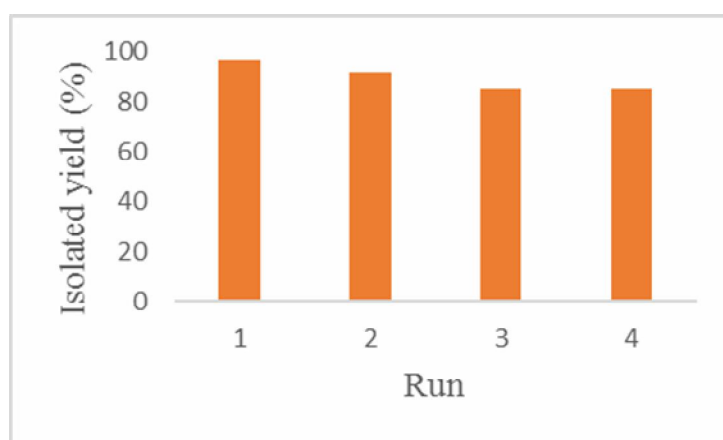
After that, as it can be seen in Table 2, a comparison was done between the present work and earlier reports for the synthesis of 4d. The results clearly demonstrate the superiority of the present work in saving time, energy and high yields of the products and also the reusability of the nanocatalyst.

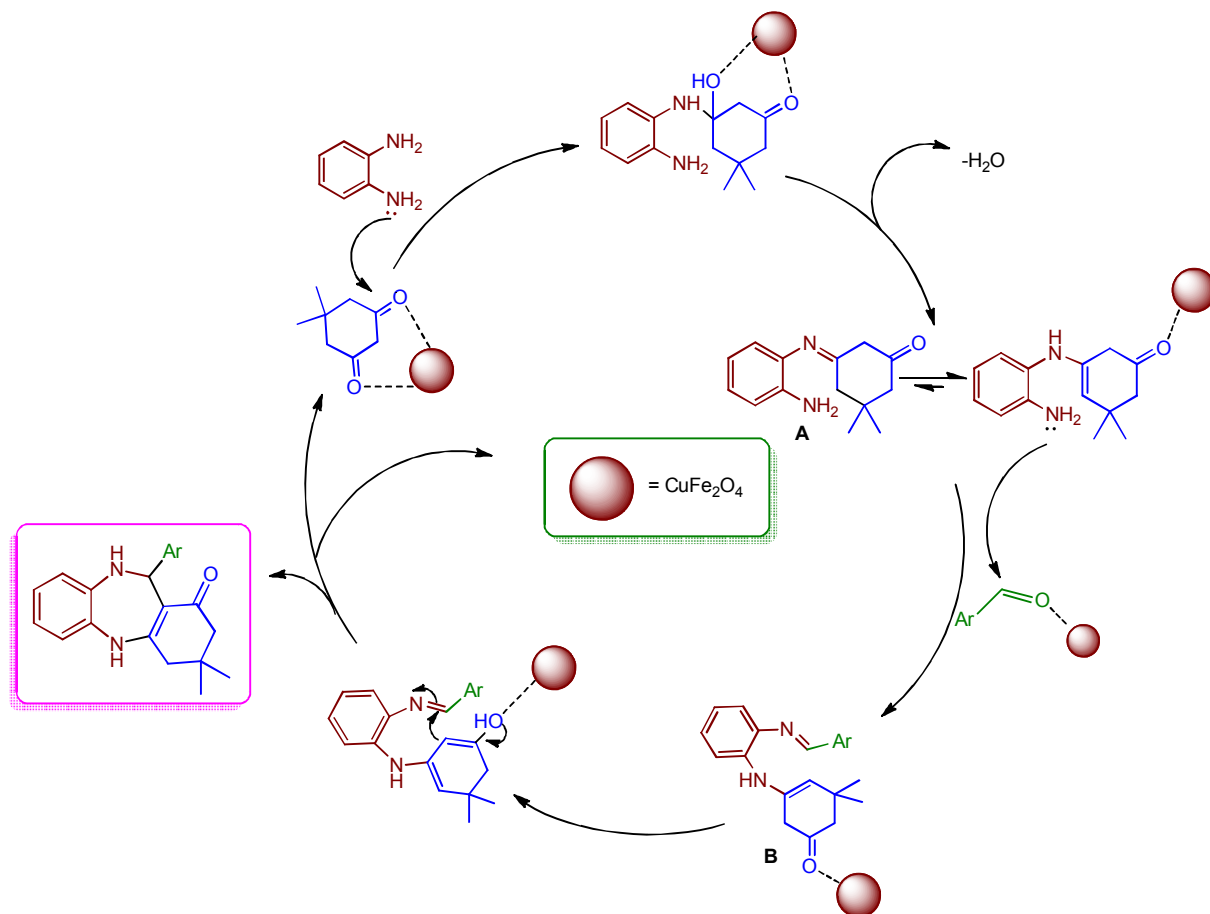
After optimization of the reaction conditions, In order to investigate the scope and generality of these conditions synthesis of a variety of 4-substituted 1,5-benzodiazepine derivatives was studied under the optimized reaction conditions. The results summarized in Table 3 show that all products are obtained in high- excellent yields after the appropriate reaction times.

Another important aspect of this active, non-toxic, and eco-friendly heterogeneous nanocatalysts CuFe₂O₄ is its high degree of recyclability. It is shown that the CuFe₂O₄ could be recovered and reused several times in the subsequent runs by using the same recovered catalyst without considerable loss of catalytic activity

Table 3. Synthesis of Benzodiazepine Derivatives 4a-n in the Presence of CuFe₂O₄ NPs

Entry	Ar	Product	Time (min)	Yield (%) ^a	Mp (°C)	
					Observed	Literature
1	4-Nitrophenyl	4a	25	98	275	274-275 [25]
2	3-Nitrophenyl	4b	25	97	145	144-146 [25]
3	2-Nitrophenyl	4c	25	91	230	230-232 [1]
4	4-Chlorophenyl	4d	25	91	237	235-237 [25]
5	2-Chlorophenyl	4e	25	90	232-233	233-235 [25]
6	2,4-Dichlorophenyl	4f	30	83	251-252	252 [25]
7	4-Hydroxyphenyl	4g	40	88	225	225 [25]
8	2-Hydroxyphenyl	4h	40	85	158	158-159 [25]
9	3-Hydroxyphenyl	4i	40	81	288-290	287-289 [1]
10	4-Methylphenyl	4j	34	87	134	134-136 [25]
11	4-Methoxyphenyl	4k	37	76	229	229-231 [1]
12	4-Dimethylamino phenyl	4l	46	68	230-231	228-230 [25]
13	Thiophene-2-carbaldehyde	4m	43	84	228	227-229 [25]
14	2-Furfural	4n	45	86	215-216	216-218 [25]

^aIsolated yields.**Fig. 5.** Recycling of CuFe₂O₄ NPs in the synthesis of 4b.



Scheme 3. The proposed reaction mechanism for the synthesis of benzodiazepines

(Fig. 5).

A plausible mechanism for the reaction is described in Scheme 3. The reaction underwent initial nucleophilic addition and subsequent dehydration to generate intermediate A. Then, the intermediate A was condensed with aromatic aldehydes to give B, which is then converted into the final product 4 through intramolecular [6 + 1] cyclization [25-27].

CONCLUSIONS

In summary, we have introduced CuFe_2O_4 NPs as a magnetically recoverable and reusable nanocatalyst and applied in the synthesis of organic compounds. Then, efficient synthesis of substituted benzodiazepines were

carried out starting from simple and readily available precursors including 5,5-dimethylcyclohexane-1,3-dione, OPDA and aromatic aldehydes. A large number of unique properties in this catalyst have caused to short reaction times, easy workup procedure, reusability of the catalyst, high atom economy, excellent yields and environmentally-benign reaction conditions. Furthermore, this method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution.

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