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Original Research

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Magnetic Nanoparticles Functionalized with Benzo[d]oxazole as an Efficient and Recyclable Magnetic Catalyst for the Synthesis of 1,4-dihydropyridine Derivatives from Barbituric Acid

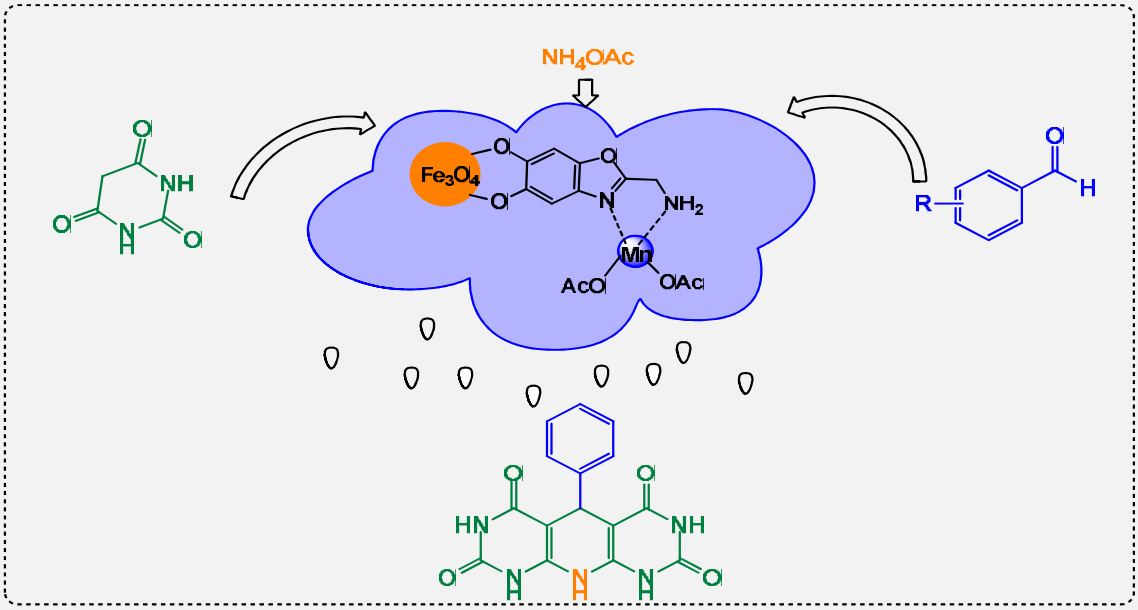
Salma Ichie[1]*, Fernando Soler[2]

[1] Department of Analytical chemistry, Mexico University, Mexico.

[2] Department of Organic Chemistry, National Autonomous University of Mexico.

Mail corresponding-author: salmaichie90@gmail.com

ABSTRACT: 1,4-dihydropyridines have a wide range of biological and medical effects and play an important role in the construction of natural products and drugs. These compounds form a group of drugs used to treat cardiovascular diseases. These compounds have biological effects such as bronchodilator, antidiabetic, antianginal, anti-AIDS, anticancer, blood pressure lowering, liver protective, etc. The synthesis of these compounds has attracted great attentionand therefore various methods for their preparation have been described. The main goal of the research was to obtain new 1,4-dihydropyridine derivatives in the presence of the Fe_3O_4@benzo[d]oxazole@Mn catalyst. In the first step, the catalyst was prepared and then the one-pot four-component reaction between barbituric acid, aromatic aldehydes, and amine was studied in the presence of the Fe_3O_4@benzo[d]oxazole@Mn catalyst. The channelizer was then evaluated using various techniques. This catalyst can be recycled for seven consecutive periods.



KEYWORDS: 1,4-dihydropyridines, Anti-AIDS, Fe_3O_4@Benzo[d]oxazole@Mn, Barbituric Acid.

Introduction

Today, chemistry plays a very important role in the development and quality of human life, and due to the important role of chemistry in the new civilization, many risks from chemical processes threaten

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human health and the environment [1,2]. The main challenge of recent chemists is the development of processes and methods that are economically, socially and environmentally beneficial [3]; Therefore, green chemists are looking to be able to replace the current processes with healthier chemical processes, or to provide healthier products to the society by replacing healthier raw materials or performing reactions in safer conditions [4,5]. Heterocyclic compounds are compounds with a cyclic structure and containing heteroatoms such as (N, O, S)[6] . These compounds have wide applications in the pharmaceutical and medical industries and have antibacterial, antifungal, antiviral, anti-inflammatory and anticonvulsant properties, as well as a medicine for the treatment of migraine and activities related to the organs in the abdominal cavity and the immune system of living beings, which during In recent years, they have been widely studied and investigated [7,8]. The most common heterocyclic compounds have nitrogen and oxygen atoms or both of them in the ring structure [9]. Nitrogenous heterocycles are very important from the point of view of medicine and biology, and the most common of these compounds include pyrrole and its analogs combined with benzene, such as indole, as well as pyridine and its analogs with benzene, such as quinoline and isoquinoline, as well as heterocycles with several heteroatoms, such as imidazole and oxazoles [10]. In recent years, much attention has been paid to the synthesis of nitrogenated heterocycles due to the medicinal importance and biological properties of these compounds. This group of compounds exists widely in nature and plays an effective role in daily life [11].

Synthesis of new derivatives of 1,4-dihydropyridines containing heterocyclic rings (oxygen and nitrogen atoms) at C4 position [12]. The reaction is performed in a one-pot and three-component manner in the presence of the acidic heterogeneous nanocatalyst of sulfonated magnetic cellulose [13]. According to the conducted studies, the compounds of five and six-membered nitrogenous heterocycles, which include more than one heterocycle ring in the molecule, can give new and significant biological properties to the molecule [14]. The ring of 1,4-dihydropyridine compounds is one of the most important heterocyclic rings that includes a wide range of medicinal compounds, for example, antagonistic properties and blood pressure control [15]. 1,4-Dihydropyridine with different substitutions at C4 position has always been considered by chemists and during the past decades, many efforts have been made to prepare new derivatives, improve the method and increase the yield of these compounds [16]. Metal nanoparticles have been widely used as catalysts in many chemical reactions [17]. The problem in this connection is that particles with a size smaller than 100 nm can hardly be separated from the reaction mixture by filtering and it will be necessary to use a supercentrifuge [18]. In order to overcome this weakness, magnetic nanoparticles can be used, magnetic nanoparticles have a high potential in the field of nano-catalysis. Among the Fe_3O_4 magnetic nanoparticles, it has been used as a catalyst in chemical reactions both directly and as a substrate and support for the catalyst [19]. Easy, high stability and easy separation from the reaction system using an external magnetic field [20]. Therefore, among metal nanoparticles, magnetic iron oxide nanoparticles have been used the most as catalyst retainers. In recent years, a large number of researchers have focused their research on different methods of manufacturing and characterizing these [20]nanoparticles, which can be divided into several general categories [21]. Synthesis in the liquid phase includes co-precipitation, soluthermal, chemical reduction, microemulsion and thermal degradation. Heterogeneous acidic nanocatalysts have been considered in the synthesis of organic compounds because they can provide a green and efficient environment for organic reactions [22]. The advantages of these catalysts include ease of preparation, low toxicity of the catalyst, compatibility of the reaction conditions with the environment, short reaction time, and their recyclability [23].

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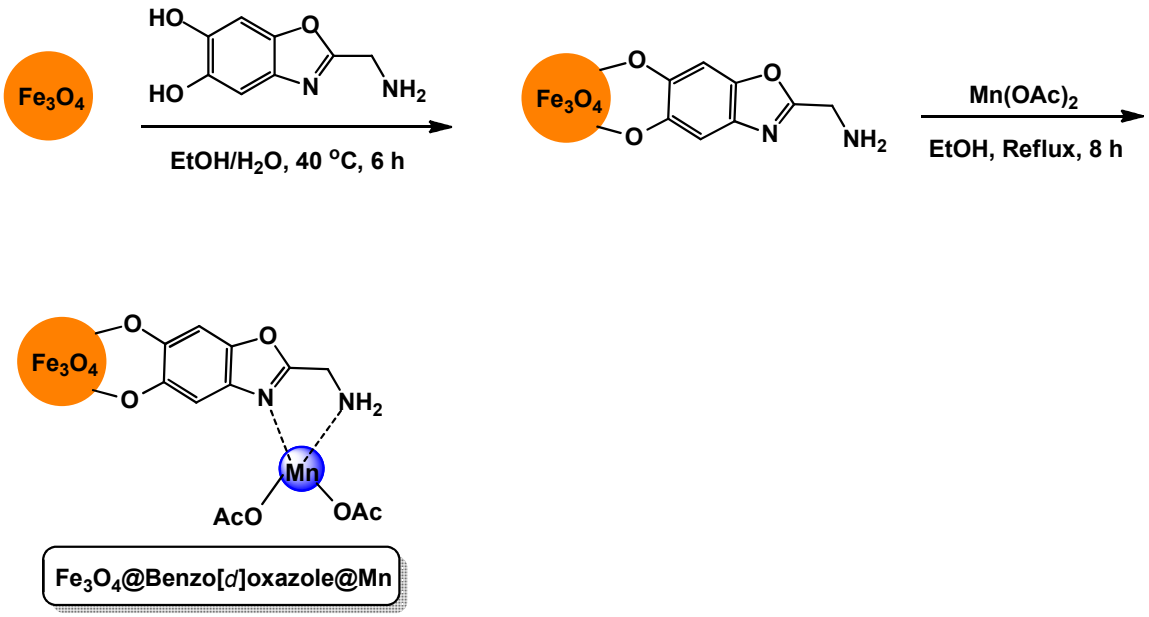
Among the magnetic catalysts, 2-(aminomethyl)benzo[d]oxazole-5,6-diol attached to Fe_3O_4 nanoparticles has been reported as a cheap, non-volatile and recyclable catalyst for the synthesis of 1,4-dihydropyridines. It has been reported for the synthesis of 1,4-dihydropyridine derivatives through the reaction of ammonium acetate with aromatic aldehydes and barbituric acid in the presence of Fe_3O_4@Benzo[d]oxazole@Mn as an efficient and recyclable catalyst in ethanol solvent.

Results and Discussion

Nanocatalyst Fe_3O_4@Benzo[d]oxazole@Mn, which was obtained from the reaction of Fe_3O_4 nanoparticles with 2-(aminomethyl)benzo[d]oxazole-5,6-diol, is shown in **Scheme 1**. Then it was identified by VSM and TGA spectroscopy methods and its properties were checked by these techniques and finally it was used in the synthesis reaction of 1,4-dihydropyridine. In the following, the results of these analyzes will be discussed.



Scheme 1. Experimental details of the fabrication of Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst.

VSM

The synthesized nanocatalyst has magnetic properties, so a magnet is used to separate it. A vibrating sample magnetometer was used to discuss the magnetic property of Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst. The hysteresis diagram was drawn in 20,000 to -20,000 Oersted fields (**Figure 1**). As it can be seen, the magnetization curve of the particles passes through the origin, and the coercive field and residual magnetization are not observed in them, which shows that the nanoparticles have superparamagnetism, which is the saturation magnetization value their gr/emu is 28/91.

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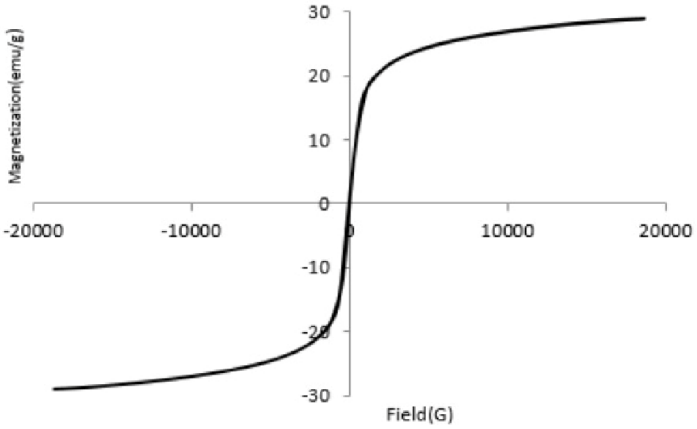

Figure 1. Hysteresis curve of Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst.

TGA

The results of thermal thermogravimetric analysis of Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst are shown in **Figure 2**. These investigations were carried out in the temperature range of 0 to 800 degrees Celsius, which is related to the thermal stability of the sample and the amount of chemical absorption of the synthesized compound. The process of weight loss in the temperature range of 200-400 °C is attributed to the loss of moisture and the destruction of organic compounds. The first weight loss in the temperature range of 212-220 °C is attributed to the evaporation of water molecules absorbed by nanoparticles. The second weight loss in the range of 600-640 °C is due to the evaporation of organic molecules remaining in the structure of the nanocatalyst. The presence of organic groups and water molecules in the structure of the synthesized nanocatalyst was proved as an impurity; Therefore, these studies show that during this temperature range, the Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst is completely thermally stable.

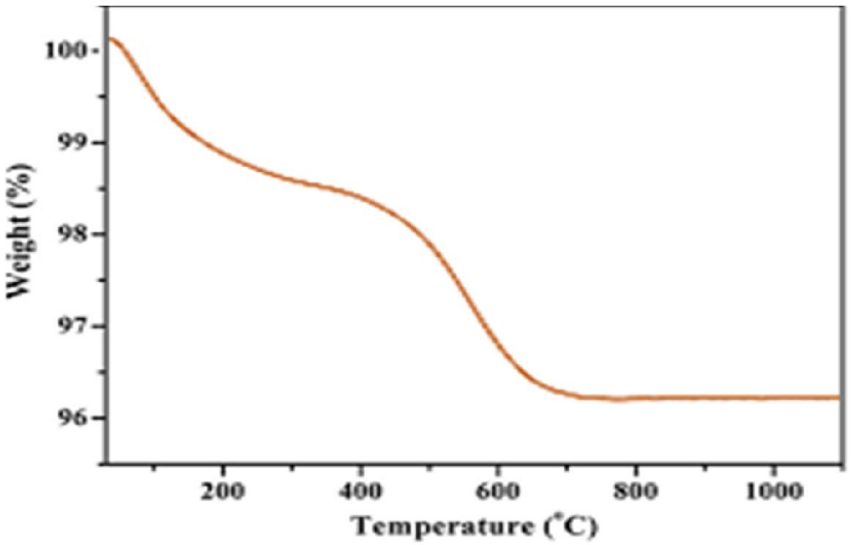

Figure 2. Graph of thermogravimetric decomposition of nanocatalyst Fe_3O_4@Benzo[d]oxazole@Mn.

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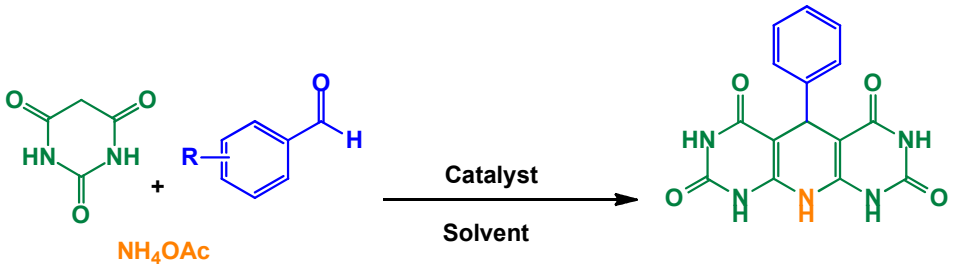
Table 1 shows the optimization of reaction conditions. In order to optimize the amount of catalyst, the reaction was performed in the presence of different amounts of Fe_3O_4@Benzo[d]oxazole@Mn (0.05, 0.1 and 0.2 mmol) (**Table 1, entries 1-5**). Satisfactory results were obtained in the presence of 0.2 mmol nanocatalyst. In the presence of smaller amounts of catalyst, the reaction time was prolonged and the yield of the product decreased. In the absence of a catalyst, even after a long time, the reaction did not take place (**Table 1, entry 6**). The use of amounts greater than 0.2 mmol did not affect the yield of the product. In order to study the solvent effect, the reaction was investigated in different polar and non-polar solvents such as chloroform, ethanol and hexane. The results showed that the reaction was less efficient in the presence of non-polar solvents. Polar solvents have the ability to promote the reaction (**Table 1, entries 7-13**). The reaction was carried out in ethanol solvent with 98% efficiency (**Table 1, entry 4**). The effect of temperature on the reaction was also investigated. The intended reaction was carried out at temperatures of 40 and 75 °C in an oil bath. Applying high temperatures did not have much effect on yield. The results showed that the optimal reaction for the synthesis of 1,4-dihydropyridine derivatives is the one-pot reaction of benzaldehyde (1 mmol) with barbituric acid (2 mmol) and ammonium acetate (1.2 mmol) in the presence of a catalytic amount (20 mg) was carried out in ethanol solvent at a temperature of 75 °C. After 1 h, 98% of the desired product 4a was obtained (**Table 1, entry 4**).

Table 1. Optimization parameters for the MCRs reaction in the presence of Fe_3O_4@Benzo[d]oxazole@Mn nanocatalyst.



3a

Entry	Catalyst (mg)	Temperature (°C)	Solvent (Tem °C)	Time (min)	Yield (%) [a]
1	5	75	EtOH	120	43
2	10	76	EtOH	60	61
3	15	75	EtOH	60	79
4	**20**	**75**	**EtOH**	**60**	**98**
5	25	75	EtOH	60	85
6	--	75	EtOH	120	--
7	20	75	DMF	60	70
8	20	45	EtOH	60	61
9	20	45	DMSO	60	49
10	20	75	Hexane	60	21
11	20	rt	THF	60	59
12	20	75	H_2O	60	70
13	20	75	CCl_4	60	12

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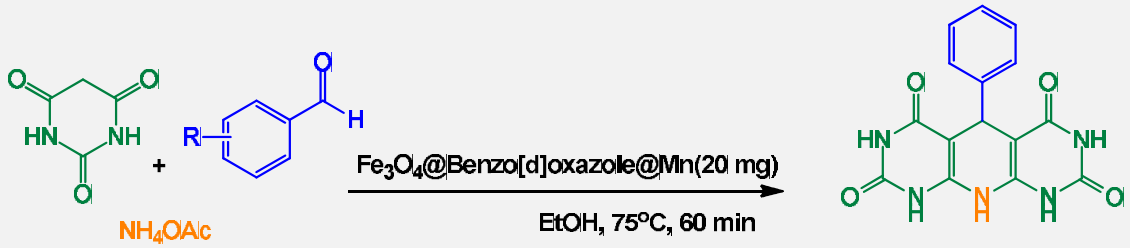
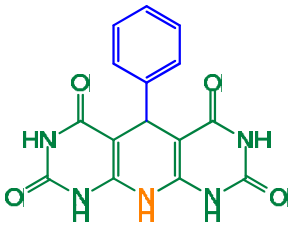
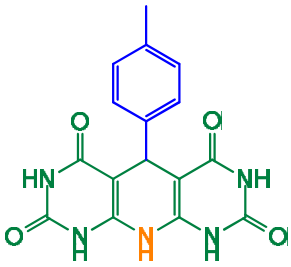
The study of this method on different aldehydes under optimized conditions showed that the reaction of different types of aldehydes with electron-donating and killing substituents can be performed with high efficiency and within 60 minutes at 75°C temperature (**Table 2**).

Table 2. Synthesis of 1,4-dihydropyridine derivatives using Fe_3O_4@Benzo[d]oxazole@Mn as a catalyst.

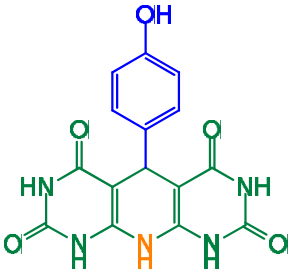




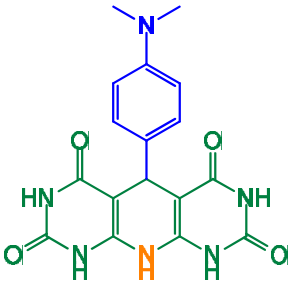
4a (98%)



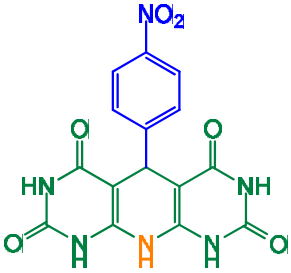
4b (97%)



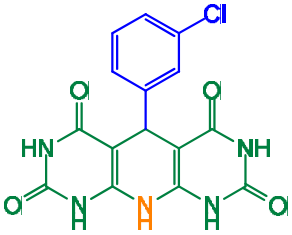
4c (95%)



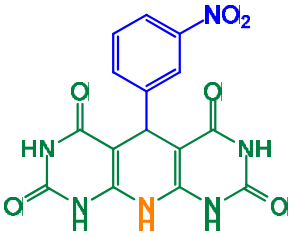
4d (92%)

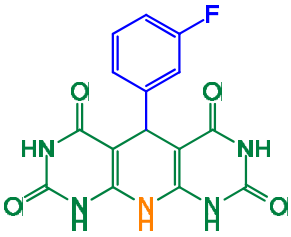


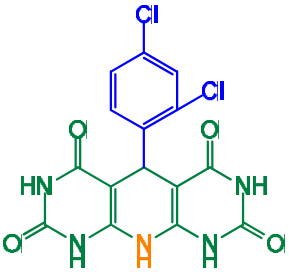
4e (88%)



4f (90%)







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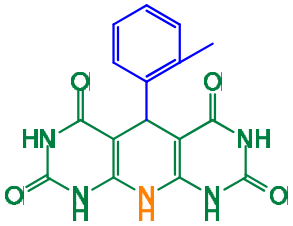
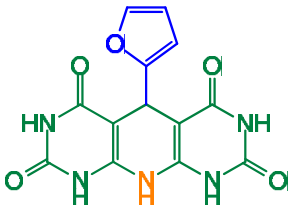
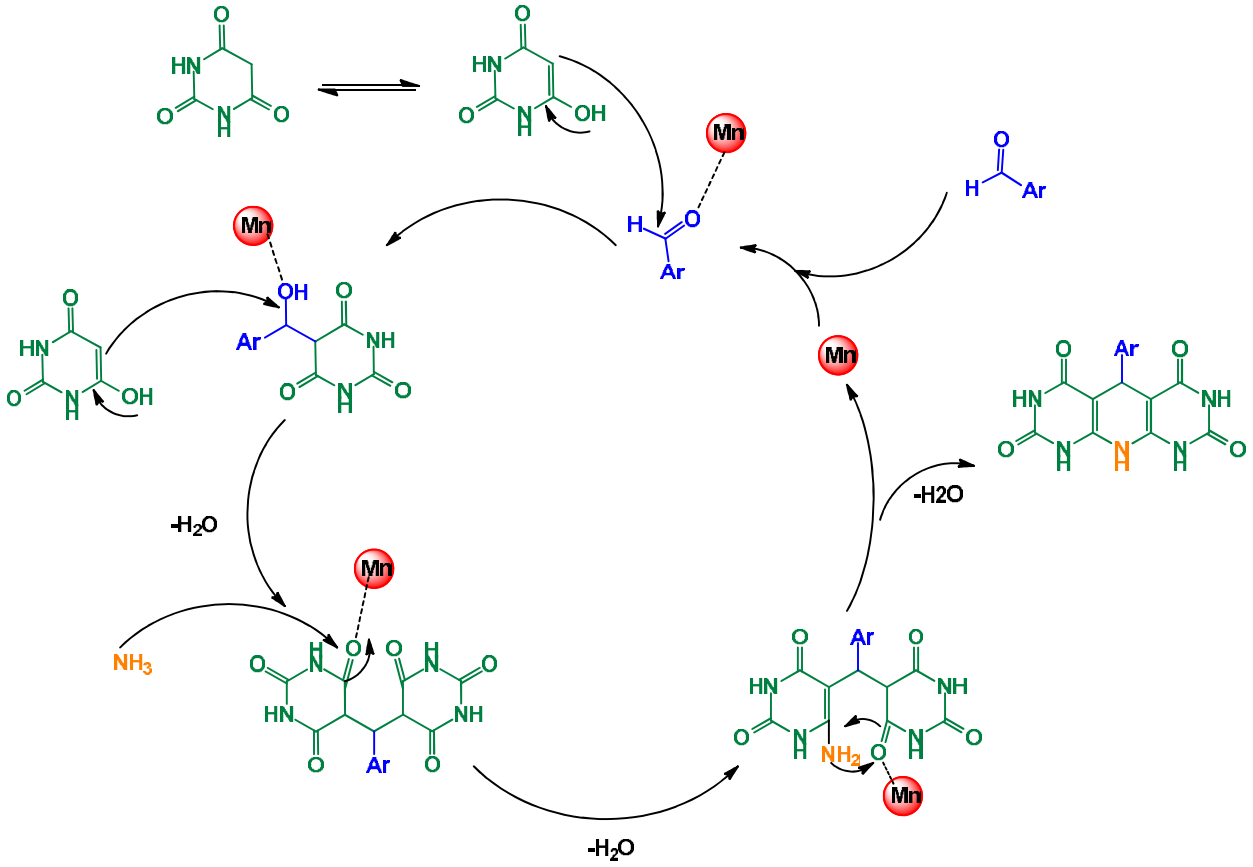
4g (91%)	4h (89%)	4i (87%)
		
4j (91%)	4k (88%)	

The possible mechanism of 1,4-dihydropyridine synthesis in the presence of Fe_3O_4@Benzo[d]oxazole@Mn catalyst is shown in **Scheme 2**. Aldehyde and barbituric are converted to benzyl alcohol barbituric in the presence of Fe_3O_4@Benzo[d]oxazole@Mn catalyst. Benzyl alcohol in the presence of another barbituric and catalyst leads to the production of bisaryl barbituric. The reaction turns pale yellow, which can be a sign of intermediate formation. Amine is added to the reaction vessel. The target product is prepared through the relevant intermediates.



Scheme 2 . Proposed mechanism for the preparation of product 4a.

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Figure 3 shows the diagram of recycling and reuse of Fe_3O_4@Benzo[d]oxazole@Mn nanoparticles in reaction Hantzsch. One of the important advantages of magnetic catalysts is the ability to recycle and reuse them in the same reaction. Nanoparticles Fe_3O_4@Benzo[d]oxazole@Mn without losing their magnetic properties maintain the ability of the reaction catalyst even after several steps. After the first use in the reaction, these magnetic nanoparticles were separated from the reaction medium with the help of a simple magnet and washed several times with distilled water. Then, it was heated at 85 degrees Celsius for 4 hours to dry. As can be seen, the magnetic nanoparticles maintained their catalytic and magnetic ability after 7 consecutive uses.

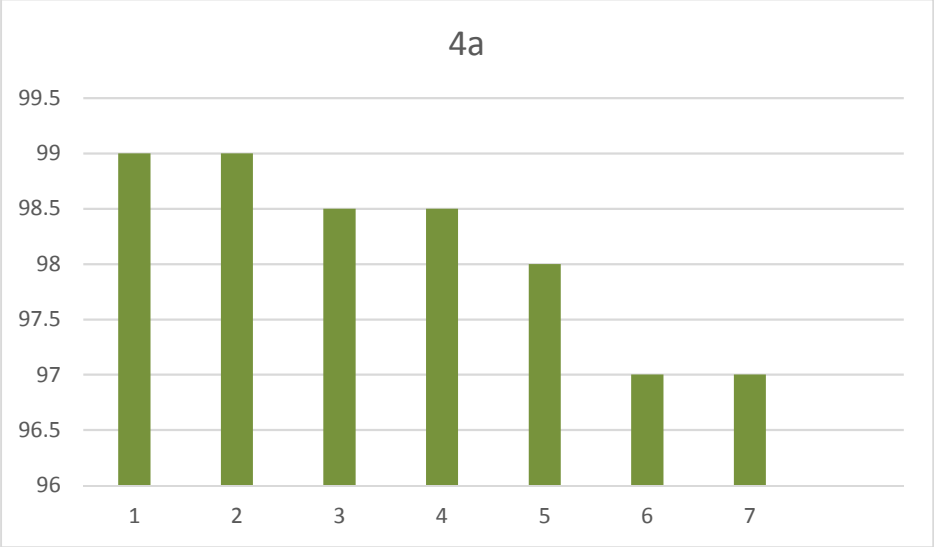

Figure 3. Reusability of Fe_3O_4@Benzo[d]oxazole@Mn catalyst in the synthesis of product 4a.

■ Conclusion

Considering that our goal is to prepare a heterogeneous acid catalyst that can be easily separated, therefore by coating Fe_3O_4 with 2-(aminomethyl)benzo[d]oxazole-5,6-diol, in addition to making the catalyst heterogeneous, it is prepared to Easy separation of nano-catalyst also helps, so it reduces the contamination of the products and also prevents the wastage of the catalyst.In this research, a number of new welded derivatives were synthesized during a four-component one-pot reaction in the presence of Fe_3O_4@Benzo[d]oxazole@Mnas a suitable catalyst with excellent yields and relatively short times. The reaction proceeded with aryl aldehydes with electron-donating and killing substitutions.

■ Experimental

Most of the chemicals used in this research were obtained from Sigma Aldrich and Merck German companies. Most of the solvents used were purchased from domestic companies. The reactions were performed on a heater. The progress of the reactions was monitored by thin layer chromatography (TLC) using Merck 60F254 silica gel plates, and the desired compound was observed by ultraviolet light irradiation or by impregnation with iodine vapors. Petroleum ether and ethyl acetate solvents were used for (TLC). The prepared products were prepared, separated and purified by extraction, recrystallization

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and thin layer chromatography techniques. Melting points were recorded by an electrothermal device. Melting points are uncorrected. Infrared IR spectra were recorded by Shimadzu spectrophotometer model IR-470 in the form of KBr tablets. 1H-NMR and 13C-spectra were recorded by Brooker model DRX400 MHz AVANCE spectrometer. Chemical shifts in δ (ppm) relative to tetramethylsilane TMS as internal standard δ = 0 ppm are provided. Coupling constants are expressed in Hertz (Hz).

Preparation of MNPs-CPTMS

Following dispersion of MNPs-CPTMS nanoparticles (1.5 g) in 250 mL of ethanol/water (1:1) with sonication for 30 minutes, 2-(aminomethyl)benzo[d]oxazole-5,6-diol (2.5 mL) was added. Under N_2 atmosphere, the reaction mixture was stirred at 40 ^oC for 6 hours. The nanoparticles were dispersed in ethanol using sonication five times, and then separated using magnetic decantation. The nanoparticle product (MNPs-CPTMS) was dried at room temperature.

Preparation of the Fe_3O_4@Benzo[d]oxazole@Mn Catalyst

Fe_3O_4@Benzo[d]oxazole (2.5 g) in absolute ethanol (50 mL) was mixed with $Mn(OAc)_2$ (5 mmol) and stirred under reflux for 8 hours. Magnetic decantation was then used to separate the synthesized nanosolid (Fe_3O_4@Benzo[d]oxazole@Mn). Several times absolute ethanol was used to wash and dry the nanomagnetic catalyst at room temperature under a vacuum.

General method of Synthesis of 1,4-dihydropyridine Derivatives

In a 50 ml liter flask, 1 ml of aldehyde, 2 ml of barbic acid generator, 1.2 ml of ammonium acid generator were added to 20 ml of warm Fe_3O_4@Benzo[d]oxazole@Mn catalyst in 5 ml of ethanol. The mixture was stirred at 75°C for the required time. After the end of the reaction, which was controlled by thin layer chromatography, the reaction mixture was cooled, then 10 ml of dilute sodium bicarbonate solution was added to it, and the mixture was produced with ethyl acetate reaction. The resulting phase was dried with Na2SO4. The obtained solution was placed under vacuum. After evaporation of the solvent, the nebulization method in ethanol is used to further purify the product.

Supporting Information

5-(4-nitrophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone

(4e): White solid; m.p: 216-218 ^0C; Yield 88%; ^1H NMR (500 MHz, DMSO) δ ppm: 5.87 (s, 1H), 6.91 (d, 2H, J= 10.0 Hz), 6.98-7.03 (m, 2H, J= 10.0 Hz), 7.07 (s, 1H), 10.05 (s, 4H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 30.83, 91.85, 114.69, 114.86, 129.09, 129.15, 141.54, 151.57, 159.82, 161.72.

5-(3-fluorophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone

(4h): White solid; m.p: 297-300 ^0C; Yield 89%; ^1H NMR (500 MHz, DMSO) δ ppm: 6.04 (s, 1H), 7.03 (s, 1H, NH), 7.41-7.45 (m, 2H), 7.80 (s, 1H), 7.88-7.89 (d, 1H, J= 1.5Hz), 9.98 (s, 4H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 31.72, 91.12, 120.61, 121.96, 129.76, 134.65, 148.54, 148.95, 151.48, 165.62.

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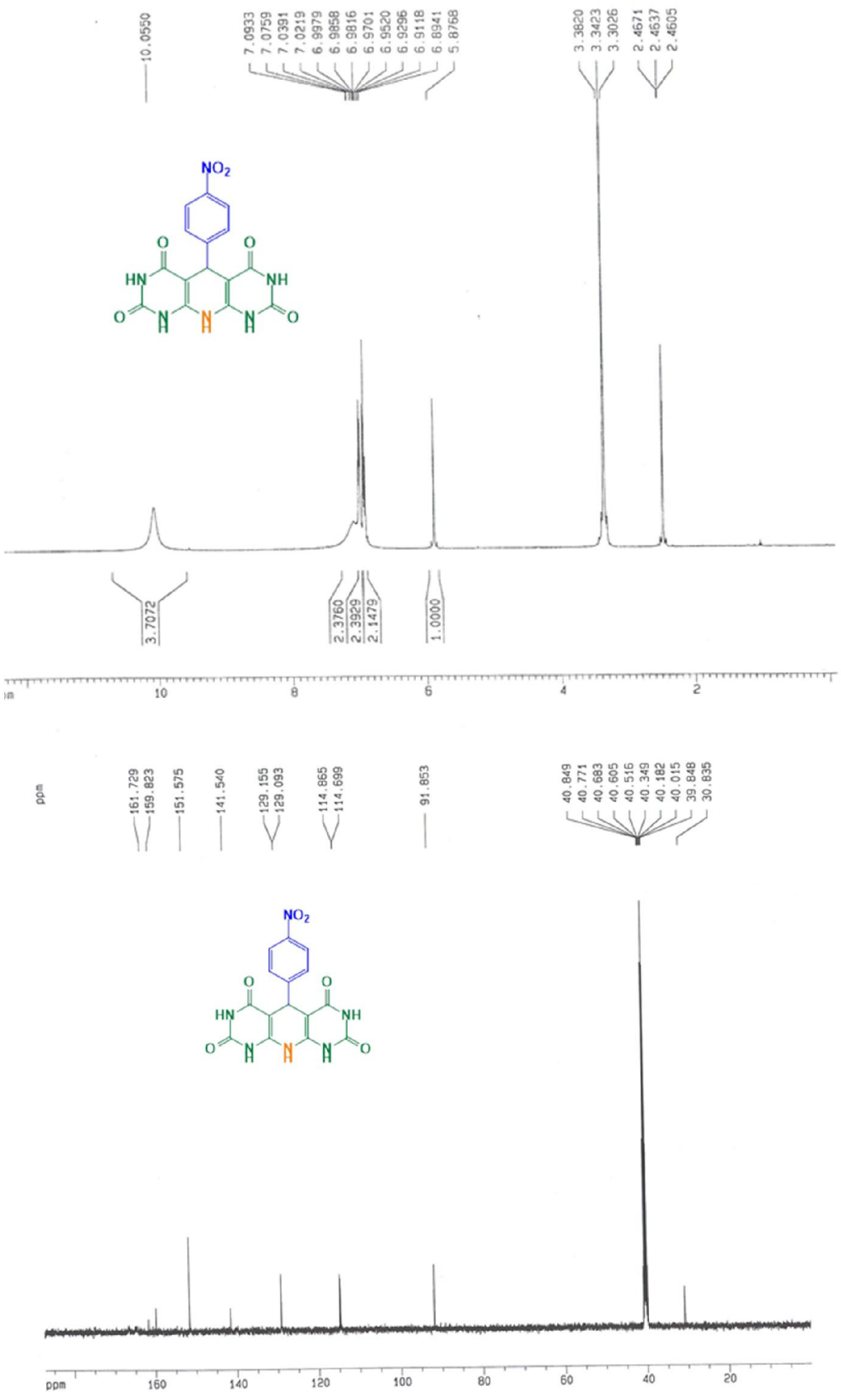

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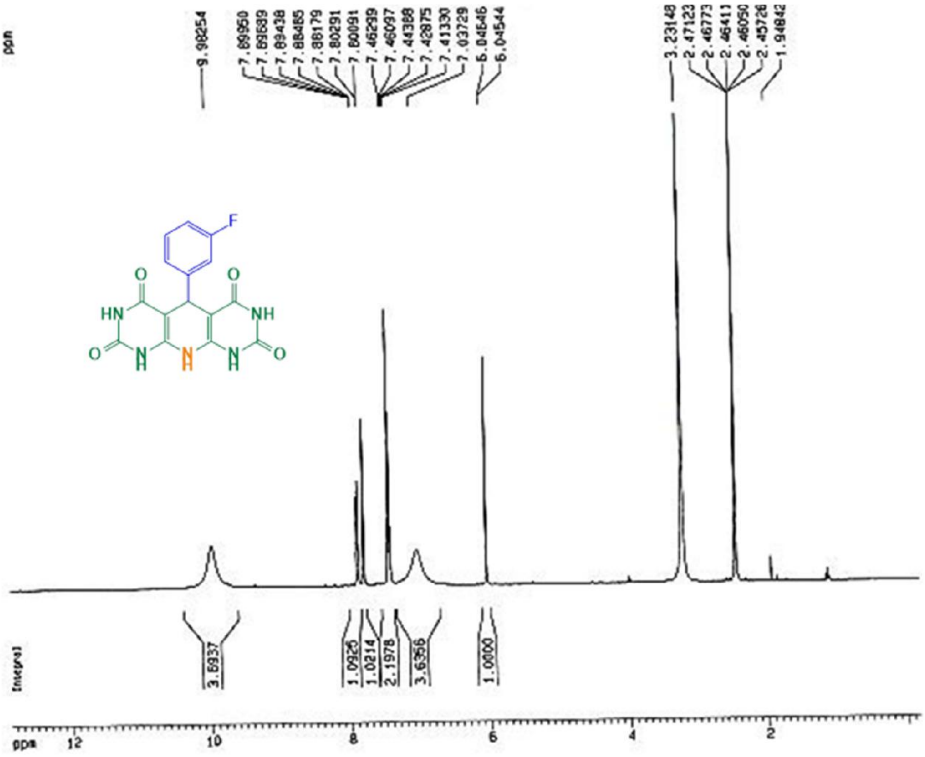

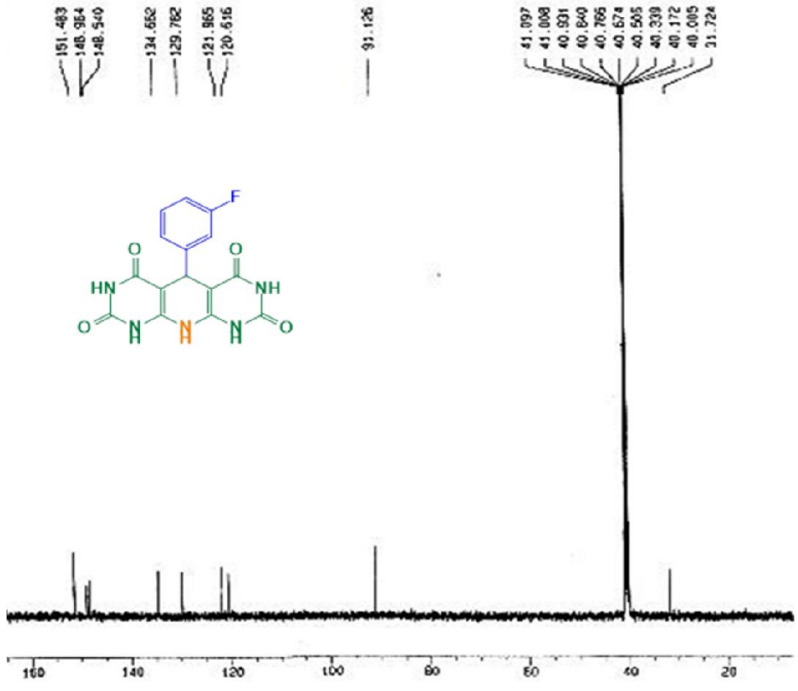

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