

Biological and Molecular Chemistry

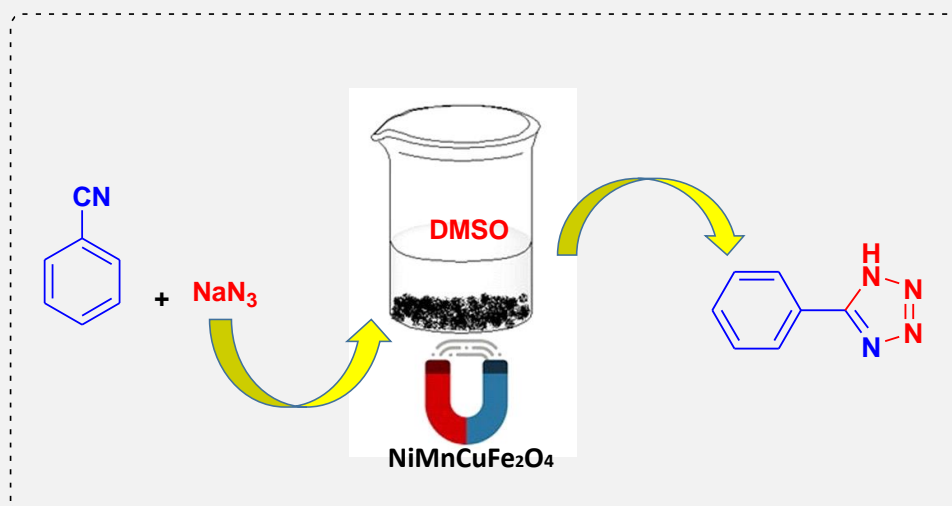
Magnetic Heterogeneous Catalyst $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$: Its Efficiency in the Synthesis of Tetrazole Heterocycles with Biological Properties

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ABSTRACT: Tetrazoles are an important group of nitrogen-rich heterocycles. These compounds have wide applications in energetic materials, pharmaceutical industries, disease treatment, biochemistry, agriculture, biological imaging, and photography. In this article, first the $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst was synthesized by the conventional hydrothermal method and then identified by inductively coupled plasma analysis, TGA, and VSM. Also, this catalyst has magnetic properties. The activity of the heterogeneous magnetic catalyst $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ for the synthesis of a wide range of H1-tetrazole derivatives from the ring addition reaction [2-3] of nitrile derivatives and sodium azide in DMSO solvent at 100 °C was checked. The main advantages of this method are its high yield, simplicity, easy product separation, and catalyst recovery. This catalyst can be easily separated from the reaction mixture by using an external magnet and used for five cycles without significant reduction in catalytic activity.

**KEYWORDS:** Tetrazoles, $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$, Hydrothermal, Reaction [2-3].

■ Introduction

Today, despite many advances in the field of diagnosis and treatment of malignant diseases, cancer is still the second leading cause of death in the world [1]. Various methods are used to treat cancer, including surgery, radiotherapy, chemotherapy, hormone therapy, and gene therapy. In most treatment protocols, chemotherapy plays the main role along with other common methods [2]. Many main compounds have

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been introduced for chemotherapy and many new compounds have been designed, developed and evaluated against cancer cells. Azoles play an important role in drug therapy and chemotherapy [3]. Currently, the framework of azoles includes Imidazole, Triazole and Tetrazole. And it is considered as the main living and basic structure for the synthesis of a wide range of effective antiviral, anti-inflammatory, anticonvulsant, antifungal, antibacterial, and antitumor agents [4]. For example, compounds with ethyl substitution have antiviral effect, indanyl tetrazole derivatives have anti-inflammatory activity, and compounds with hydrogen and amine substitution have anticonvulsant effect [5]. Also, tetrazolium derivatives have been used as antibacterial compounds (such as sefonisid and flumoxef) in humans. Tetrazoles are a group of synthetic organic heterocyclics that have a ring containing four nitrogens and one carbon [6]. Dimethyl thiazolyl diphenyl tetrazolium bromide (MTT) is a well-known tetrazole that is used to evaluate cell viability. In recent years, many attempts have been made to synthesize and use new tetrazole derivatives for use as analgesic, antihypertensive, antibacterial, antifungal, and anticancer agents [7]. Some of these drugs have entered the pharmaceutical market in many countries, such as Losartan and Valsartan. In some of these derivatives, tetrazole is used as the main component in the synthesis of metal complexes [8]. For example, the antitumor activity of platinum II complexes synthesized from tetrazoloquinolines has been investigated [9].

A part from medicinal applications, nitrogen-rich rings also find use in photography, biological imaging, and explosives research. Since tetrazoles have N=N and C-N bonds, they have a positive heat of formation [10]. By burning these compounds, a large amount of N₂ gas is released into the atmosphere, which is the most abundant gas in the atmosphere [11]. There will be no environmental pollution from using these compounds. When energy-rich materials are used conventionally, they often contain high levels of carbon, which produces a large amount of carbon dioxide, carbon monoxide, and unburned carbon particles like soot during combustion [12]. These pollutants pollute the environment and cause many problems. Due to their less toxicity, less smoke production, and greater power, these materials can be used in place of TNT [13]. Also, due to their high potential energy and low sensitivity to impact and friction, they are widely used as green energy materials in military industries, propellants, the production of pyrotechnic products with less smoke, and gas generators, and they show less sensitivity to heat and shock [14]. Due to the widespread use of tetrazoles in various fields of synthesis, the tetrazole core has received attention in the last two decades [15]. Among the various methods that have been proposed for the synthesis of substituted tetrazoles, the most common method is the 1,3-dipolar ring addition of nitriles and organic/mineral azides, which was first reported by Hantsch and Vogt [16]. The previously reported methods had disadvantages such as the use of expensive and toxic organometallic azide complexes such as tin or silicon, very sensitive reaction conditions to humidity, the use of amine salts, strong Lewis acid and hydrazoic acid which are very toxic, explosive and volatile [17]. In 2001, Demko and Sharpless reported a green method for the synthesis of these compounds in water and in the presence of stoichiometric amounts of zinc (II) salt catalysis. The reaction was carried out at high temperatures (170-140 °C) for aromatic nitriles with steric hindrance [18]. High or inactive alkyl nitriles are one of the disadvantages of this method. Various homogeneous and heterogeneous catalysis systems have been reported for the synthesis of tetrazoles with different substitutions. In homogeneous catalysis processes, the method of separation and recovery of catalysts has limited their use [19]. Therefore, the replacement of heterogeneous catalysts is very desirable due to their very easy separation and ability to recover and reuse them and has attracted increasing attention [20]. Among the heterogeneous catalysts, the use of magnetic particles as a catalyst makes the catalyst separation process much easier at the end of the reaction, and by applying an external magnetic field, it

can be easily separated and recovered from the reaction environment [21]. On the other hand, reduction of the active surface is one of the disadvantages of heterogeneous catalysts [22]. Therefore, due to the widespread use of tetrazolium derivatives and the possibility of separating and recovering heterogeneous catalysts, in this research, the preparation, identification and application of magnetic catalyst $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ was considered.

■ Results and Discussion

One of the main goals in selecting these catalysts is to investigate the simultaneous effect of Cu and Ni elements along with Mn. The synthesis of this catalyst was done for the first time by hydrothermal method. An outline of its synthesis method is shown in Fig. 1..

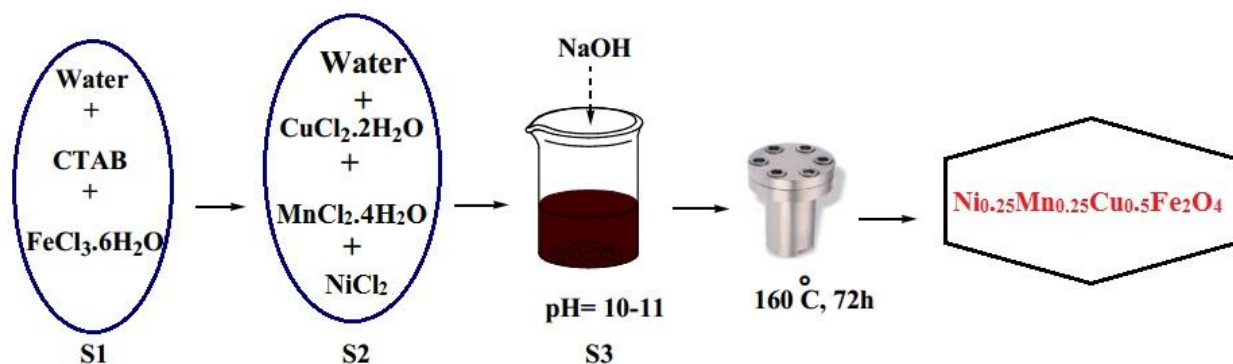


Figure 1. The synthesis of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst.

The percentage of components contained in the catalyst structure was ascertained using the inductively coupled plasma method to guarantee that it was proper. One of the emission spectroscopic techniques, inductively coupled plasma, uses plasma created by an inert gas, primarily argon, to help atomize samples. The obtained results fully agree with the intended formula ($\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$). The stated analysis findings are displayed in Table 1.

Table 1. Determining the percentage of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst elements by method ICP.

Sample title	Fe (mass %)	Cu (mass %)	Ni (mass %)	Mn (mass %)
$\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$	30.98	8.09	5.18	4.26

The magnetic properties of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst were measured by a vibrating sample magnetometer. The loop hysteresis curve of this catalyst is shown in Fig. 2. The magnetometric results of the vibrating sample show that this catalyst is magnetic and its saturation magnetization is 29 emu/g, while this value is reported for Fe_3O_4 magnetic nanoparticles, 55 emu/g. These magnetic properties allow easy and quick separation of the catalyst from the reaction mixture using an external magnet.

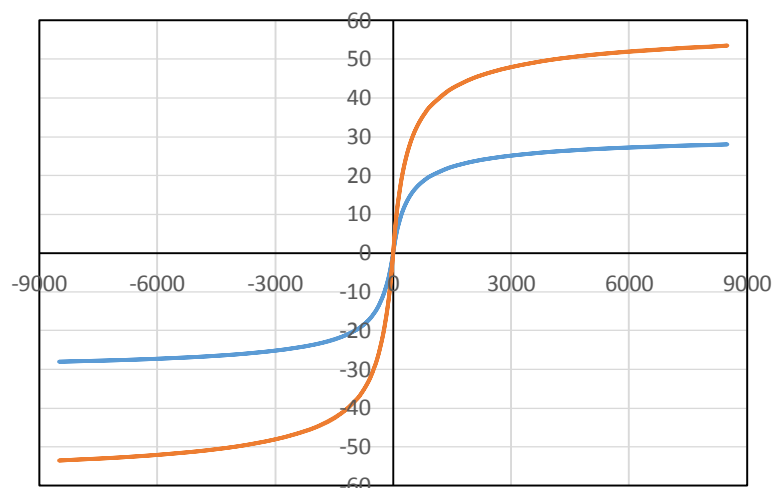


Figure 2. VSM magnetization curve of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst.

The thermal stability of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst was investigated by thermal gravimetric analysis in argon atmosphere at a speed of 10 K/min. **Fig. 3** shows that the catalyst has a weight loss of 6.5% up to a temperature of about 210 degrees Celsius, which can be due to the presence of moisture in the catalyst. Therefore, the $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst has a very good stability in the reaction conditions (temperature of 120 °C).

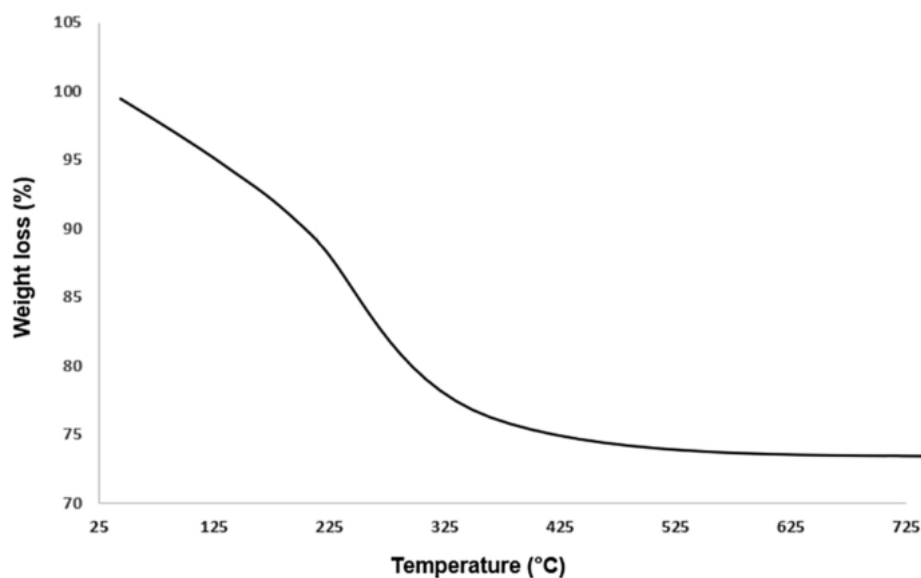
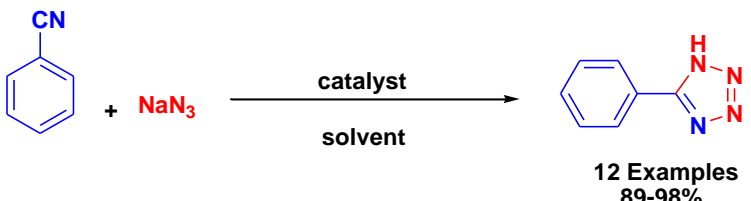


Figure 3. TGA of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst.

Selecting the optimal reaction conditions that provide the maximum yield in the shortest amount of time requires examining the characteristics and factors affecting the tetrazole synthesis reaction. The kind of solvent, temperature, and catalyst quantity are the three most crucial variables. To ascertain the ideal circumstances, the cyclization reaction [2–3] between sodium azide and benzonitrile was selected as a model reaction. The outcomes demonstrate that yield and reaction time are significantly impacted by the

solvent's composition. This reaction is greatly enhanced by aprotic solvents (such as alcohol or water) that do not possess the solvation power of dian (azide ion) (**Table 2**). High temperatures are also helpful for this process. Temperatures above 100 °C cause the reaction efficiency to remain constant, whereas temperatures below 100 °C cause it to decline. Additionally, the ideal quantity of catalyst was established. Less than 0.02 grams of catalyst was linked to a relative decrease in reaction efficiency; however, no discernible change in reaction efficiency was seen at quantities more than 0.02 grams. Consequently, the ideal amount of this catalyst was determined to be 0.02 grams. Furthermore, the catalytic mechanism employed in this reaction demonstrated no sensitivity to oxygen or air. As a result, no inert environment was used throughout any of the processes.

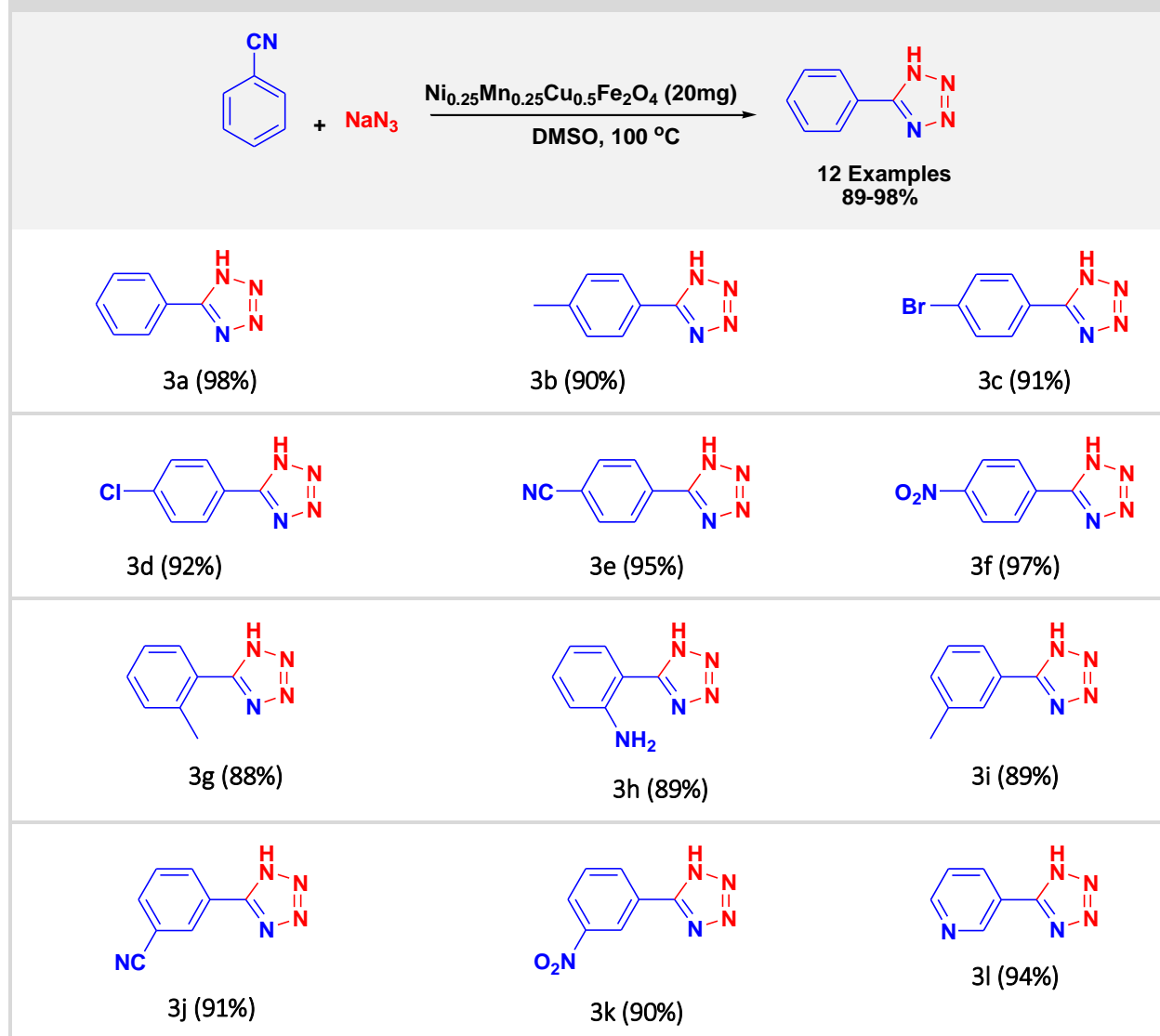
Table 2. Optimizing the reaction conditions of 5-phenyl-H1-tetrazole synthesis in the presence of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst^a



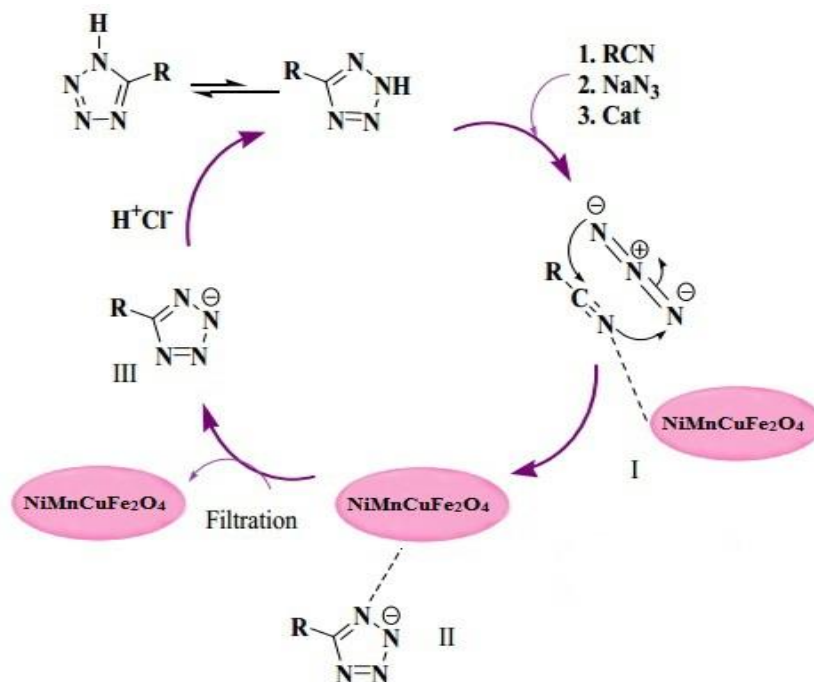
Entry	Catalyst (mg)	Solvent	Tem (°C)	Yield (%) ^a
1	--	DMSO	100	No
2	5	DMSO	100	25
3	10	DMSO	100	60
4	10	DMSO	60	29
5	15	DMSO	100	69
6	15	DMSO	60	38
7	20	DMSO	RT	71
8	20	DMSO	60	68
9	20	DMF	100	86
10	20	Water	100	41
11	20	EtOH	100	63
12	20	DMSO	100	98

^a Isolated yields

Investigating the ring addition reaction [2-3] with different types of benzonitrile derivatives and sodium azide makes it possible to make a correct and logical judgment about the effectiveness or not of the catalyst in this reaction. The results of this study, which are compiled in **Table 3**, show the effectiveness of this catalyst in this reaction. Among the factors affecting the efficiency of this reaction, we can mention the type of substitution attached to benzonitrile. Due to the fact that the cyclization reaction of sodium azide and nitrile is carried out by the attack of the azide ion as a diene on the center of nitrile (diene-friendly), when the substituent attached to the diene-friendly is an electron-withdrawing group, making this center more positive increases the rate of cyclization and ultimately the reaction speed of tetrazole synthesis. The position of this substitution is also very effective in the speed of the loop reaction, so that substitution in the para position is more efficient.

Table 3. Scope of reaction of benzonitrile and sodium azide in the presence of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ ^a^a Isolated yields

Scheme. 1 It shows an acceptable proposed route for the synthesis of tetrazole with substitution at 5 position in the presence of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst. At first, the interaction of nitrogen and azide atoms with the catalyst that contains metal ions leads to the formation of intermediate I, which leads to the acceleration of the cyclization stage. Also, this interaction leads to an increase in the electron-loving nature of CN group nitrogen and the reaction speed. Increases ring formation. The ring addition reaction [2-3] between the C≡N bond of nitrile and azide ion is easily performed by the formation of intermediate II. After separating the catalyst from the reaction mixture, the protonation of compound III is done with HCl and the tetrazole product is obtained.



Scheme 1. Proposed mechanism for tetrazole synthesis.

A heterogeneous catalyst's capacity to be recycled is essential to its effectiveness. Apart from its exorbitant cost, copper poses a significant constraint on catalyst performance. This limit can be somewhat reduced because copper can be recycled and used repeatedly for this purpose. Less than one unit reduction was attained after six reuses of the same compound, as **Fig. 4** illustrates. For five cycles in a row, Ni_{0.25}Mn_{0.25}Cu_{0.5}Fe₂O₄'s high activity and selectivity were maintained.

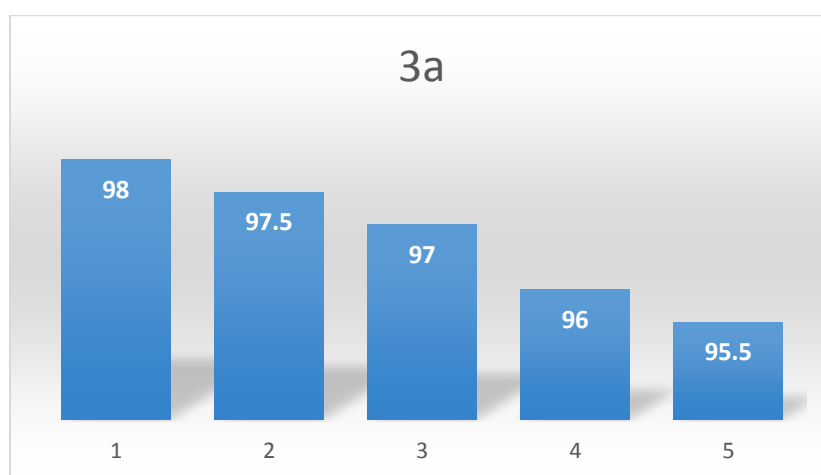


Figure 4. Reusability of Ni_{0.25}Mn_{0.25}Cu_{0.5}Fe₂O₄ catalyst in the synthesis of product 3a.

Conclusion

Using a hydrothermal technique, the magnetic catalyst $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ was first created in this study. A vibrating sample magnetometer was used to examine the catalyst's magnetic characteristics and its heat stability was assessed using TGA. Then, in the cyclization process [2–3] of nitrile derivatives and sodium azide, its catalytic characteristics were studied for the production of H1-tetrazole derivatives with 5-position. These reactions produced extremely good yields of H1-tetrazole derivatives with transference at the 5-position when 0.02 g of catalyst was added to DMSO solvent at 100 °C. The most efficient reaction was one involving substituents that withdrew electrons in the para position. The fact that this catalyst may be recovered, reused, and has a short half-life are some of its benefits.

■ Experimental

Materials and devices used

All materials and solvents needed for the reactions were purchased from Fluka, Aldrich and Merck companies and were used without purification. The melting point was measured by an electrothermal device and the values are reported without correction. Infrared spectra were recorded using potassium bromide tablets and Nicollet 800. The progress of tetrazole synthesis reactions was followed by thin layer chromatography method. Magnetic resonance spectra of hydrogen and carbon nuclei (500 and 125 MHz respectively) were recorded by Bruker Avance device and in all cases tetramethyl silane was used as internal standard. Dispersion of particles was carried out using Elma digital terasonic ultrasound machine. The magnetic properties of the particles were investigated using a magnetometer.

Synthesis of $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ catalyst by hydrothermal method

In a 100 ml Erlenmeyer flask equipped with a magnetic stirrer, 1 gr (2.74 mmol) of cetyltrimethylammonium bromide (CTAB) was dissolved in 35 ml of distilled water and stirred with a magnetic stirrer until complete dissolution. Then 1 gr (3.7 mmol) of Fe(III) chloride hexahydrate ($\text{FeCl}_6 \cdot 6\text{H}_2\text{O}$) was added to it and the solution was stirred for 15 minutes in order to completely dissolve Fe(III) chloride at ambient temperature (Solution No. 1). In another Erlenmeyer flask, 0.157 gr (1.1 mmol) of copper(II) chloride dihydrate ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$) was dissolved in 15 ml of distilled water and stirred at room temperature with a magnetic stirrer. After complete dissolution. This compound, 0.15 grams (0.46 mmol) of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ was slowly added to this solution with stirring. Then 0.063 gr (0.45 mmol) Ni(II) chloride (NiCl_2) was added to the solution and stirred for 15 minutes until its complete dissolution (Solution No. 2). Stirring was added (solution number 3). The pH of solution number 3 was adjusted to about 10 to 11 using 5 M NaOH. Finally, solution number 3 was transferred to an autoclave and heated in an oven at 160 °C for 72 hours. After 3 days, the autoclave was removed from the oven and cooled at ambient temperature, and the precipitate was washed several times with distilled water and dried at room temperature. 0.6 gr of brown solid catalyst $\text{Ni}_{0.25}\text{Mn}_{0.25}\text{Cu}_{0.5}\text{Fe}_2\text{O}_4$ was obtained.

General method for the synthesis of tetrazoles

In a 10 ml flask equipped with a magnetic stirrer, 1 mmol of nitrile derivative, 1.3 mmol of sodium azide, 0.02 g of catalyst and 2 ml of DMSO solvent were mixed together and heated at 100 °C. The progress of the reaction was followed by thin layer chromatography in 30-minute intervals, and in the best solvent ratio (n-hexane and ethyl acetate). After finishing the reaction and cooling the reaction mixture at ambient

temperature, the catalyst was separated from the reaction mixture with a magnet. Then, 10 ml of ethyl acetate, 10 ml of distilled water and 5 ml of HCl (5 molar) were added to the filtered solution. The organic and aqueous phases were separated and in order to complete the extraction of the product, 10 ml of ethyl acetate, 5 ml of distilled water and 5 ml of HCl (5 ml) were added to the aqueous phase and the separation of the phases was done again. The total organic phases were dried over magnesium sulfate. After filtering the magnesium sulfate, it was evaporated by a rotary evaporator and the reaction product is tetrazole derivatives.

Supplementary Data

1-(4-(1H-tetrazol-5-yl) benzonitrile (3e): ^1H NMR (500 MHz, DMSO): $\delta_{\text{H}}= 17.18$ (br, 1H), 8.23 (d, $J= 8.2$ Hz, 2H), 8.18 (d, $J= 7.6$ Hz, 2H) ppm. ^{13}C NMR (125 MHz, DMSO): $\delta_{\text{C}}= 151.3, 138.7, 129.3, 128.2, 127.4$ ppm.

2-(1H-tetrazol-5-yl)benzonitrile (3j): ^1H NMR (500 MHz, DMSO): $\delta_{\text{H}}= 17.26$ (br, 1H), 8.14 (t, $J= 8$ Hz, 2H), 7.98 (t, $J= 8.1$ Hz, 1H), 7.85 (t, $J= 7.8$ Hz, 1H) ppm. ^{13}C NMR (125MHz, DMSO): $\delta_{\text{C}}= 134.8, 132.6, 131.4, 129.6, 127.9, 117.3, 110.1$ ppm.

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NMR spectral data

