Synthesis of (E)-2-(1H-tetrazole-5-yl)-3-phenylacrylenenitrile Derivatives Under Green Conditions Catalyzed by New Thermally Stable Magnetic Periodic Mesoporous Ognosilica Embedded With ZnO Nanoparticles

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Abstract

ZnO nanoparticles embedded on the surface of magnetic isocyanurate-based periodic mesoporous organosilica (Fe₃O₄@PMO-ICS–ZnO) was prepared through modified environmental-benign procedure for the first time and was properly characterized by appropriate spectroscopic and analytical methods or techniques used for mesoporous materials. The new thermally stable Fe₃O₄@PMO-ICS–ZnO materials with proper active sites, uniform particle size and surface area were investigated for the synthesis of medicinally important tetrazole derivatives through cascade condensation and concerted reactions as a representative of the Click Chemistry concept. The desired 5-substituted-1H-tetrazole derivatives were smoothly prepared in high to quantitative yields and good purity under green conditions. Low catalyst loading, very short reaction time and the use of green solvents such as EtOH and water instead of carcinogenic DMF as well as the possibility of easy separation and recyclability of the catalyst for at least five consecutive runs without significant loss of its activity are notable advantages of this new protocols compared to other recent introduced procedures.

Introduction

Since its first introduction by Barry Sharpless in 1999, “Click Chemistry” has been a very popular topic at the synthesis of heterocyclic compounds. In 2001, Sharpless introduced “Click Chemistry” as a set of reactions with specific characteristics such as: modular, wide-range, high-yield only to produce a harmless byproduct that can be removed by non-chromatographic separation techniques⁴⁻⁶. Synthesis of tetrazole derivatives can be achieved in an eco-friendly approach such as using green models in particular water as solvent, room temperate, easy separation, low cost and with good to excellent yields⁷⁻¹¹. 1,3-dipolar cycloaddition reactions are one of the most popular “click chemistry” reactions. When such concerted reactions are performed through multicomponent reaction (MCR) strategy, they can be widely used in the synthesis of heterocyclic compounds including tetrazole derivatives¹²⁻¹⁴. The presence of four nitrogen atoms in the heteroaromatic five-membered ring of tetrazole gives rise to electron-rich planar structural features¹⁵⁻²⁰. Furthermore, the acidic nature of tetrazoles is due to the presence of free N-H in their structure and this property can lead to the formation of more complex aliphatic and aromatic heterocyclic compounds²¹⁻²³. On the other hand, the heterocyclic tetrazole moiety can stabilize the negative charge using charge displacement and show same pKa values of the corresponding carboxylic acids.⁷ As a result, tetrazoles can be used as a metabolic substitutes (bioisoesteres) for carboxylate groups. Indeed, these two groups of compounds are similar at pKa = 4.9 and become deprotonated at physiological pH. Also, tetrazoles have higher nitrogen content than other heterocycles and require almost the same electronic space as carboxylates. Consequently, these features have improved their uses in a wide range of applications including pharmaceuticals and drug design, explosives, agrochemicals, materials science, etc.²⁴⁻³⁰ Especially, the tetrazole structures are similar to the pharmacological core of the Saran's family, which are in fact angiotensin II receptor blockers. These drugs are used to lower blood pressure and heart failure. Angiotensin II is a bioactive peptide that narrows the vessels through the contraction of the muscles around the heart.³¹ Among the most important drugs in this category of
Drugs are Losartan and Valsartan (Figure 1). Indeed, these two active pharmaceutical ingredients (API) the first of a new class of drugs to be introduced for clinical use in hypertension 32,33. Many chemical studies on other analogue compounds have preserved antibacterial and antifungal properties. Tetrazole derivatives also show anti-inflammatory, analgesic, anti-cancer, anticonvulsant and diabetic kidney disease activities26.

More than a hundred years since the invention of the first tetrazole compound, many scientists have come up with different methods for preparation of the tetrazole compounds faster, easier, and less dangerous. The most common of these methods is a 1,3-dipolar cycloaddition reaction between nitrile and azides, first reported by Hunch and Walgett in 1901 during the reaction of azide ions and hydrosodic acid under pressure during a [3 + 2] cycloaddition reaction. The chemistry approach has been achieved34–36. Sharples and his colleagues reported among the available methods an augmented [3 + 2] ring between an azide and p-toluenesulfonyl cyanide (p-TSCN) under solvent-free conditions and good yields and easy separation37–40. There are disadvantages to all these protocols that have not been applied, given the high toxicity of the materials, the explosive nature, and the low boiling point of hydrazoic acid (37 °C), the use of solvents that contaminate the environment. Hence, the use of high pressure systems has been shown an alternative to these methods. The most recent method for the synthesis of tetrazoles involves the multicomponent reactions (MCRs) strategy between aldehydes, sodium azide and nitriles. One of the advantages of this strategy is the use of available, easy and inexpensive basic compounds, namely aldehydes and sodium azide along with relatively expensive nitriles, which has made these reactions economically viable and easy to do on an industrial scale be economical and applicable41–45.

Periodic mesoporous organosilicas (PMOs) have been emerged as one of the important issues of research in recent years. PMOs materials which were reported for the first time in 1999 is a new branch of mesoporous materials, organic-inorganic hybrid with high-ordered structures have uniform pore size organic9,46–59. PMOs are essentially unique because of the advantage of combining a strong organic-inorganic porous framework, with the inherent properties of organic components49,60–63. In this regard, precursors of bridged organosilica having hetero-aromatic isocyanurate moieties with high thermal stability and low toxicity would be very desirable59,62–65. On the other hand, PMOs demonstrate unique characteristics such as large and hollow spaces, high surface area, regular cavity wall structure, low density and good membrane permeability, material loading in large quantities62,63,66–81. Therefore, PMOs have been used effectively in many applications such as catalysis, drug and gene delivery, gas and molecule absorption and sensors. Hence, we decided to use well-dispersed that have as an efficient catalyst for three component synthesis of functionalized tetrazoles in water as a green solvent and very short reaction times.

To address the above challenges, we tried to explore the catalytic activity of the new ZnO nanoparticles embedded on the surface of magnetic isocyanurate-based periodic mesoporous organosilica (Fe₃O₄@PMO-ICS–ZnO) for the cascade reaction of different aromatic aldehydes and malononitrile to
afford the corresponding Knoevenagel intermediate and subsequent $[3 + 2]$ cycloaddition with sodium azide ($\text{Scheme 1}$). Recovery and reuse of catalysts is an important aspect of catalytic reactions, especially in organic synthesis. Compared to conventional methods for catalyst separation from reactants, the use of a magnetic catalyst that is easily separated by a magnet near the reaction solution is an intelligently approach that increases separation speed, high efficiency, and less wastage catalyst and product during separation.$^{64,83,84}$

**Results And Discussion**

After preparation of Fe$_3$O$_4$@PMO-ZnO, FT-IR spectrum were used for confirmation in the synthesis of as-made catalyst is presented in **Figure 2**. During this analysis, it was observed that the O-H bond peaks in the silanol groups present on the PMO surface were at 3415 cm$^{-1}$. Also, due to the presence of heterocyclic isocyanurate within the framework of prepared nanocatalyst, sharp absorption peak was observed in 1471 and 1689, which is related to the vibrations of carbonyl and C-N in the isocyanurate rings, respectively. The signals appearing in 2889 and 2939 are related to the stretching vibrations of the aliphatic portion, and in particular the C-H bonds. The resulting wave numbers at 943, 1056, and 1108 correspond to the symmetric and asymmetric stretching vibrations of the siloxane Si-O-Si bonds. Due to the magnetic properties and presence of iron atoms, the signals at the frequency of 570 cm$^{-1}$ are due to the tensile vibration of the Fe-O-Fe bond. Zn-O bonding vibrations are a relatively weak peak at 493 cm$^{-1}$, which merges with the observed peak for Fe-O.

A vibrating sample magnetometer was used to measure the magnetism of the as-made catalytic sample at 300 K. As can be seen in the **Figure 3**, the hysteresis phenomenon is not found, and the "S" like curve is also a proof of the para magnetism of the compound synthesized at room temperature. The magnetization value was strongly enhanced by the external magnetic field strength at the low field region, with a saturation value of magnetization 50 emu/g for Fe$_3$O$_4$@PMO-ZnO at -15 K0e to 15 K0e.

Thermo gravimetric analysis (TGA) was measured for the prepared catalyst at temperatures between 40°C and 800 °C. **Figure 4** shows the weight loss of Fe$_3$O$_4$ magnetized PMO with modified ZnO nanoparticles embedded on surface. Also due to the presence of isocyanurate bridging incorporated into the silica framework containing organic parts, the composite has been showed high thermal stability of about 480 °C. The decrease observed in mass at intense heat is also due to the organic nature of the PMO compounds.

The structure of Fe$_3$O$_4$@PMO-ZnO nanoparticles was analyzed by XRD spectroscopy. The wide angle XRD patterns in **Figure 5** determined the crystallinity and arrangement and show a broad diffraction peak of $2\theta$ near to 3.9° and five sharp peaks at $2\theta= 29.5^\circ, 35.4^\circ, 43.2^\circ, 56.9^\circ, 62.7^\circ$ corresponding reflections of amorphous silica and Fe$_3$O$_4$ phase, respectively.

The use of high-resolution field emission scanning electron microscope (FE-SEM) is an appropriate detecting method for specification sample sizes on a nano to micron scale. Due to the different imaging
modes in this system, the size of the synthesized particles can be completely characterized; the morphology and distribution of the particles can be analyzed.

**Figure 6a-b** clearly show the porous structure for the catalyst as well as the ZnO particles on the surface of the PMO holes. **Figure 6c** shows the particle size in the range of 45 to 60 nm, indicating homogeneity and well-defined distribution of particles and suitable morphology for the Fe$_3$O$_4$@PMO-ZnO nanocatalyst.

The energy dispersive X-ray (EDX) spectrum of the catalyst has been shown in **Figure 7**. This analysis was carried out to study the presence of expected elements in the material framework. The signals of iron, nitrogen, silicon, carbon, oxygen and zinc were observed in the sample. It is well known that for magnetic iron oxides three peaks are observed in the EDX spectrum for iron. These analyses are successfully confirming ZnO nanoparticles well embedded onto the magnetic catalyst.

Furthermore, nitrogen adsorption and desorption isotherms were determined using BET and BJH methods, respectively, to determine the specific surface area of the catalyst and the pore size of the mesoporous for the sample (**Figure 8**). The obtained results demonstrated that this material has a typical mesoporous structure and a type IV isotherm that characterizes the presence of cylindrical pores on the mesoporous scale. Specific surface area is approximately 194.88 m$^2$/g, average pore size is 7.312 nm and volume pore is 0.3564 cm$^3$/g.

**Optimization of conditions for the synthesis of tetrazole derivatives in the presence of magnetic Fe$_3$O$_4$@PMO-ZnO nanocatalyst (1)**

The effects of different loading catalyst, solvent and temperature in reaction time, yield reaction were systematically investigated in this step. The results have been summarized in **Table 1**. Considering the important effect of amount of catalyst, temperature, and type of solvent as well as the use or avoiding the use of solvent in the chemical reaction were investigated in order to obtain optimal conditions in the synthesis of derivatives of 1$H$-tetrazoles. Hence, the reaction of 4-chlorobenzaldehyde (4a, 1 mmol), malononitrile (2, 1 mmol) and sodium azide (3, 1.2 mmol) were selected as the model reaction. Initially, the model reaction was examined in the absence of catalyst under various conditions such as in EtOH solvent at ambient temperature and under reflux conditions. The dependence of the model reaction to catalyst and temperature was evident because of the very low yield of the desired product (E)-3-(4-chlorophenyl)-2-(1$H$-tetrazol-5-yl)acrylonitrile 5a. The higher temperature conditions and the use of EtOH under reflux conditions afforded a much better result. (entries 1 and 2, **Table 1**) The latter have investigated the effect of the catalyst loading, over different parameters including, reaction time and product output. (entries 3-5, **Table 1**) As well as, increasing the catalyst content from 10 mg to 15 and 20 had very little effect on product efficiency. This scrutiny demonstrates the high potential of the catalyst in the expected composition synthesis, that originated from very large surface area of the PMOs. In the following, the effect of solvents such as water, water/EtOH mixture, toluene, DMF, ethyl acetate and acetonitrile on the reaction were inquired. The remarkable thing in this assessment is that the reaction in
water solvent in terms of time and efficiency is much closer to reflux in EtOH. But due to of the high solubility of the desired product in EtOH and the formation of the product as a precipitate in the water solvent, the optimum conditions for EtOH reflux were considered. In other catalysts with catalyst 1, the result was that the reaction time when using non-operating PMO and magnetic PMO was not efficient as the use of the newly designed catalyst, and this show effective role of ZnO nanoparticle in progress of reaction under ideal conditions (entries 17,18, Table 1).

**Table 1.** Optimization of conditions in the reaction of malononitriles (2), 4-chlorobenzaldehyde (4a) and NaN₃ (3) under different conditions.
| Entry | Catalyst | Loading catalyst (mg) | Solvent | Temperature (°C) | Time (min) | Yield (%) |
|-------|----------|-----------------------|---------|-----------------|------------|-----------|
| 1     | -        | - s.f                 | rt      |                 | 24h        | 78        |
| 2     | -        | - EtOH                | reflux  |                 | 20h        | 62        |
| 3     | Fe₃O₄@PMO-ZnO | 10 | EtOH | Reflux  | 3 | 98        |
| 4     | Fe₃O₄@PMO-ZnO | 15 | EtOH | Reflux  | 5 | 97        |
| 5     | Fe₃O₄@PMO-ZnO | 20 | EtOH | Reflux  | 5 | 98        |
| 6     | Fe₃O₄@PMO-ZnO | 10 | Water | Reflux  | 5 | 95        |
| 7     | Fe₃O₄@PMO-ZnO | 10 | Water/EtOH | Reflux | 40 | 80        |
| 8     | Fe₃O₄@PMO-ZnO | 10 | Toluene | Reflux  | 45 | 90        |
| 9     | Fe₃O₄@PMO-ZnO | 10 | DMF | Reflux  | 60 | trace     |
| 10    | Fe₃O₄@PMO-ZnO | 10 | Ethyl acetate | Reflux | 30 | 72        |
| 11    | Fe₃O₄@PMO-ZnO | 10 | Acetonitrile | Reflux  | 10 | 70        |
| 12    | Fe₃O₄@PMO-ZnO | 10 | Solvent free | 100  | 20 | 97        |
| 13    | Fe₃O₄@PMO-ZnO | 10 | EtOH | 60      | 7 | 86        |
| 14    | Fe₃O₄@PMO-ZnO | 10 | EtOH | 80      | 5 | 88        |
| 15    | Fe₃O₄@PMO-ZnO | 10 | EtOH | 100     | 3 | 98        |
| 16    | Fe₃O₄@PMO-ZnO | 10 | EtOH | rt      | 10 | 97        |
| 17    | PMO       | 10 | EtOH | Reflux  | 45 | 70        |
| 18    | Fe₃O₄@PMO | 10 | EtOH | Reflux  | 40 | 78        |

*a Reaction conditions: Malononitriles (2, 1 mmol), 4-Chlorobenzaldehyde (4a, 1 mmol), and NaN₃ (3, 1.2 mmol) in the presence of 20 mg Fe₃O₄@PMO-ZnO (1).

*b Isolated Yields.

Expanding the optimum conditions for the preparation of 1Htetrazole derivatives in the presence of magnetic PMO with ZnO nanoparticles

Excellent yields are obtained from a variety of aromatic, heterocyclic and aliphatic aldehydes within a few minutes at specified temperature. As the data in Table 2 shows, the high to excellent in a very short time...
was achieved for desired products 5a-v, respectively. In this regard, other aromatic aldehyde compounds with electron withdrawing groups were tested after the model reaction, such as 2-chlorobenzaldehyde (entry 9, Table 2) 3-bromobenzaldehyde (entry 13), 4-nitrobenzaldehyde (entry 4, Table 2) and so on. The aldehyde derivatives with electron donating groups such as 4-methoxybenzaldehyde, 2-hydroxybenzaldehyde, 4-methylbenzaldehyde, and 2,4-dimethylamino benzaldehyde (entries 6,8,3,15 Table 2, respectively) also involved the reaction in very good time and at good yield. The response time of these aldehydes is generally less than that a complete electron withdrawing group such as NO2.

Heterocyclic aldehydes also complete the reaction at the appropriate time, such as donor groups, due to the presence of an atom with a free electron pair that increases the electron charge in the aldehyde and increases the velocity in these derivatives (entries 10,11, Table 2).

**Table 2.** Synthesis of 5-substituted-1$H$-tetrazole derivatives 5a–v catalyzed by Fe$_3$O$_4$@PMO-ZnO (1) via the three component reaction strategy.
Proposed mechanism for the preparation of 5-substituted-1\textit{H}-tetrazole derivatives

A synthetic pathway for the one-pot preparation of (\textit{E})-2-(1\textit{H}-tetrazole-5-yl)-3-phenylacrylenitrile derivatives compounds using acidic ZnO nanoparticles embedded on the surface of magnetic isocyanurate-based periodic mesoporous organosilica (Fe$_3$O$_4$@PMO-ICS–ZnO, 1) is shown in Scheme 2. In the first reaction step, the aromatic aldehydes (4) are activated by Fe$_3$O$_4$@PMO-ICS–ZnO step by step to condensate with the malononitrile C–H acid (2) and finally affording the Knoevenagel
aryl/heteroarylidine malononitrile intermediate (III). This intermediate is subsequently involved in a cascade reaction with sodium azide (3) to the produce 5-membered tetrazole ring by the concerted [3 + 2] cycloaddition. The desired products 5a-v are separated easily from the reaction mixture after completion of using an external magnet.

**Comparison of the catalytic activity of nano-ordered Fe₃O₄@PMO-ICS–ZnO (1) in the synthesis of tetrazole derivatives with other catalysts**

*Table 3* compares the previously reported methods in the scientific literature for the synthesis of tetrazole derivatives with the present method. In the past, the use of inappropriate and adverse to environmental health solvents and extremely high reaction times have made these methods less commonly used in the synthesis of these compounds with biological properties. Now, the proposed method, using EtOH as a green solvent as well as a very short reaction time and excellent yield, easy separation of the catalyst due to its magnetization and pure separation of the product without the use of any dangerous and toxic reagents are the advantages of the present strategy.

*Table 3* Comparison of the catalytic efficiency of Fe₃O₄@PMO-ZnO (1) with other heterogeneous or homogeneous catalysts for the synthesis of 5a
| Entry | Catalyst                  | Catalyst loading | Conditions                | Time (hour) | Yield 4a | Ref. |
|-------|--------------------------|------------------|---------------------------|-------------|----------|------|
| 1     | NiO Nanoparticle         | 0.06 mmol        | DMF/70 ºC/reflux          | 6           | 87%      | 93   |
| 2     | SMA, Silica Molybdic     | 0.2 gr           | Mw/50 ºC/water            | 20 min      | 91%      | 87   |
| 3     | Zn, (M)                  | 2.0 eq           | H$_2$O/50 ºC              | 3           | 68%      | 86   |
| 4     | Fe(OAC)$_2$              | 10% mol          | DMF/H$_2$O (9:1) 80 ºC    | 24          | 89%      | 94   |
| 5     | (CuOTF)$_2$C$_6$H$_6$    | 10% mol          | Toluene/rt                | 7           | 81%      | 95   |
| 6     | Clay: Montmorillonite k-10 | 10 mg          | Water                     |             | 29%      | 96   |
| 7     | Cu(OAC)$_2$              | 25% mol          | DMF/120 ºC                | 12          | 96%      | 97   |
| 8     | Catalyst-Free            | _                | s.f                       | 24          | 78%      | -    |
| 9     | OPNSA                    | 20% mol          | s.f                       | 8           | 90%      | 98   |
| 10    | H$_3$PW$_{12}$O$_{40}$ (HPA) | 0.7 mol    | s.f/120 ºC                | 6           | 93%      | 99   |
| 11    | NH–Cu(II)@MNP            | 20 mg            | EtOH/ 80 ºC               | 5           | 92%      | 92   |
| 12    | Fe$_3$O$_4$@PMO-ZnO      | 10 mg            | EtOH/Reflux               | 3           | 99%      | -    |

Investigating the recyclability of magnetic periodic mesoporous organosilica nanocatalyst

One of the advantages of using heterogeneous catalysts is their easy separation from the reaction mixture and their reuse in catalytic systems. Heterogeneous catalysts with magnetic properties have the greatest ease of separation. The catalytic activity and efficiency of periodic mesoporous organic silica for the preparation of 5-substituted 1$H$-tetrazoles were evaluated by model reaction. Result in four consecutive times the use of the catalyst was a slight decrease in reaction yield after and no noticeable change in reaction time. These indicate the ability of the catalyst to be reused, with structural stability and high efficiency. The diagram of the catalyst recycling is given below (Figure 9).

Experimental

Reagents and instruments
Chemical reagents with high purity were purchased from Merck and Aldrich and only liquid aldehydes were distilled before use. All reactants and the purity of the products were monitored by thin-layer chromatography (TLC) using aluminum plates with 0.2 mm think coated with silica gel F254 plates (Merck) and the UV lamp with wavelength of 245 nm was also used in this experiment. Product identification was performed using Shimadzu infrared spectroscopy with potassium bromide and a 500 MHz Advance Broker core magnetic resonance spectroscopy was performed for hydrogen and carbon nuclei in DMSO solvent and at room temperature. The BET specific surface area analysis was performed with ASAP 2020™ and Thermal gravimetric analysis was obtained by Bahr company STA 504 equipment. X-ray diffraction pattern was performed with STOE apparatus and Field emission scanning electron microscopy images were recorded by Zeiss (EM10C) device. Melting points were measured using an electro thermal 9100 device.

**Typical Procedure for the Preparation of PMO-ICS**

A new periodic mesoporous organosilica named PMO-ICS was denoted first time in 2004 by Jaroniec and his co-workers. This novel PMO was synthesized by self-assembly of tris[3-(trimethoxysilyl) propyl] isocyanurate (ICS, Aldrich), tetraethyl orthosilicate (TEOS from Aldrich) and the poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) triblock copolymer (Pluronic 123 from Aldrich, average Mw ≅ 5800 Dalton) under acidic conditions. In a typical experiment, weigh 2 g of P123 into a baker and slowly add a mixture of 15 mL deionized water and 60 mL hydrochloric acid solution (2M) and stirred until P123 is completely dissolved in acid and water. Then, 0.01 mol (3.08 g) of tris-[3-trimethoxysilyl) propyl] isocyanurate (ICS, Aldrich) and 0.03 mol tetraethyl orthosilicate (TEOS, 3.12 g)) was added dropwise into that solution. The obtained white gel and precipitates was stirred at room temperature for 24 h in a round bottom balloon. The mixture was aged at 100 °C for 48 h without stirring. The solid was filtered off and washed thoroughly with hot EtOH/HCl (60 mL of EtOH 96% and 2 mL of 12 M HCl) using a soxhelet apparatus for 72 h to remove the surfactant molecules. The obtained white powder was dried in air at 100 °C overnight.

**General procedure for the preparation of the Fe₃O₄@PMO catalyst**

Magnetic PMO synthesis involves the use of Fe²⁺ and Fe³⁺ in the presence of ammonia. By first dispersing 2 g of PMO-ICS in 20 mL toluene at room temperature. After 15 Minutes stirring, 2.0 g of FeCl₂.4H₂O and 4.0 g of FeCl₃.6H₂O was added to the above mixture under nitrogen atmosphere. The reaction mixture was heated in an oil bath at 80 °C during stirring, then 20 mL of ammonia (25% w/w) was added dropwise over the mixture over a period of 30 minutes until the pH reached 11 and allowed to rotates for 1h at the same temperature. The black precipitate is finally washed with water and EtOH and dried at 100 °C.

**Preparation of ZnO NPs supported on mesoporous Fe₃O₄@PMO**
At this stage, zinc acetate in the presence of PEG-600 surfactant was used to embedded ZnO nanoparticles onto the catalyst surface. First dissolve 0.1 g of zinc acetate and 0.1 g of PEG in 50 ml of twice-distilled water then add NH$_3$ dropwise solution to reach pH=10 and finally solution heated for 8 h at 80 °C and then cooled to ambient temperature.

**General procedure for the synthesis of 5-substituted-1H-tetrazoles derivatives**

The reaction mixture of 4-chlorobenzaldehyde (1mmol), malononitrile (1mmol) and sodium azide (1.2mmol) was heated in the presence of nanoporous catalyst (1) at 80 °C under EtOH reflux conditions (Table 1). Under the conditions mentioned, the reaction progress was monitored by TLC (EtOAc/n-hexane, 1:3). After completion of the reaction in a very short time it was easily separated using a catalyst external magnet and the desired product was obtained by adding distilled water to the bottom of the container. The organic layer obtained was washed several times with distilled water to remove impurities from it until the solution was discolored. The solid product was easily re-crystallized in EtOH solvent for purification. The formation of our desired product was confirmed by $^1$H NMR and $^{13}$C NMR measurements, melting point, FT-IR and comparison with reported data.

**Conclusions**

ZnO nanoparticles embedded on the surface of magnetic isocyanurate-based periodic mesoporous organosilica (Fe$_3$O$_4$@PMO-ICS–ZnO) has been prepared through modified environmental-benign procedure for the first time and properly characterized by appropriate spectroscopic and analytical methods or techniques used for mesoporous materials. The new thermally stable Fe$_3$O$_4$@PMO-ICS–ZnO materials with proper active sites, uniform particle size and surface area was found to be a superior magnetic catalyst for the synthesis of medicinally important tetrazole derivatives through cascade condensation and concerted reactions as a representative of the Click Chemistry concept. The desired 5-substituted-1H-tetrazole derivatives were smoothly prepared in high to quantitative yields and good purity under green conditions. Low catalyst loading, very short reaction time and the use of green solvents such as EtOH and water instead of carcinogenic DMF as well as the possibility of easy separation and recyclability of the catalyst for at least five consecutive runs without significant loss of its activity are notable advantages of this new protocols compared to other recent introduced procedures.

**Declarations**

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**Figures**
Figure 1

Losartan and Valsartan as two active pharmaceutical ingredients with tetrazole.

Figure 2
Represent FT-IR spectra of PMO-ICS and its functionalized state Fe3O4@PMO-ZnO (1).

**Figure 3**

VSM diagram for Fe3O4 and Fe3O4@PMO-ZnO (1).

**Figure 4**

TG (mg) graph for PMO-ICS and Fe3O4@PMO-ZnO.
TGA analysis shows structural stability of Fe3O4@PMO-ZnO (1) catalyst.

Figure 5

X-ray powder diffraction (XRD) pattern for Fe3O4@PMO-ZnO nanoporous catalyst (1).
Figure 6

FE-SEM images of magnetic nanoporous Fe3O4@PMO-ICS–ZnO catalyst (1).

Figure 7

The EDX spectrum of the magnetic Fe3O4@PMO-ZnO mesoporous catalyst (1).
Figure 8

BET isotherm show adsorption/desorption of Fe3O4@PMO-ZnO nanocatalyst.

| Sample         | BET surface area (m²/g) | Total pore vol. (cm³/g) (P/P₀: 0.989) | Pore size (nm) |
|----------------|--------------------------|---------------------------------------|----------------|
| PMO-ICS        | 570.03                   | 5                                     | 4.160          |
| Fe₃O₄@PMO-ZnO  | 194.88                   | 3.564×10⁻¹                            | 7.312          |
Figure 9

Reusability data for the magnetic Fe3O4@PMO-ICS-ZnO mesoporous catalyst (1) in the synthesis of 5a.

Supplementary Files

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