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FULL PAPER

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Copper coordinated-poly(α-amino acid) decorated on magnetite graphene oxide as an efficient heterogeneous magnetically recoverable catalyst for the selective synthesis of 5- and 1-substituted tetrazoles from various sources: A comparative study

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In this work, poly(α-amino acid)-Cu(II) complex immobilized on magnetite graphene oxide (GO/Fe_3O_4@PAA-Cu-complex) was prepared *via* a multistep synthesis and employed as an efficient, heterogeneous, magnetically recyclable nanocatalyst for one-pot, three component synthesis of 5- and 1-substituted tetrazoles using different substrates including benzaldehydes, benzonitriles, and anilines in mild conditions. The different approaches were mechanically investigated and compared. The catalyst was fully characterized by Fourier transform infrared (FTIR), thermogravimetric analysis (TGA), X-ray diffraction (XRD), vibrating sample magnetometer (VSM), energy dispersive X-ray spectroscopy (EDX), inductively coupled plasma (ICP), FE-SEM and TEM analyses. The magnetic nanocatalyst could be readily separated from the reaction mixture by an external magnet and reused for several times without significant loss of catalytic activity. Also, the spectroscopic analysis revealed the stability and durability of the catalyst. Finally, the chemoselectivity of the method was investigated by the various combinations of aldehyde, nitrile, and oxime.

KEYWORDS

copper complex, graphene oxide, poly(α-amino acid), 5-substituted 1*H*-tetrazole, 1-substituted-1*H*-1,2,3,4-tetrazoles

1 | INTRODUCTION

Tetrazoles and their derivatives are one of the most applicable *N*-heterocyclic compounds, which their application has increased rapidly over the past few years due to their unique biological properties such as: antibiotic, antialergic, antifungal,[1] antihypertensive, anticonvulsant agents, anti-inflammatory, anti-HIV activities, etc.[2,3] Furthermore, widespread applications have been reported for tetrazole derivatives in agriculture, photography,[4] and industry.[5] They are also efficient ligand and widely used in coordination chemistry.[6] In chemistry, tetrazoles are used for the preparation of nitrogen-containing compounds for design of therapeutic drugs, and isosteric substituent for carboxylic acids.[2] In material science, they have role in the production of explosive and rocket propellants.[7]

Different approaches have been developed for the preparation of tetrazole derivatives by different starting materials including: aldehyde,[8] oxime,[9] nitrile,[10] and amine.[11] Two main categories of tetrazoles are 5-substituted-1*H*- and 1-substituted-1*H*-1,2,3,4-tetrazoles. Two main routes have been developed for the preparation of 1-substituted-1*H*-1,2,3,4-tetrazoles using (a) cycloaddition between isocyanide and hydrazoic acid, and (b) the reaction of amines with orthoformate or orthocarboxylic acid ester in the presence of an azide salt.[12,13] Various catalytic systems have been developed for the preparation of 1-substituted-1*H*-1,2,3,4-tetrazoles including: silica sulfuric acid,[12] Brønsted acidic ionic liquids,[13] Fe_3O_4@silica sulfonic acid,[14] Fe_3O_4@WO_3-EAE-SO_3H (aminoethanesulfonic acid immobilized on epichlorohydrin functionalized Fe_3O_4@WO_3),[15] Fe_3O_4@Quindiol@Cu nanocatalyst,[16] silver oxide,[17] and tributylmethylammonium chloride (TBMAC).[11] Recently, Pharandeh and co-workers reported a isocyanide based synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles under ultrasonic conditions.[18]

On the other hand, the straightforward and facile route for the preparation of 5-substitited-1*H*-tetrazoles first developed by Hantzsch and Vagt through a [3+2] cycloaddition of azide ion with nitriles as a main and popular method.[9] This method involves high reaction temperature, tedious work-up, expensive and toxic solvent, that is not efficient from environmentally considerations point of view. Thus, numerous efforts made by scientists for finding more sustainable and economic friendly alternative methods. The literature demonstrating various routes to reach 5-substituted-1*H*-tetrazoles. Among recent advances can be point to: Pd-SMTU@boehmite (SMTU= *S*-methylisothiourea),[19] $Ni(OH)_2$ NPs,[20] choline azide,[10] MCM-41@AMPD@Zn (2-amino-2-methyl-1,3-propandioal),[21] and Sm@*l*-MSN,[22] and Cu-MOF nanocatalyst (MOF=metal organic framework).[23]

However, some impediments and drawbacks are still associated with them such as: high reaction temperature, use of toxic solvents, long reaction times, expensive and/or toxic catalyst and so on, which development of a novel, safe, inexpensive and general protocol for preparation of the various types of tetrazoles is required.

The preparation and development of a heterogeneous catalytic system is of great interest in organic synthesis because of reusability, manipulation for a specific goal, and also from eco- and economic viewpoint. So, various solid supports have been developed for this goal including: carbon nanotube (CNT), zeolite, graphene, MCM-41, KCC-1, clay, carbon, etc.[15,16,19,21,23] Among them, graphene oxide with the interesting properties such as sheet structure, nano-size dimension with high surface area, high thermal/ chemical stability and possibility of functionalization with various organic compounds become as one of the most suitable solid support for organic synthesis.[24–26] Further improvement in heterogeneous catalysts lead to preparation of magnetic nanoparticles that facilitates the separation of catalyst by an external magnetic field.[27] Fe_3O_4 nanoparticles are one of the most applicable magnetic nanoparticles due to their widespread applications in various fields of area such as catalyst and biomedical applications.[28,29] Some advantages are associated with them including low cost, high thermal stability, non-toxic, chemical stability, strong magnetization, and high crystalline structure, which conducted them for magnetization of other solid supports. This is a smart strategy for magnetization of solid supports, in this case nano graphene oxide, which has been used extensively in the last decades.[25,27]

In this article, given the notable properties and inevitable application of tetrazole derivatives in various fields of area, herein, in the development of sustainable chemistry, we have prepared Cu(II) complex of a synthetic poly (α-amino acid) and then immobilized on GO/Fe_3O_4 NPs (as a nano-magnetic support) as an efficient magnetically recoverable catalyst for the efficient transformation of aldehyde, amine, nitrile and oxime to the corresponding tetrazoles. Mild reaction conditions, low catalyst amount, versatility of the catalyst toward a variety of substrates, applicable in various reaction conditions, low metal leaching, preparation of the catalyst from cheap and available starting materials, free of any toxic/hazardous reagent, easy reuse and recovery without any pre-activation, durability, high thermal stability and high chemoselectivity are some advantages of the present method, which makes it superior to previously reported catalysts for efficient and reliable preparation of 5- and 1-substituted tetrazoles from various sources. The main objective of this paper is study on the preparation of tetrazole ring through a various approaches based on the used substrate as well as introduction of an efficient and general method for preparation of a variety of 1- and 5-substituted tetrazoles using different substrates. For each transformation a mechanism was proposed and discussed.

2 | EXPERIMENTAL

2.1 | Materials and apparatus

All chemicals were obtained from Sigma and Fluca supplier and used as received without further

purification. All the solvents were distilled and dried before use. Progress of the reactions and purity of products were monitored by thin layer chromatography (TLC) on silica gel and/or gas chromatography (GC) on a Shimadzu-14B gas chromatography equipped with HP-1 capillary column and N_2 as carrier gas. For GC analyses, anisole was used as an internal standard. Purification of imines and oximes was achieved by recrystallization from ethanol. FTIR spectra were obtained using a JASCO FT/IR 4600 spectrophotometer using KBr pellet. The ^{1}H NMR (250 MHz) and ^{13}CNMR (62.9 MHz) spectra were recorded on a Bruker Avance DPX-250 spectrometer in $CDCl_3$ and DMSO-d_6 as solvent (ESI). Field emission scanning electron microscopy (FE-SEM) images were obtained on a TESCAN MIRA3. Transmission electron microscopy (TEM) images were taken on a Philips EM208 microscope and was operated at 100 kV. The presence of the elements was detected by EDX spectroscopy using field emission scanning electron microscope (FE-SEM, JEOL 7600F), equipped with a spectrometer of energy dispersion of X-ray from Oxford instruments. Size distribution of the nanoparticles were measured by dynamic light scattering (DLS) analysis on a HORIBA-LB550 instrument. TGA of the samples have been performed on a NETZSCH STA 409 PC/PG in nitrogen atmosphere with a heating rate of 10 °C /min in the temperature ranges of 25-1000 °C. The magnetic behavior of the samples was conducted on Lake Shore vibrating sample magnetometer (VSM) at room temperature. ICP experiments were accomplished using VARIAN VISTA-PRO CCD simultaneous ICP-OES instrument.

2.2 | Methods

2.2.1 | Preparation of PAA

In order to preparation of poly(α-amino acid) (PAA), firstly, poly salicylaldehyde (PSA) was prepared according to a previously reported procedure.[28–30] PSA (0.1 g, $\bar{M}_n$=2226) was added to 20 ml of water, then NaCN (0.5 g, 10 mmol) and NH_4Cl (0.5 g, 10 mmol) were added to the reaction mixture. The reaction was refluxed at 50 °C for 12 hr. The resultant orange product (mp > 400°C, $\bar{M}_n$= 2400), poly(α-amino nitrile) **3**, was isolated by simple filtration followed by drying into oven (50 °C) for 5 hr. Poly(α-amino nitrile) was transformed to poly(α-amino acid) by hydrolysis of nitrile groups; 0.2 g of **3** was added to 15 ml of water and along with several drops of H_2SO_4 refluxed at 80 °C for 12. The reaction mixture was cooled to room temperature and neutralized with 0.5 N KOH solution. Poly(α-amino acid) **4**, was filter off, drying and isolated as a stable powder (mp > 400 °C). Scheme 1 shows the preparation of PAA **4** *via* the multistep reactions.

2.2.2 | Preparation of GO

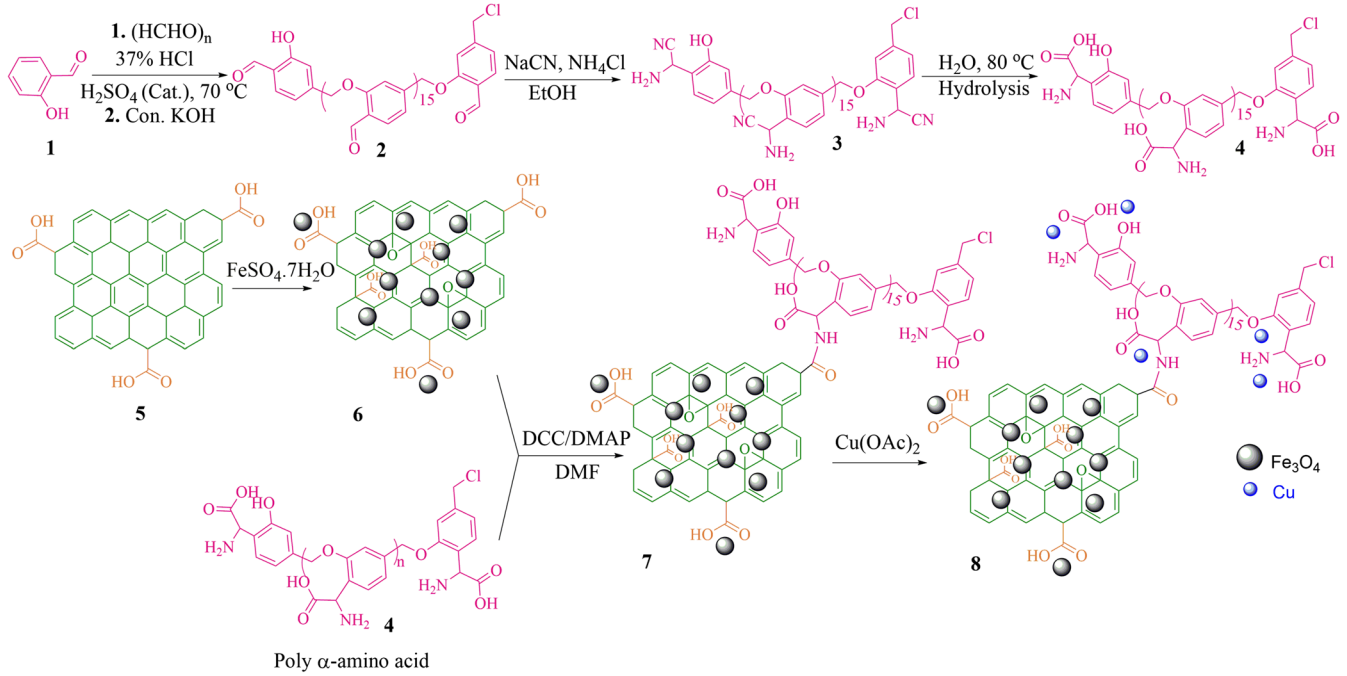
Graphene oxide (GO) was prepared according to a modified Hummer's method from purified natural graphite.[31,32]

2.2.3 | Preparation of GO/Fe_3O_4 hybrids

GO–Fe_3O_4 hybrid was prepared *via* a chemical co-precipitation method according to the slightly modified literature procedure.[33,34] GO/Fe_3O_4 NPs were prepared with a mass ratio of 1: 5 (GO: $FeSO_4$). This premium ratio provides a suitable response to a magnetic field for the readily separation of the NPs.[26] In a typical process, GO (25 mg) was first sonicated in 150 ml deionized water for 10 min. The mixture was stirred and heated to 80 °C in an oil bath. Then, NH_4OH 25% solution was added dropwise to the mentioned solution until the pH adjusted to 11. Then, $FeSO_4.7H_2O$ (125 mg) along with sodium dodecyl sulfate (SDS) was added into the aqueous dispersion GO solution. The resulting mixture was stirred under N_2 atmosphere for 24 h at 80°C. The GO/Fe_3O_4 nanoparticles were collected by an external magnetic field followed by washing with deionized water several times in order to eliminate excess iron salts. Finally, the product was separated by a simple external magnet, then dried in vacuum (40 °C) for 4 hr (Scheme 1).

2.2.4 | Preparation of GO/Fe_3O_4@PAA-cu complex

For the preparation of Go/Fe_3O_4@PAA-Cu complex, 20 mg of GO/Fe_3O_4 in 50 ml of DMF was ultra-sonicated for 1 hr, and then 0.2 g of *N,N′*-dicyclohexylcarbodiimide (1.0 mmol, DCC) and 4-dimethylaminopyridine (DMAP) along with 0.5 g of PAA were added into the solution. The resultant mixture was stirred for 8 hr at 80 °C under N_2 atmosphere. Complexation of copper ions to GO/Fe_3O_4@PAA was carried out by sonication of GO/Fe_3O_4@PAA (1.0 g) in 20 ml EtOH followed by addition of $Cu(OAc)_2.H_2O$ (10 mg) to the solution. The product, Go/Fe_3O_4@PAA-Cu complex (**8**), was separated using an external magnetic field, and then washed with water for several times until the pH reached to **7**, then dried into oven (60°C).



SCHEME 1 A schematic synthesis route for the preparation of GO/Fe3O4@PAA-Cu-complex (8)

2.2.5 | General procedure for catalytic preparation of 5-substituted-1*H* tetrazoles by GO-Fe_3O_4@PAA-Cu-complex form aldehyde, nitrile or amine

From aldehyde: Aldehyde (1.0 mmol) and hydroxyl amine hydrochloride (1.5 mmol) along with Fe_3O_4@PAA-Cu-Complex (0.02 g, 1.0 mol%) was added to 3 ml of water. The mixture was stirred for 30 min at 70 °C, then 1.5 mmol NaN_3 was added to the mixture. The reaction progress was monitored by TLC according to aldehyde consumption. Upon reaction completion, the mixture was diluted by 15 ml of ethyl acetate and the catalyst was separated by an external magnetic field. The organic layer was washed with HCl (10 ml, 4N) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resultant crude product was purified by flash chromatography.

From oxime: Preparation of nitrile from oxime was performed as same as aldehyde.

From amine: In a dried 25 ml round bottom flask, a mixture of amine (1.0 mmol), triethyl orthoformate (1.2 mmol), Fe_3O_4@PAA-Cu-Complex (0.02 g, 1.0 mol% Cu) and NaN_3 was heated at 100 °C for a sufficient time with vigorous stirring. After completion of the reaction, the mixture was cooled to room temperature, and then extracted with ethyl acetate (3 × 15 ml). The catalyst was magnetically removed and the combined organic layers, were dried over Na_2SO_4 and concentrated under reduced pressure. The products were re-crystalized with EtOAc-hexane to afford the desired 1-substituted tetrazole.

From nitriles: A mixture of nitrile (1.0 mmol) and NaN_3 (1.5 mmol) in the presence of 0.02 g (1.0 mol%) of Fe_3O_4@PAA-Cu-Complex was stirred at 100°C in PEG-400. The reaction progress was monitored using TLC. After completion of the reaction, the mixture was cooled to room temperature and the catalyst was removed magnetically. The residue was treated by HCl (4N, 10 mL) and the desired tetrazole product was extracted by ethyl acetate (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and then the solvent was removed under reduced pressure to give the desired tetrazole.

All the tetrazole products are known and characterized by spectral analysis or melting point then, compared with the previously reported spectra.

3 | RESULTS AND DISCUSSION

3.1 | Catalyst characterization

According to GPC analysis of the prepared poly(α-amino nitrile), M_w = 2400, it could be calculated that the present nitrile functions per mole of poly(α-amino nitrile) is 17/2400 = 7 mmol. So, assuming that all of the nitrile groups are converted to acid; the poly(α-amino acid) contain 7.0 mmol acid functions per gram of PAA.

FTIR spectra of 5-chloromethyl salicylaldehyde, **2**, **3**, **4**, GO (**5**), **6**, **7**, **8** are shown in Figure 1. The characteristic

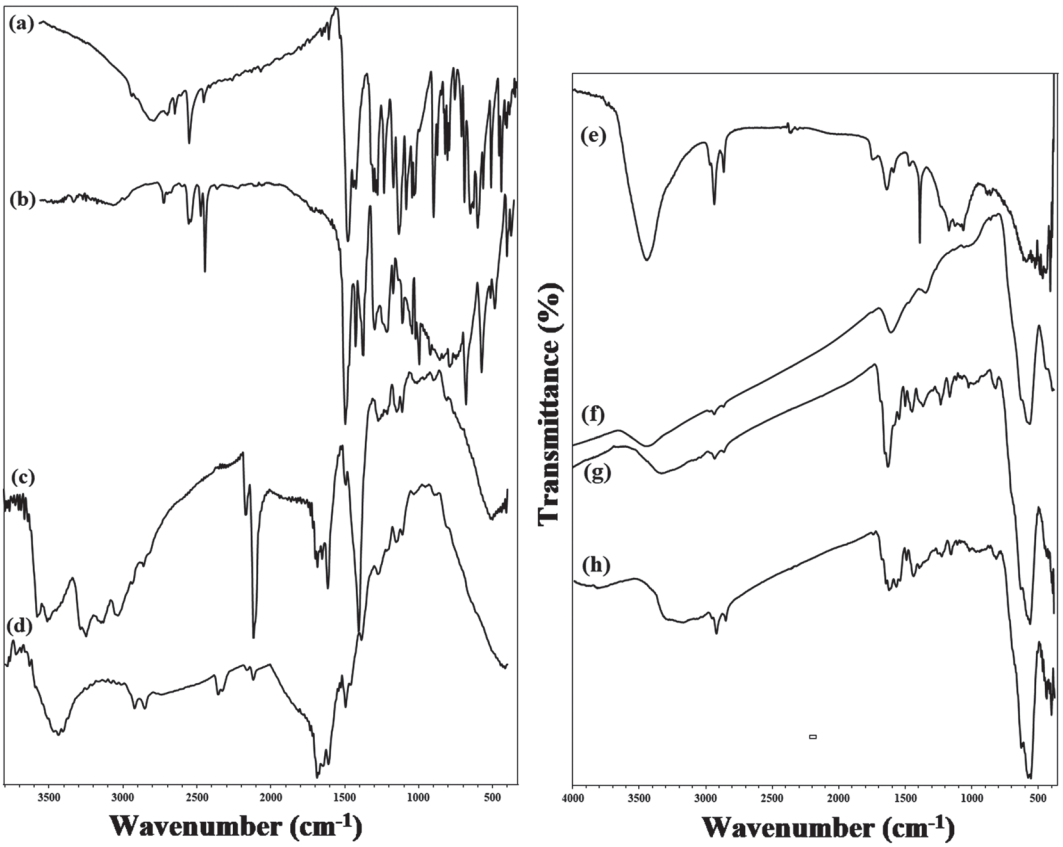


FIGURE 1 FTIR spectra of (A) 5-chloromethyl salicylaldehyde, (B) poly salicylaldehyde (2), (C) poly(α-aminonitrile) (3), (D) poly(α-amino acid) (4), (E) GO (5), (F) Fe3O4@GO (6), (G) Go/Fe3O4@PAA (7), (H) Go/Fe3O4@PAA-Cu(II) (8)

peaks at 725 cm^{-1}, 1481 cm^{-1}, and some series vibrations at 2900-2950 cm^{-1} are related to C-Cl (Str.), C-H (Aliphatic, Bend.), and C-H (Aliphatic, Str.) vibrations, respectively, which completely confirmed the chloromethylation of salicylaldehyde (Figure 1A).[28–30] The polymerization of 5-chloromethyl salicylaldehyde causes to a large reduction of O-H stretching vibration intensity at 3400 cm^{-1}, confirming that the polymerization takes place through the ether bond formation (Figure 1B).[29] The preparation of α-amino nitrile *via* the Strecker synthesis was characterized by a strong peak at 2110 cm^{-1} related to CN groups (Figure 1C). Moreover, two characteristic peaks at 3500 and 3550 cm^{-1} demonstrating amino groups in **3**. Elimination of the sharp peak refer to nitrile at the spectrum of **4**, confirmed clearly their transformation to carboxylic acids (Figure 1D). This intensity reduction along with a red shift of the amino groups in FTIR spectrum of poly(α-amino acid), could be related to the formation of COO^- NH_3^+, that is characteristic for the typical amino acids.[35] Figure 1E, shows the FTIR spectrum of graphene oxide. A peak at 1735 cm^{-1} was assigned to the stretching vibration of C=O for carboxylic groups (Figure 1E). The intense bond at 3422 cm^{-1} is attributed to the stretching vibration of hydroxyl groups of GO surface. The peak at 1626 cm^{-1} represents C=C stretching vibrations for aromatic rings related to the unoxidized graphene oxide.[36] Advent of a strong absorption at 572 cm^{-1} at GO/Fe_3O_4 FTIR spectrum indicates the Fe-O (Str.) vibration, confirming the incorporation of Fe_3O_4 NPs on the GO. Another characteristic peak was the reduction of O-H bond intensity due to the decoration of Fe_3O_4 on the graphene oxide (Figure 1F). Figure 1G, shows the amide bond linkage in **7** at 1622 cm^{-1}. A shoulder at 1635 cm^{-1} could be attributed to free C=O carboxylic bonds. Also, vibrations about 1400 cm^{-1} represents the bending vibrations of methylene groups in the polymer (Figure 1G). Reduction in intensity of peaks at carboxylic region, confirmed the successful coordination of copper cations through these functional groups as indicated in Scheme 1 (Figure 1H). Furthermore, advent of a peak at 450 cm^{-1} shows the Cu-O bond stretching vibration,[8] confirming the successful coordination of Cu.

The magnetic property of the samples was studied by VSM analysis. The samples give a suitable and satisfactory response to the applied magnetic field (Figure 2A). No hysteresis phenomenon was found for the samples, which is characteristic of superparamagnetic

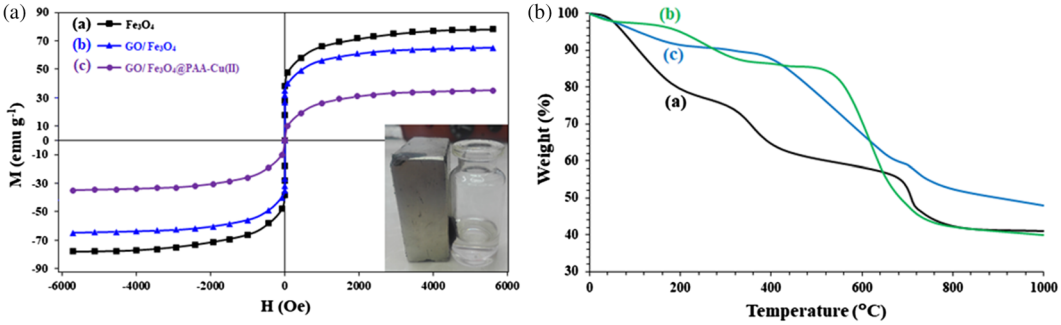


FIGURE 2 (A) VSM curves of (a) Fe3O4, (b) GO/Fe3O4, and (c) GO/Fe3O4@PAA-Cu(II). (B) TGA spectra of (a) GO/Fe3O4, (b) GO/Fe3O4@PAA and (c) GO/Fe3O4@PAA-Cu(II)

nanoparticles. These results confirmed the incorporation of Fe_3O_4 NPs on GO. For comparison, Fe_3O_4 NPs were separately prepared and studied by VSM. The analyses show 78 emu.g^{-1}, 65 emu.g^{-1}, and 35 emu.g^{-1} saturation magnetization for Fe_3O_4, GO/Fe_3O_4, and GO/Fe_3O_4@PAA-Cu(II) respectively (Figure 2A, a-c). The results indicate a large decrease in magnetization for catalyst **8**, which represent the functionalization of GO in each step (Figure 2A-c).

The samples were further characterized by TGA analysis. TGA spectrum of GO/Fe_3O_4 indicates three main weight losses (Figure 2B-a). In the first stage, slow weight loss takes place near 80°C correspond to 9% weight loss due to desorption of water.[24] Another weight loss occurs around 220°C with a mild slope, which last to 440°C. This 18% weight loss exhibited the vaporization and decomposition of various functional groups (Figure 1A) on GO framework (Figure 2B-a). Finally, decomposition of $-COO^-$ groups provide a weight loss of 12% above 600°C in agreement with the literature.[24,25] An enhancement in the thermal stability of GO/Fe_3O_4@PAA was observed, demonstrating the influence of the coated PAA on GO/Fe_3O_4 hybrid. Again, the small weight loss is due to the release of water on the GO/Fe_3O_4@PAA at 180°C (10% weight loss). A main weight loss in the temperature range of 550-820°C represents the decomposition of PAA on the GO/Fe_3O_4 (Figure 2B-b). This weight loss is equal to 40% and confirming the loading amount of PAA on the NPs. Coordination of copper to GO/Fe_3O_4@PAA-Cu(II) showed an enhance in its thermal stability, which the overall weight loss was found to be 53% at 1000°C (compared to GO/Fe_3O_4@PAA-Cu(II) with 57% weight loss). This difference may be attributed to the coordinated copper in the GO/Fe_3O_4@PAA-Cu(II) (Figure 2B-c). Also, the peak refer to the decomposition of polymer takes place in lower temperatures with a milder slope, that could be attributed to the effect of coordinated copper to PAA.

The morphology of the NPs was studied by FE-SEM technique. As shown in Figure 3A,B, the images clearly demonstrated the chemical deposition of Fe_3O_4 NPs on GO framework. The results from TEM analysis, also, confirmed the preparation of GO/Fe_3O_4@PAA-Cu(II) hybrid with an average size of 28 nm for the particles (Figure 3C). The results obtained from DLS analysis (Figure 3D), revealed that the main size distribution of the NPs are in the range of 20-30 nm. The mean size of the NPs was found to be 30 nm with a deviation of 10.2, in agreement with the corresponding TEM image.

XRD patterns of GO, GO/Fe_3O_4 and GO/Fe_3O_4@PAA-Cu is shown in Figure 4A. GO represents an amorphous peak at 2θ=10.8 related to (001) plane, that is characteristic for the graphene oxide.[26] Figure 4A-a, shows the XRD pattern of GO/Fe_3O_4 with six characteristic peaks at 2θ = 30.3°, 35.5°, 43.2°, 53.8°, 57.5°, 62.9°, which were assigned to their indices (220), (311), (440), (442), (511), and (440) respectively.[25,26] These reflections were in agreement with the crystal structure of Fe_3O_4 NPs (JCPDS no. 19-0629). As shown in Figure 4A-b, the intensity of the peak at 10.8° is largely reduced. This behavior suggests that the Fe^{2+} ions act as a reducing agent for graphene oxide.[25,27] The crystal structure of the catalyst **8**, was also demonstrated the peaks for Fe_3O_4 crystal structure as well as a new amorphous peak at 2θ = 11°. Compared to the GO/Fe_3O_4 XRD pattern, this peak could be assigned to the amorphous PAA, that is coated on the GO framework. Furthermore, the results also proved that the functionalization of GO/Fe_3O_4 with PAA doesn't lead to phase change of Fe_3O_4 NPs.

The presence of the elements in the catalyst **8** was detected by EDX analysis. As shown in Figure 4B, the elements C, O, N, Cu, and Fe were detected, confirming the structure of **8**.

The amount of Cu in Go/Fe_3O_4@PAA-Cu(II) was also determined by ICP analysis which is 0.50 mmol g^{-1}. This

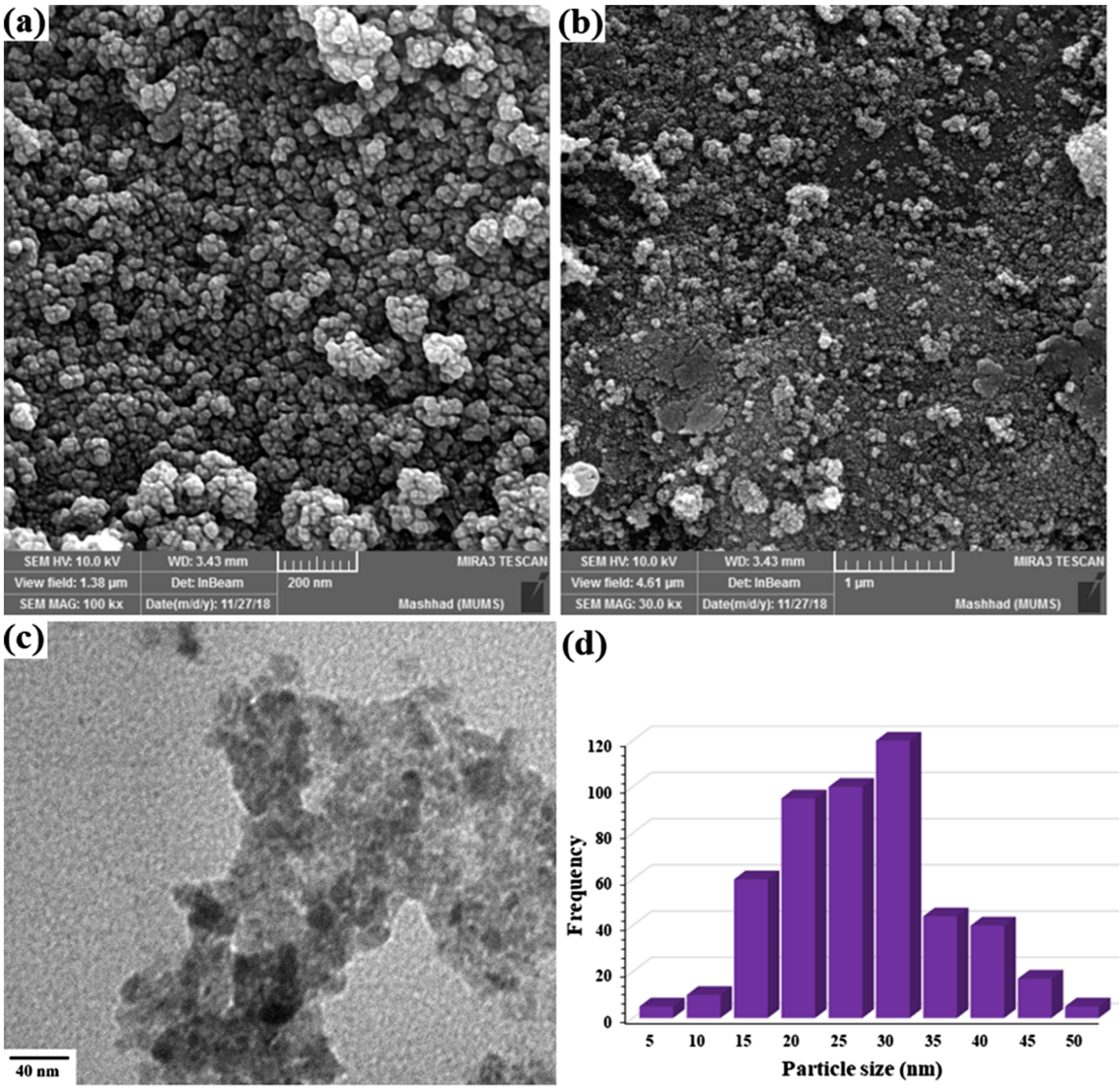


FIGURE 3 (A), (B) FE-SEM images, (C) TEM image, and (d) DLS analysis of GO/Fe3O4@PAA-Cu(II)

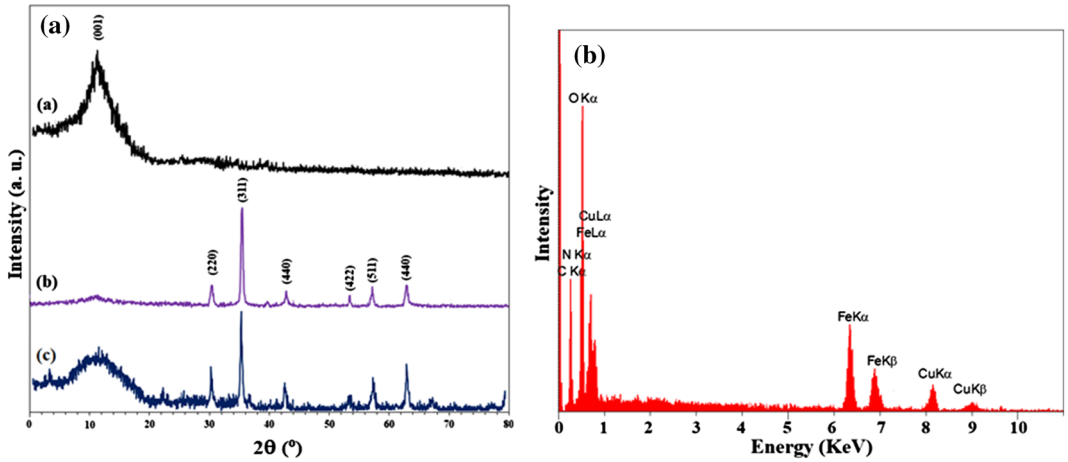


FIGURE 4 (A) XRD patterns of (a) GO, (b) Go/Fe3O4, (c) Go/Fe3O4@PAA-Cu. (B) EDX spectrum of Go/Fe3O4@PAA-Cu

amount was completely in agreement and consistence with the results from TGA analyses (Figure 2B-c).

3.2 | Optimization of reaction parameters

In order to find optimum conditions for each experiment, we applied three model reactions of: (1) benzaldehyde, NaN_3, $NH_2OH.HCl$, catalyst; (2) benzonitrile, NaN_3, catalyst; and (3) aniline, NaN_3, triethyl orthoformate and catalyst. All of reactions were performed in the presence of the optimum amount 0.02 g of the catalyst. The highest possible efficiency was obtained in this amount for all cases (Table 1). No detectable progress was found for values greater than 0.02 g for all of them and the efficiencies remain constant at higher amounts. In following, effect of solvent and temperature over transformation of benzaldehyde, benzonitrile, and aniline to the corresponding tertazoles were investigated (Figure 5A). Polyethylene glycol, DMSO, and DMF were found to be an efficient solvent for all of the substrates; however, in water as a green solvent, benzaldehyde was transformed to the corresponding 5-phenyl-1*H*-tetrazole with 95% yield for 2 hr. On the other hand, PEG was the best choice in the case of benzonitrile with 98% yield. These results proposed two different routes for transformation of aldehyde and/or benzonitrile to the desired tetrazole (Figure 5A). Preparation of 1-phenyl-1*H*-1,2,3,4-tetrazole give 85% isolated yield in PEG at 120 °C, while under solvent-free conditions excellent yield (96%) was obtained. So, preparation of the desired tetrazole by benzaldehyde, benzonitriles and amines were performed under water, PEG and solvent-free conditions, respectively. The results were summarized in Figure 5A.

Temperature was another effective parameter on the transformation of all substrates to the corresponding tetrazoles. As shown in Figure 5B, the highest possible efficiency was found for 5-phenyl-1*H*-tertazole at 100 °C in PEG. The reaction efficiency remains constant at higher temperatures. 5-Phenyl-1*H*-tertazole could be generated from benzaldehyde at moderate temperature (70 °C) in water. Preparation of 1-phenyl-1*H*-1,2,3,4-tetrazole from aniline were

TABLE 1 Effect of catalyst amount on the transformation reactions of benzaldehyde, benzonitrile, and aniline to the corresponding tetrazole catalyzed by Go/Fe_3O_4@PAA-Cu(II) complex

		From benzaldehyde[a]		From benzonitrile[a,b]		From aniline[c]	
Entry	Cat. amount (g)	Time (h)	Yield (%)[d]	Time (h)	Yield (%)[d]	Time (h)	Yield (%)[d]
1	0.010	2	68	7	55	0.5	70
2	0.015	2	84	7	80	0.5	86
3	0.020	2	95	7	98	0.5	96
4	0.030	2	95	7	98	0.5	96
5	0.040	2	96	7	96	0.5	96

[a]Reaction conditions: benzaldehyde (1.0 mmol), NaN_3 (1.5 mmol), hydroxyl amine hydrochloride (1.5 mmol), catalyst, water (3 ml), 70°C.
[b]Reaction conditions: Nitrile (1.0 mmol), NaN_3 (1.5 mmol), catalyst, PEG-400, 100°C.
[c]Reaction conditions: Amine (1.0 mmol), triethyl orthoformate (1.2 mmol), catalyst, NaN_3 (1.5 mmol), 100 °C.
[d]Isolated yield

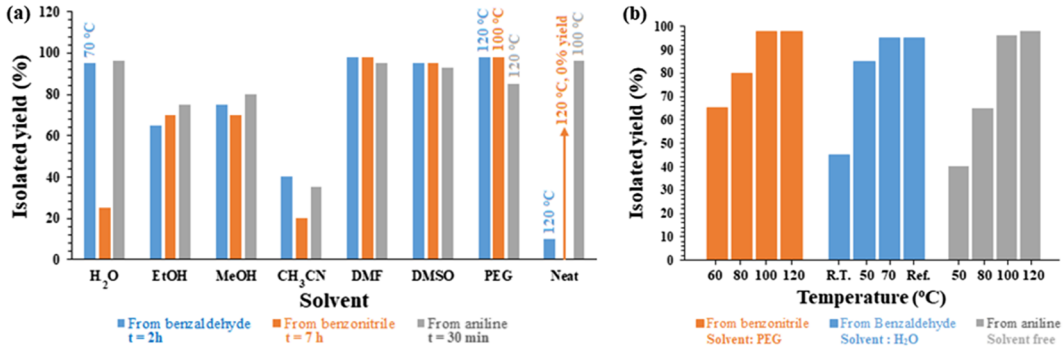
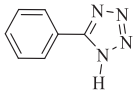
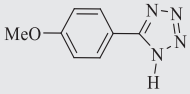
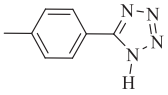
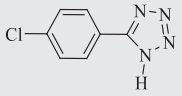
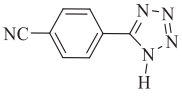
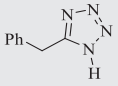


FIGURE 5 Effect of (A) solvent and (B) temperature on the preparation of 1- and 5-substituted tetrazoles frombenzaldehyde (blue columns), benzonitrile (orange columns) and aniline (grey columns) catalyzed byGo/Fe3O4@PAA-Cu(II) complex. Except noted, the reactions were performed under reflux conditions (3 ml of each solvent was used) in the presence of 0.02 g catalyst

performed at 100 °C under solvent-free conditions. Effectiveness decreases sharply at low temperatures for all three reactions.

With optimum conditions in hand, a series of benzaldehydes, benzaldehyde oximes and benzonitriles were subjected to preparation of 5-substituted-1*H*-tetrazoles in the presence of Go/Fe_3O_4@PAA-Cu(II) complex as a catalyst. The results were tabulated in Table 2. Aldehydes/ nitriles/ oximes bearing activating and/or deactivating group afforded high to excellent yields; however, the deactivating group delays the reaction (Table 2, entries 4,5), nevertheless they provide approximately similar efficiency to the aldehydes bearing electron donating groups (Table 2, entries 2,3). The lowest efficiency was obtained for 5-benzyl-1*H*-Tetrazole (Table 2, entry 6). As a conclusion, the reaction efficiencies in terms of time and isolated yield were better for oximes/ aldehydes than nitriles. The conversion of tetrazole from nitrile has a significantly higher time than either oxime or aldehyde. As the "Mechanism study" section will be discussed, these

TABLE 2 Go/Fe_3O_4@PAA-cu(II) complex-catalyzed preparation of 5-substituted 1*H*-tetrazole

			From aldehyde[a]		From oxime[a,c]		From nitrile[d]		
Entry	Product 9		Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]	Time (h)	Yield (%)[b]	Mp. (°C)[Lit.]
1		**9a**	120	95	85	98	7	98	213-215[19]
2		**9b**	90	95	75	96	4	98	230-233[21]
3		**9c**	150	77	120	80	5	95	249-250[19]
4		**9d**	120	92	85	92	7	93	255-258[20]
5		**9e**	340	95	320	97	8	95	225[19]
6		**9f**	340	66	340	75	14	70	121-122[8]

[a]Reaction conditions: Aldehyde (1.0 mmol), NaN_3 (1.5 mmol), hydroxyl amine hydrochloride (1.5 mmol), catalyst (0.02 g, 1.0 mol%), water (3 ml), 70 °C.
[b]Isolated yield
[c]Aldoxime (1.0 mmol)
[d]Reaction conditions: Nitrile (1.0 mmol), NaN_3 (1.5 mmol), catalyst (0.02 g, 1.0 mol%), PEG-400, 100 °C.

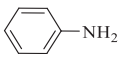
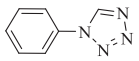
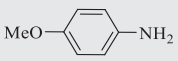
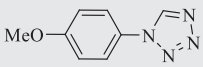
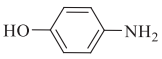
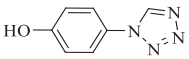
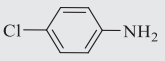
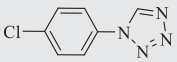
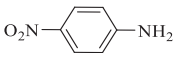
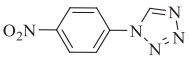
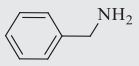
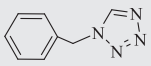
results suggest a different mechanism pathway from oxime or aldehyde. In this point of view, the present method, proposed a promising way for the preparation of oximes form aldehydes. Nitriles afforded the corresponding tetrazoles in much higher reaction times than oxime or aldehyde. However, high reaction yields were obtained in this case.

Encouraged by the good results obtained from the preparation of 5-substituted-1*H*-tetrazoles, we then examined the versatility of the present method toward the preparation of 1-substituted-1*H*-1,2,3,4-tetrazole from amines. Table 3 shows the scope of this reaction with a different spectrum of amines in the presence of triethyl orthoformate and the catalyst. High to excellent yields were achieved at low reaction times for 1-substituted-1*H*-1,2,3,4-tetrazole derivatives in the presence of amines bearing electron donating or electron withdrawing groups. In this case, also, amines containing electron donating groups (Table 3, entries 2,3) provide more efficiency than the inactive amines (Table 3, entries 4,5). Benzyl amine afforded the lowest efficiency (88% for 1h) for 1-benzyl-1*H*-tetrazole.

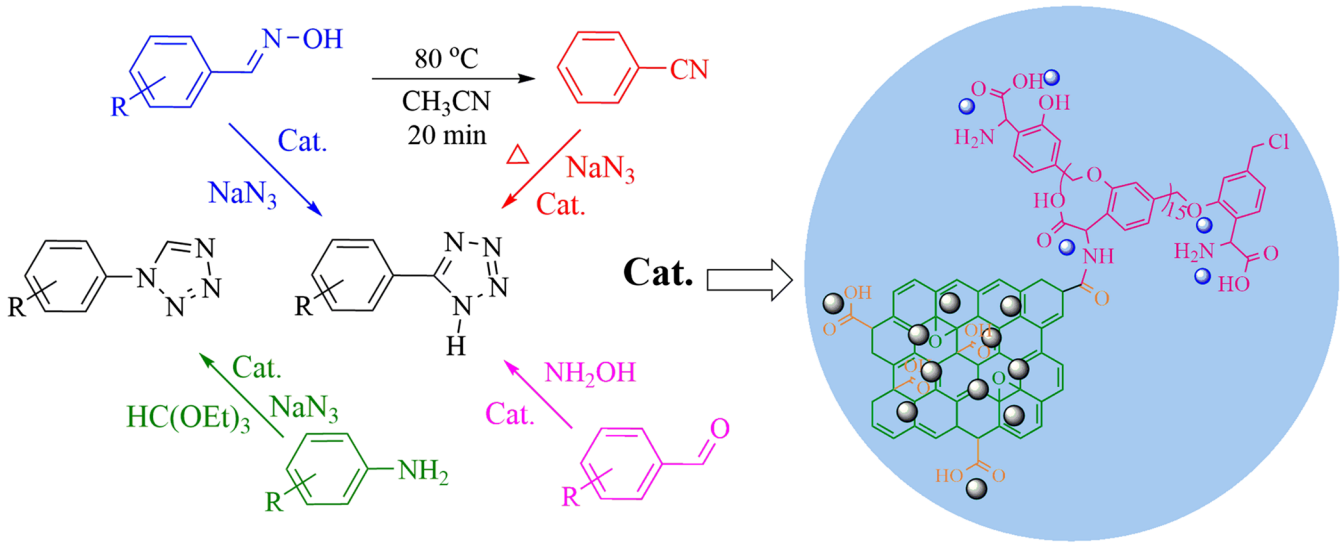
3.3 | Mechanism study

For the Cu-catalyzed 1- and 5-substituted tetrazole synthesis, various mechanisms have been proposed according to a used substrate. It has been shown that tetrazole could be directly formed through nitrile,[10] or oxime intermediate[8] at two different mechanisms.[36] Oxime could be directly transformed to tetrazole in milder conditions than nitrile.[10,37–39] Underwent reaction conditions, didn't found any benzonitrile in the reaction of benzaldehyde, NaN_3, $NH_2OH.HCl$ in the presence of the catalyst in water. On the other hand, we prepared the benzonitrile form benzaldehyde oxime in CH_3CN at 80 °C for 20 min (Scheme 2). These results propose that the preparation of 5-substituted-1*H*-tetrazole from oxime crosses another route. Another support for this claim

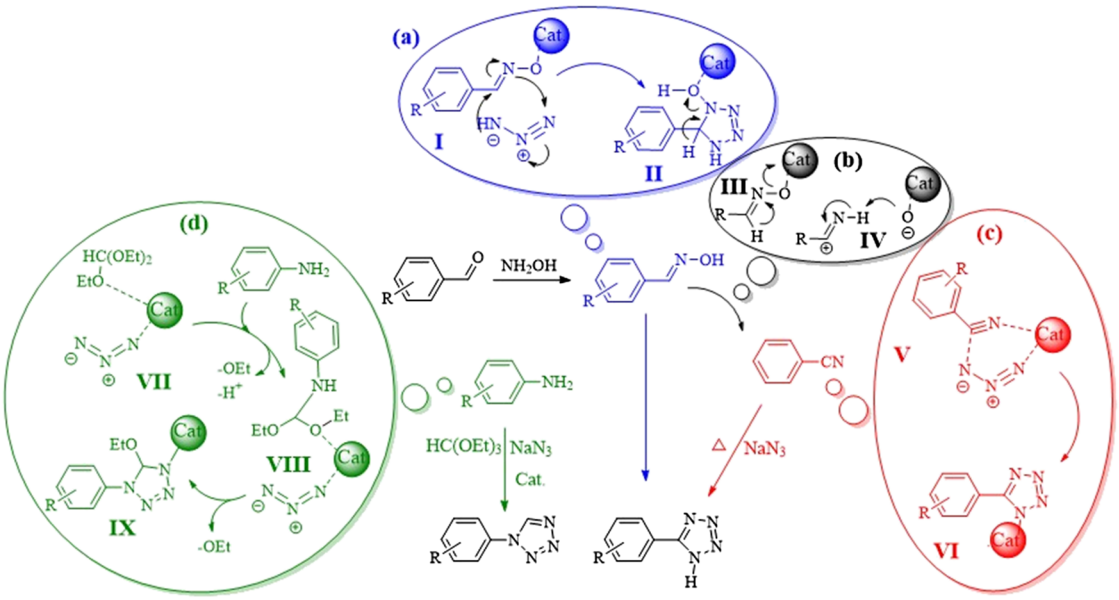
TABLE 3 Go/Fe_3O_4@PAA-Cu(II) complex-catalyzed preparation of 1-substituted-1*H*-1,2,3,4-tetrazoles[a]

Entry	Substrate	Product 10		Time (min)	Yield (%)[b]	M.P. (°C)[Lit.]
1			**10a**	30	96	64-65[16]
2			**10b**	30	94	114-115[16]
3			**10c**	40	95	185-187[30]
4			**10d**	80	96	157-158[16]
5			**10e**	95	90	201-202[16]
6			**10f**	60	88	130-132[30]

[a]Reaction conditions: Amine (1.0 mmol), triethyl orthoformate (1.2 mmol), catalyst (0.02 g, 1.0 mol%), NaN_3 (1.5 mmol), 100 °C.
[b]Isolated yield



SCHEME 2 Preparation of 1- and 5-substituted tetrazole catalyzed by GO/Fe3O4@PAA-Cu-complex



SCHEME 3 Preparation of Cu-catalyzed 5-substituted 1H-tetrazole through different sources and their most possible corresponding mechanisms

comes from successful isolation of benzaldehyde oxime in the presence of benzaldehyde, $NH_2OH.HCl$ and catalyst in water in absence of NaN_3. Scheme 3 represents the general suggested mechanisms for these transformations. Moreover, the results from solvent effect (Figure 5A), proposed that interaction of the catalyst works better with aldehyde and oxime through oxygen atom (than nitrile) in water (Scheme 3).

Absence of any nitrile intermediate for transformation of oxime to tetrazole catalyzed by GO/Fe_3O_4@PAA-Cu complex as well as being different reaction conditions between transformation of oxime and nitrile to tetrazole, convinced us that oxime goes through another mechanism to get tetrazole. In this point of view, transformation of oxime to nitrile followed by nitrile to tetrazole takes place in harsher conditions than the corresponding direct transformation of oxime to tetrazole (Scheme 2, 3). A plausible mechanism in agreement with the literature,[8,28,39] was proposed, wherein, it was started with activation of oxygen atom of oxime by Cu sites (Intermediate I) followed by a facile [3+2] cycloaddition between N_3^- ion and C=N bond in oxime. Finally, the desired 5-

substututed-1*H*-tetrazole is formed by remove of a water molecule (Scheme 3a-II). The transformation of oxime to nitrile takes place by a hydride shift after chelation of the catalyst to the oxygen of oxime. Then the nitrogen is deprotonated and gives the nitrile (Scheme 3b-III and IV). The most acceptable mechanism for the preparation of 1-substituted tetrazole from aniline was sketched in Scheme 4d.[37–39] According to this mechanism, the catalyst is linked to azide ion and orthoformate, to form intermediate VII (Scheme 3d). The reaction is proceeding by the nucleophilic attack of amine to the activated orthoformate. As shown in Scheme 3d, the catalyst facilitates the cleavage of C-O bonds by activation of ethoxy groups.[40] Then, the [3+2] cyclization with azide in (VIII) along with elimination of ethanol produces intermediate (IX). Elimination of another EtOH generates the desired tetrazole product.

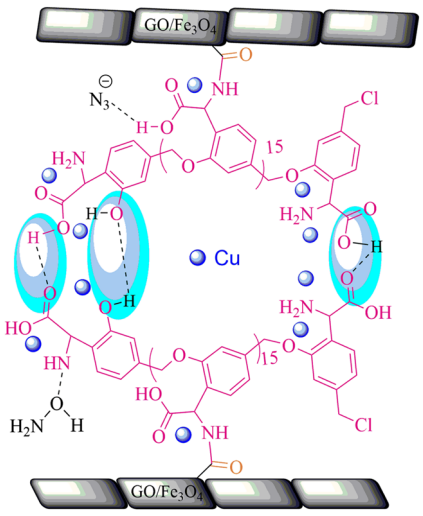
Note to presence of poly(α-amino acid) chains on GO/Fe_3O_4 NPs, a series of H-bonding could be probable between carboxylic acid and hydroxyl functional groups (Scheme 4). In this way, the catalyst provides a suitable medium for the possible interaction of the reactants that are insoluble in water. Also, azide as well as hydroxyl amine ions could be readily interact with the functional groups present on the PAA chains, lead to raise of effective concentration and progress of the reaction. This phenomenon is shown in Scheme 4, where GO/Fe_3O_4@PAA-Cu-complex nanoparticles could be readily close to each other by H-bonding.

In order to chemoselectivity investigation of the present method, we design three combinations of 4-methoxy benzaldehyde, 4-nitrobenzonitrile and benzaldehyde oxime (Table 4). The catalyst was completely selective toward preparation of 5-(4-methoxyphenyl)-1*H*-tetrazole (**9b**) in a mixture of 4-methoxybenzaldehyde and 4-nitrobenzonitrile. Some 4-MeO-benzaldehyde oxime was detected in this mixture. In another experiment, benzaldehyde oxime was specifically transferred to **9a** in the presence of 4-nitrobenzonitrile. It shows the facile preparation of 5-subtituted-1*H*-tetrazole form oxime in competition with nitriles. Interesting results were obtained from the mixture of 4-MeO-benzaldehyde and benzaldehyde oxime. The products were spread in this combination, which 60% and 30% conversion was obtained for **9a** and **9b** respectively. Moreover, 10% 4-MeO-benzaldehyde oxime and benzaldehyde oxime were also detected in the mixture. As a conclusion, oxime and/or aldehyde could be efficiently transferred to its corresponding tetrazole without interfere of nitrile. The results provide another evidence for transformation of 5-substituted tetrazole in a different route.

TABLE 4 Chemoselectivity behavior of the catalyst **8** in the presence of aldehyde, oxime or nitrile

		Conversion (%)[a]		
Entry	**Sample[b]**	**9a**	**9b**	**9e**
1[c,d]	MBzA+ NBzN	-	70	15
2[e]	BzAO + NBzN	100	-	0
3[f,g]	MBzA + BzAO	55	30	-

[a]GC analysis. Internal standard: anisole
[b]Definition: MBzA: 4-methoxybenzaldehyde; NBzN: 4-nitrobenzonitrile; BzAO: benzaldehyde oxime
[c]Reaction conditions: MBzA (1.0 mmol), NBzN (1.0 mmol), hydroxyl amine hydrochloride (1.5 mmol), catalyst (0.02 g, 1.0 mol%), NaN_3 (1.5 mmol), PEG (3 ml).
[d]15% 4-MeO-benzaldehyde oxime was found.
[e]Reaction conditions: BzAO (1.0 mmol), NBzN (1.0 mmol), catalyst (0.02 g, 1.0 mol%), NaN_3 (1.5 mmol), PEG (3 ml).
[f]Reaction conditions: MBzA (1.0 mmol), BzAO (1.0 mmol), hydroxyl amine hydrochloride (1.5 mmol), catalyst (0.02 g, 1.0 mol%), NaN_3 (1.5 mmol), PEG (3 ml).
[g]10% 4-MeO-benzaldehyde oxime and benzaldehyde oxime was found.



SCHEME 4 A possible reaction mechanism for GO/Fe3O4@PAA-Cu-complex catalyzed preparation of 5-substituted-1H-tetrazole

The recoverability of Go/Fe_3O_4@PAA-Cu was investigated for the reaction of benzaldehyde with NaN_3 in water, the reaction of benzonitrile with NaN_3 in PEG-400, and the reaction of aniline with triethyl orthoformate/ NaN_3. The results were summarized in Figure 6. As shown in the figure, there is not any change in conversion for the first cycle (Figure 6). An insignificant loss in reaction conversion was observed in other 5th cycles for all experiment. Just a perceptible increase in time was seen for the recycles, especially in the case of the reaction of aniline with triethyl orthoformate/ NaN_3 (Figure 6, purple pyramids).

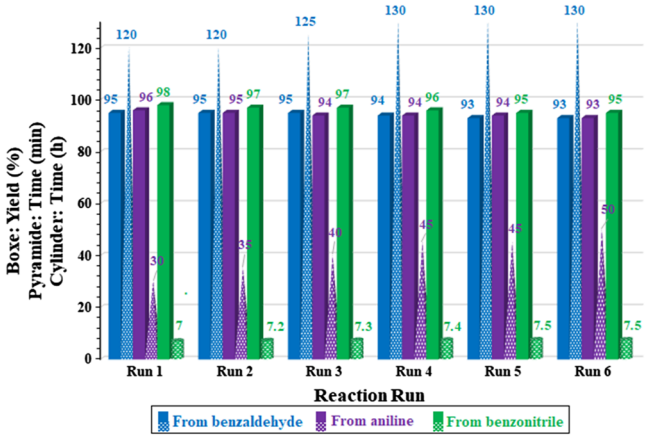


FIGURE 6 Recycling of the Go/Fe3O4@PAA-Cu for the preparation of 5-phenyl-1H-tetrazole (from benzaldehyde and benzonitrile) and 1-phenyl tetrazole (from aniline) through three different approaches

To show durability of the catalyst, the recovered catalyst after 6th run in the reaction of benzonitrile with NaN_3 catalyzed by GO/Fe_3O_4@PAA-Cu-complex in PEG-400 at 100°C, was separated magnetically, washed with deionized water and ethanol, dried into oven and analyzed by SEM, TEM, VSM, and FTIR to show its morphology, size, magnetic behavior and structure respectively. Figure 7A,B, shown the SEM and TEM images of the recovered catalyst with as same morphology and size as the corresponding fresh catalyst. The catalyst remains its magnetic property even after 6th run. As shown in Figure 7C, the saturation magnetization of the recovered catalyst (33.5 emu.g^{-1}) was as much as the fresh ones. Finally, the FTIR spectrum of the recovered catalyst confirmed its structure (Figure 7D).

In order to manifest the heterogeneous nature of the catalyst, the hot filtration experiment was applied on the reaction of benzonitrile with NaN_3 catalyzed by GO/Fe_3O_4@PAA-Cu-complex in PEG-400 at 100 °C. The catalyst was magnetically separated after 3 h of the reaction time. The afforded tetrazole product in this time was 36%. The reaction was allowed to proceed for further 4 h without the catalyst. There is not found any progress in the reaction, which the conversion reached to 38 % after this time. The results show that no metal leaching was happened to promote any catalytic reaction in the medium. In this way, for more elucidation, the leaching amounts were measured on the aforementioned reaction for six consecutive reaction cycles. The residue was analyzed by ICP to measure the Cu contents in the mixture after separation of the catalyst from the mixture. Furthermore, Fe amount was also measured in each cycle to clarify the stability of the catalyst. The results show an insignificant metal leaching in each cycle. It is worth noting that no iron leached to the solution (0 %, ICP

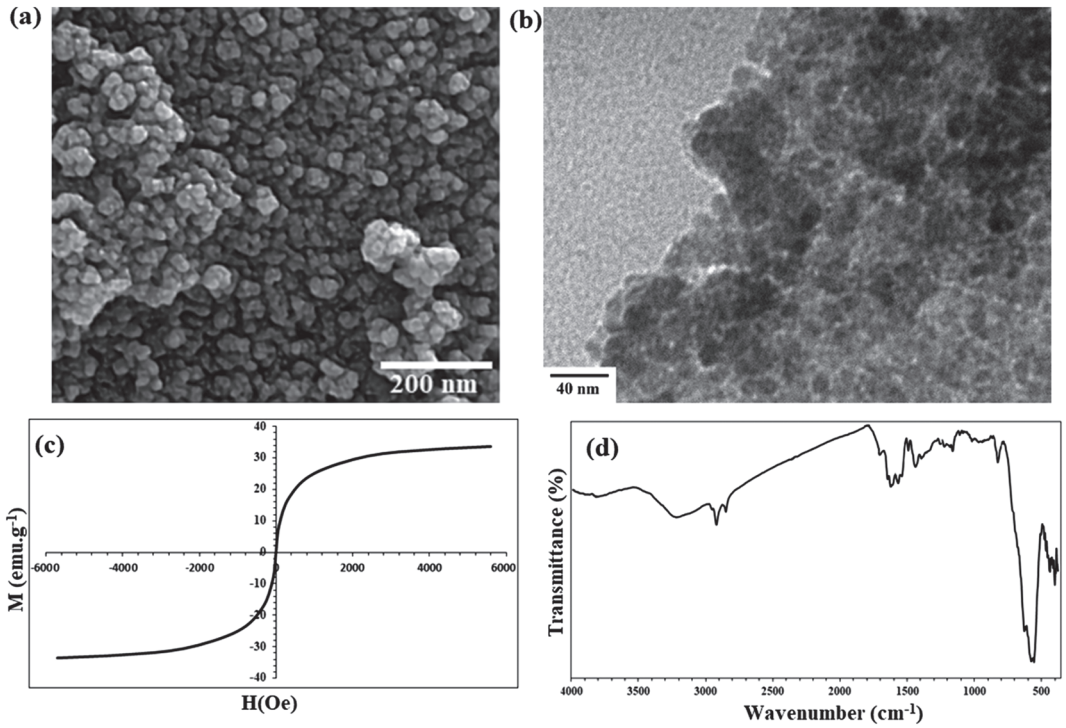


FIGURE 7 (A) FE-SEM, (B) TEM images, (C) VSM curve, and (D) FTIR spectrum of the recovered Go/Fe3O4@PAACu after 6th run

analysis). Cu leached for 1th to 6th was as order of: 0.3%, 0.8%, 1.0%, 1.3%, 1.5%, 1.9% respectively. This indicates that the catalyst is stable during reactions, which cannot be found any deactivation in terms of leaching.

4 | CONCLUSION

In this paper, we have reported a simple and selective method for the transformation of a wide variety of aldehydes, amines and nitriles into the corresponding 1- and 5-substituted tetrazoles using GO/Fe_3O_4@PAA-Cu complex as an efficient catalyst. The catalyst was studied from various aspects including: FTIR, TGA, VSM, FE-SEM, TEM, XRD, EDX, DLS and ICP analyses. High to excellent yields were obtained for all approaches in various conditions. It was suggested that aldehyde and oxime could be transformed to 5-substituted-1*H*-tetrazoles *via* a different milder approach than nitrile. The catalyst bearing α-amino acid polar groups, provide a suitable medium for the transformation of aldehyde and oxime through a three-component click chemistry in water. The recyclability of the catalyst was investigated for six consecutive recycles without any remarkable reactivity loss. Also, an insignificant metal leaching was observed for the catalyst during recycling. The durability and stability of the catalyst was studied by some analytical methods such as FTIR, FE-SEM, TEM and VSM analyses.

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