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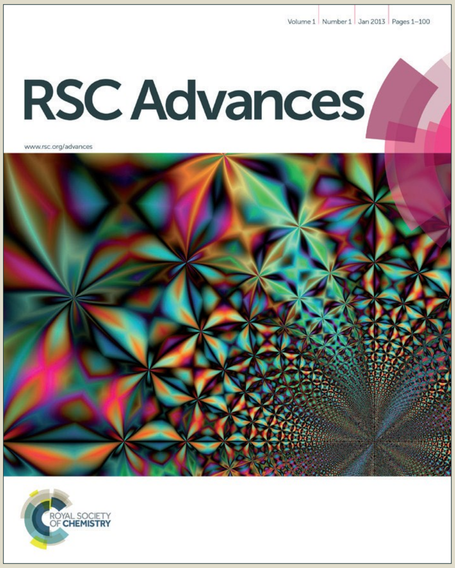

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Magnetic Starch Nanocomposite as a Green Heterogeneous Support for Immobilization of Large Amounts of Copper Ions: Heterogeneous Catalyst for Click Synthesis of 1,2,3-triazoles

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Abstract

A new magnetic heterogeneous copper catalyst was prepared by immobilization of copper ions onto a cross-linked polymeric nanocomposite composed of starch grafted polyacrylamide and functionalized Fe_3O_4 magnetic nanoparticles. The resulting support was loaded with large amounts of copper ions (1.6 mmol g^{-1}). The prepared catalyst is highly active in Huisgen 1,3-dipolar cycloaddition reaction of different azides and alkynes at low catalyst amount. Various corresponding 1,2,3-triazoles were produced with high yields in mild condition. The catalyst was easily recovered and reused for ten cycles of reaction and no significant loss of catalytic activity was observed.

Keywords: Huisgen cycloaddition, copper catalysis, magnetic nanoparticles, polymeric supports, green catalytic system

Introduction

The concept of click chemistry, first introduced by Sharpless *et al.*, refers to the reactions that are modular, wide in scope and highly efficient, performing with high regio- and sterio-selectivity under mild conditions.[1] In recent years, these kinds of reactions have attracted much attention in different fields of organic chemistry, material science and drug discovery.[2-4] The most well-known example of click reactions is catalytic 1,3-dipolar cycloaddition of organic alkynes and azides.[5,6] This reaction is very attractive since it can be used for synthesis of 1,2,3-triazole derivatives, a class of compounds that have been recognized possessing biological and pharmaceutical activities.[7,8]

However the original non-catalyzed form of this reaction, known as Huisgen cycloaddition reaction, has slow rate and low yield at room temperature due to high kinetic energy barrier of the reaction.[9,10] It has been recognized that Cu(I) is an appropriate catalyst for Huisgen reaction since it accelerates the rate of the reaction and significantly improves its regioselectivity.[11,12] Although both homogeneous and heterogeneous catalysts were used in this reaction, heterogeneous catalysts have more advantages than homogenous ones, because of facile separation and reusability of the catalyst and simple isolation of the product.[13-16] These properties are especially very important for pharmaceutical purposes since it is essential to remove trace amount of catalysts remained in the final product. Moreover, in drugs synthesis process the supported materials, used for immobilization of copper, should be biocompatible to prevent the possible leached contamination from solid catalysts to final products.

A variety of heterogeneous catalytic systems were prepared by immobilization of copper ions onto different solid supports such as magnetic nanoparticles,[17] silica,[18] zeolite,[19] alumina,[20] and polymers[21], and were used for click synthesis of 1,2,3-triazoles. In these systems, the catalyst can be separated from the reaction medium by simple filtration or centrifugation. However, using magnetic nanoparticles makes separation and recovery of the catalyst faster and more convenient in comparison with non-magnetic catalysts. The catalyst can be easily removed after the completion of the reaction by using a magnet.[22-24]

In spite of the great advantageous of heterogeneous catalytic systems, loading amounts of the active spices (copper ions) in these systems is usually low and thus a large amount of solid catalyst is required to perform the reaction. This resulted to using large amounts of solvent for reaction mixing and catalyst separation. Plus, increasing in the amount of used catalyst leads to an increase in the contamination of final products. In many cases, the activity of the catalyst also decreases after immobilization on solid supports. High catalyst leaching and low thermal stability of the catalyst are other drawbacks of heterogeneous catalytic systems. As a consequence, it is still demanded to develop an efficient heterogeneous catalytic system with high loading, high stability and easy separation.

Polymeric materials with different structures, compositions and functionalities have been prepared and employed as supports in heterogeneous catalytic systems.[25-27] However, natural polymers, especially polysaccharides, are more attractive since they are easily available, inexpensive, nontoxic, and biodegradable.[28-30] There are also many functional groups in the structure of natural polymers being able to interact with metal ions and nanoparticles. These properties make polysaccharides and other natural polymers excellent candidates for being used as supports in heterogeneous catalytic systems.

Herein, we report preparation of copper immobilized magnetic starch-based heterogeneous catalytic system for 1,4-disubstituted 1,2,3-triazols. The catalyst is easily prepared by simultaneous polymerization, grafting and crosslinking of acrylamide onto the starch in the presence of magnetic nanoparticles.

Experimental

Materials

Acrylamide was purified by recrystallization in methanol. Starch, tetraethylorthosilicate (TEOS), 3-(trimethoxysilyl) propylmethacrylate (MPS), sodium ascorbate, sodium azide (NaN_3), $FeCl_2.4H_2O$, $FeCl_3.6H_2O$, ammonium persulfate (APS), N,N`-methylenebisacrylamide (MBA), $CuCl_2$, ammonia solution (25%) and ethanol all were obtained from Merck and Aldrich and used without further purification.

Fourier transform infrared (FTIR) spectra were recorded on ABB Bomem MB 100 spectrophotometer. X-ray diffraction (XRD) patterns were obtained by a Siemens D5000 diffractometer with Cu K_α radiation in 2θ range of 5-80°. Scanning electron microscopy (SEM) images were taken on Mira3 Tescan microscope. Thermogravimetric analysis (TGA) was performed at heating rate of 10 °C under nitrogen atmosphere using Perkin-Elmer Pyris1 instrument. Transmission electron microscopy (TEM) experiments were carried out by a Philips CM30 electron microscope. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker (Avance DRX-400) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The magnetic properties of samples were measured with a vibrating sample magnetometer (VSM, PPMS-9T) in Kashan University, Iran.

Synthesis of MPS functionalized silica-coated Fe_3O_4 nanoparticles (MNPs)

Fe_3O_4 magnetic nanoparticles were prepared by coprecipitation of Fe (II) and Fe (III) salts. Typically, 200 mL distilled water was poured in a round-bottom flask equipped with a mechanical stirrer. 5 mmol (1.0 g) $FeCl_2.4H_2O$ and 10 mmol (2.7 g) $FeCl_3.6H_2O$ were added and stirred to dissolve. Then, ammonia solution was added to the flask dropwise until the pH of the solution reached to 10. The mixture was stirred vigorously at 60 °C for 1 h. The black precipitate was collected by a magnet and washed with water (5×50 mL) and dried at 60 °C.

In order to prepare silica-coated Fe_3O_4 nanoparticles, 1.0 g of the prepared magnetic nanoparticles were dispersed in 80 mL 4:1 ethanol/water solution in a round-bottom flask and sonicated for 20 min. Then, 0.5 mL tetraethylorthosilicate (TEOS) was added and the pH of the solution was adjusted to 10 using ammonia solution. The mixture was refluxed for 12 h. Afterward, the flask was cooled to room temperature and the resulting particles were washed with water (3×50 mL) and ethanol (2×25 mL) and dried in an oven at 60 °C.

Fe_3O_4@SiO_2 nanoparticles were then functionalized with MPS using the same procedure mentioned above for synthesis of Fe_3O_4@SiO_2. 0.7 g Fe_3O_4@SiO_2, 3 mL MPS and 1 mL ammonia were refluxed in 100 mL 4:1 ethanol/water solution. After 12 h, the prepared particles were washed with water (3×20 mL) and ethanol (2×20 mL) and dried at 60 °C (MNPs).

Preparation of the catalyst (MNP@SPAAm/Cu)

Magnetic polymeric support was prepared according to the following procedure: 0.5 g MNPs were dispersed in 20 mL water in a round-bottom flask and sonicated for 20 min. Then, 0.5 g starch was added to flask. After all starch was dissolved, 0.05 g APS was added to solution and mixture was put in an oil bath at 70 °C. Then, a mixture of 2.0 g acrylamide and 0.4 g MBA in 10 mL water was added to flask and polymerization was performed for 1 h. The prepared hydrogels were washed with ethanol, dried at 50 °C and sieved through an 80-mesh sieve for further use.

For loading of copper, 0.5 g of the prepared polymeric nanocomposite was added to an aqueous solution of $CuCl_2$ (0.3 g in 25 mL). The mixture was stirred for 24 h at 50 °C and the solid particles were then magnetically separated, washed with water (5×25 mL) and ethanol (2×25 mL) and dried at 60 °C.

General procedure for synthesis of 1,2,3-triazoles

Alkyne (1 mmol), alkyl halide (1 mmol) and NaN_3 (1.3 mmol) were added to 3 mL water in a round-bottom flask. 3.1 mg of the prepared catalyst and 0.02 g sodium ascorbate (10 mol%) were added and the flask content was stirred at room temperature. The completion of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the catalyst was separated magnetically and the flask content was extracted with ethyl acetate. The catalyst was washed with ethanol three times and dried at 60 °C and used for next runs. All the products are known compounds and the spectral data and melting points were identical to those reported in the literature.[17-24]

Results and discussion

Preparation of the Catalyst

The heterogeneous catalyst was prepared by immobilization of Cu (II) ions in the structure of cross-linked solid polymeric nanocomposite. The polymeric support was prepared by simultaneous polymerization, grafting and cross-linking of acrylamide onto starch as a biodegradable backbone. Using starch makes the prepared catalyst more biodegradable and environmentally friendly. The polymerization was performed in the presence of APS as initiator and MBA as cross-linking agent. While cross-linking polymerization was performed, MNPs were entrapped into the polymeric matrix. The presence of acrylate groups on the surface of MNPs causes the covalent attachment of MNPs to polymer. Moreover, acrylate functionalized MNP acts as a second cross-linker and improves the stability of solid support. The presence of magnetic nanoparticles into the polymeric support facilitates the separation and recyclability of the catalyst. The copper ions were then loaded onto the surface of magnetic nanocomposite by complextion with numerous amide groups of MNP@SPAAm.

This leads to high loading and low leaching of copper ions in the prepared catalyst. The synthetic route of the prepared catalyst is illustrated in Fig. 1.

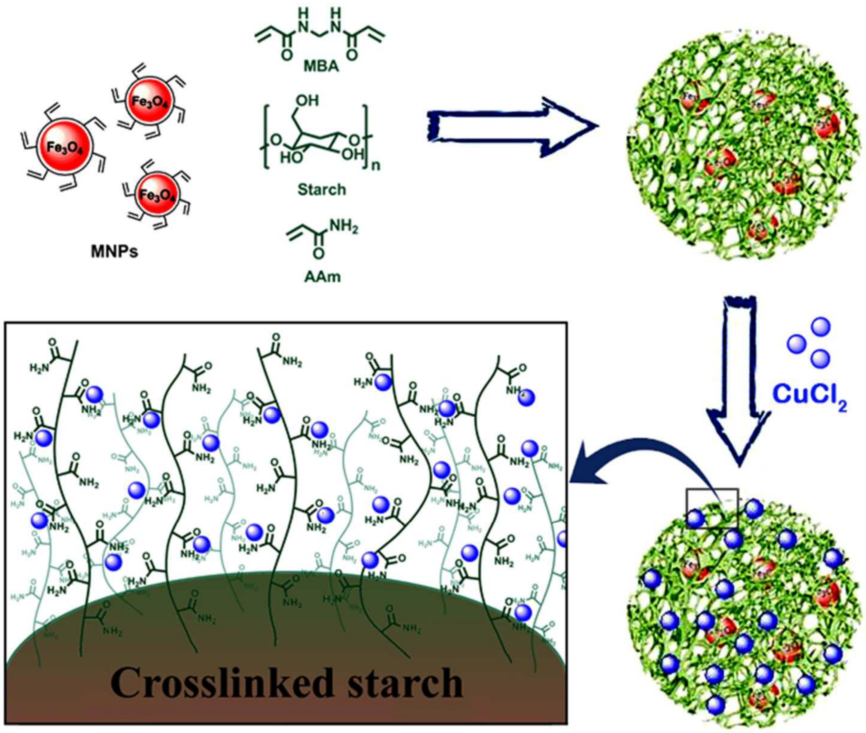


Fig. 1 The synthetic route of MNP@SPAAm/Cu catalyst.

Characterization

FTIR spectra of Fe_3O_4, Fe_3O_4@SiO_2, Fe_3O_4@SiO_2@MPS and MNP@SPAAm are shown in Fig. 2. The peak appeared at 570 cm^{-1} is characteristic peak of Fe-O stretching vibrations of Fe_3O_4. The strong peak appeared at 1100 cm^{-1} is attributed to Si-O stretching vibrations of silica layer coated on Fe_3O_4. In the spectrum of Fe_3O_4@SiO_2@MPS (Fig. 1c), the extra weak peak appeared at 1725 cm^{-1} is related to C=O stretching band and confirms that MPS was successfully coated onto Fe_3O_4@SiO_2 nanoparticles. The peaks appeared in the spectrum of MNP@SPAAm are due to different functional groups present in the structure of starch and polyamide. The peaks appeared at 3500, 2950 and 1670 cm^{-1} are related to O-H, C-H and C=O amide stretching bands of polymer matrix, respectively.

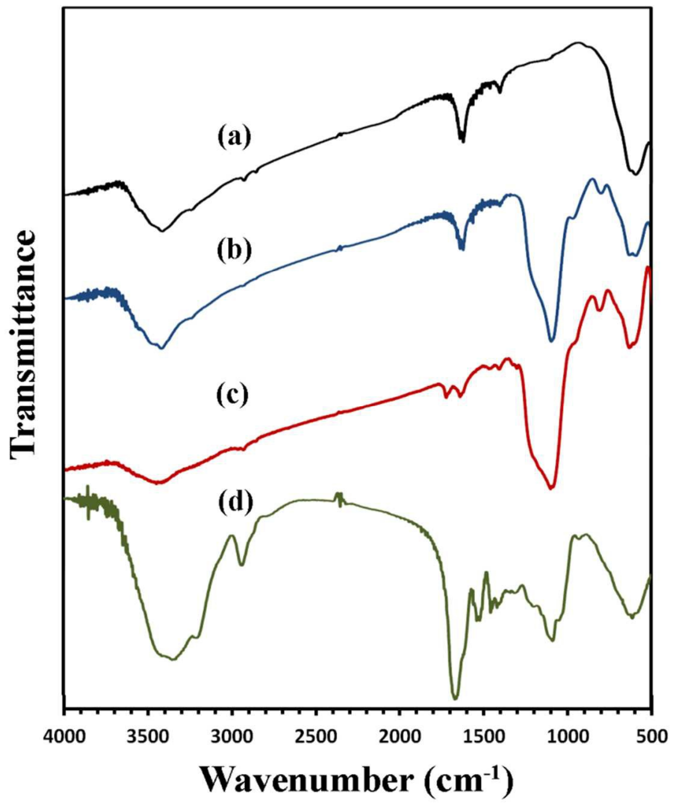


Fig. 2 FTIR spectra of Fe_3O_4 (a), Fe_3O_4@SiO_2 (b), Fe_3O_4@SiO_2@MPS (c) and MNP@SPAAm (d).

Fig. 3a shows the TEM image of Fe_3O_4 nanoparticle, synthesized by coprecipitation method with size of 5-9 nm. These sizes of MNPs are suitable for catalytic application, due to high magnetization and fast separation. The TEM image of MNP@SPAAm/Cu (Fig. 3b) shows that magnetic nanoparticles (dark spots) are well-dispersed in the polymeric matrix (gray shell). The SEM image of MNP@SPAAm/Cu (Fig. 3c) also shows that the prepared particles have semispherical morphology with rough surface. Such rough structure of the catalyst increases surface area of catalyst and improves its catalytic activity. The presence of copper as well as iron and silica in the structure of the catalyst was also confirmed by EDX analysis (Fig. 3d).

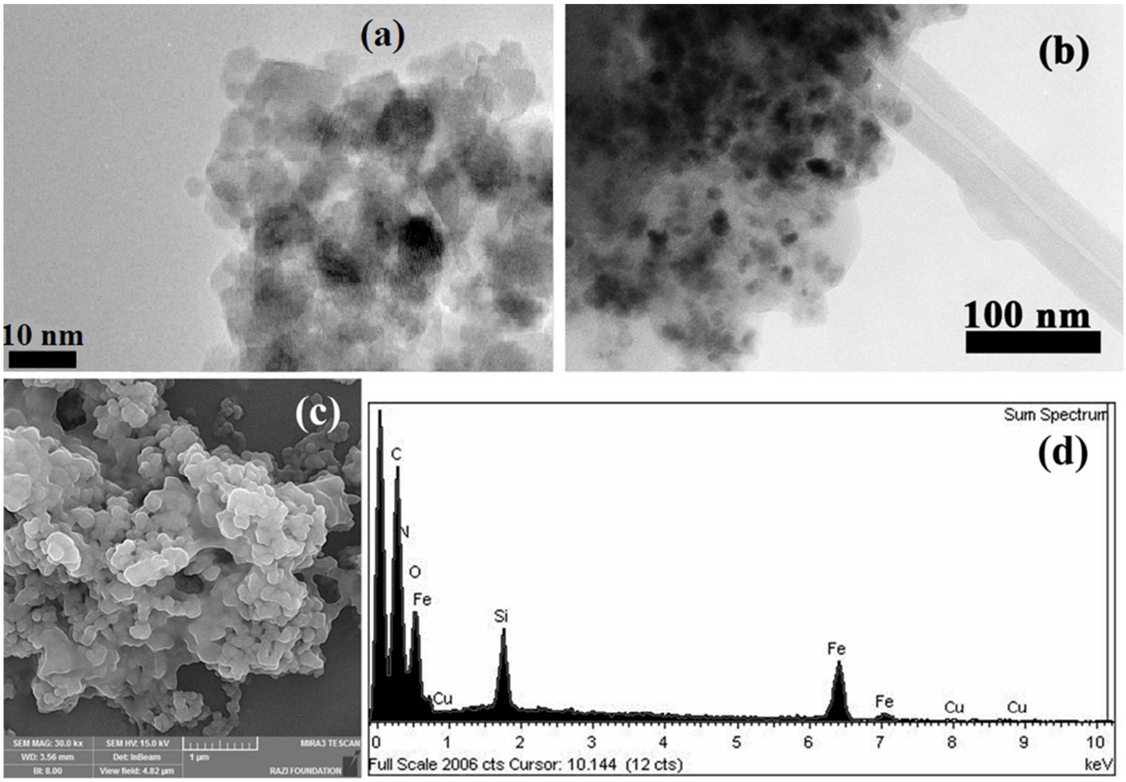


Fig. 3 HRTEM images of Fe_3O_4 (a) and MNP@SPAAm/Cu (b) and SEM (c) image and EDX analysis (d) of MNP@SPAAm/Cu.

The loading of copper on the surface of support was calculated using ICP-OES and the value of 1.6 mmol g^{-1} was obtained. The high loading of copper obtained here is due to the polymeric nature of support surface with large chelating groups on the surface of support. The loading level of catalytically active species on the surface of solid supports is an important feature of catalysts since high loadings reduce weight percent of catalyst required for the reaction. This feature is especially more prominent for large scale applications.

The XRD pattern of MNP@SPAAm/Cu is shown in Fig 4. Six peaks appeared at 2θ values about 30, 36, 43, 53, 57, and 62° are characteristic peaks of Fe_3O_4 particles, indicating the crystalline phase of Fe_3O_4 nanoparticles did not changed during the catalyst preparation. The broad peak at 2θ range of 20-30° is related to amorphous silica layer in MNPs.

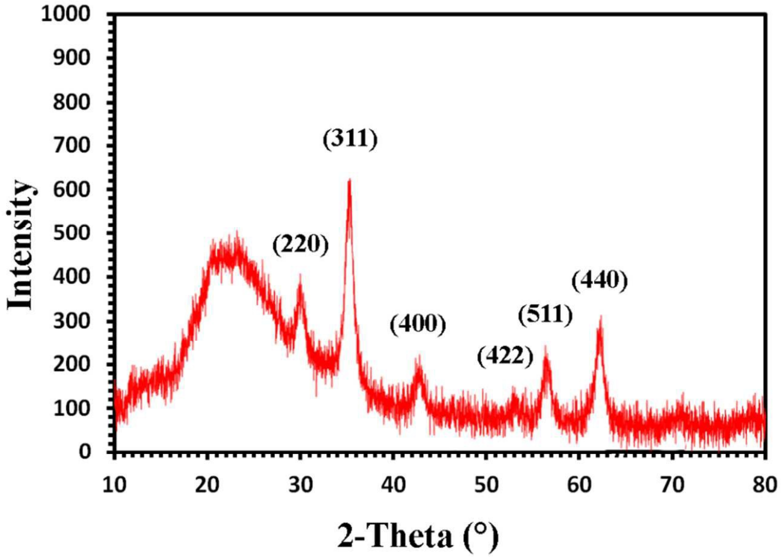


Fig. 4 XRD pattern of MNP@SPAAm/Cu.

Magnetic properties of bare Fe_3O_4 and MNP@SPAAm/Cu were investigated by VSM and the related magnetization curves are depicted in Fig. 5. It is observed that magnetic hysteresis loop of both samples exhibits superparamagnetic characteristic at room temperature. Saturation magnetizations of MNPs and MNP@SPAAm/Cu are 64 and 22 emu g^{-1}, respectively. Although saturation magnetization decreases after embedment of MNPs into the structure of polymeric network, it is still high enough to be readily separated by an external magnetic field.

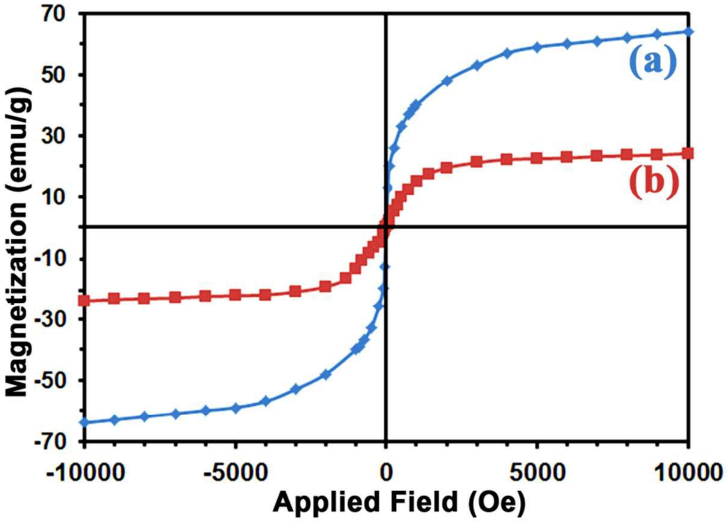


Fig. 5 Magnetization curve of MNPs (a) and MNP@SPAAm/Cu (b).

TGA curves of Fe_3O_4@SiO_2, Fe_3O_4@SiO_2@MPS, pure starch and MNP@SPAAm/Cu are shown in Fig. 6a-d. The weight loss observed at about 100 °C in all curves is related to removal of physically adsorbed water molecules. The weight loss occurred at 250-450 °C in TGA curve of Fe_3O_4@SiO_2@MPS is due to degradation of propylmethacrylate groups grafted onto Fe_3O_4@SiO_2. The main thermal degradation of pure starch occurs at 200 °C and about 90 wt% of starch is degraded up to 700 °C. TGA curve of MNP@SPAAm/Cu shows a two-step degradation behavior, the first of which occurs at 250 °C and is related to degradation of starch. The second degradation step of MNP@SPAM/Cu starts at 320 °C and about 40 wt% of the sample is lost in this step due to decomposition of grafted polyacrylamide.

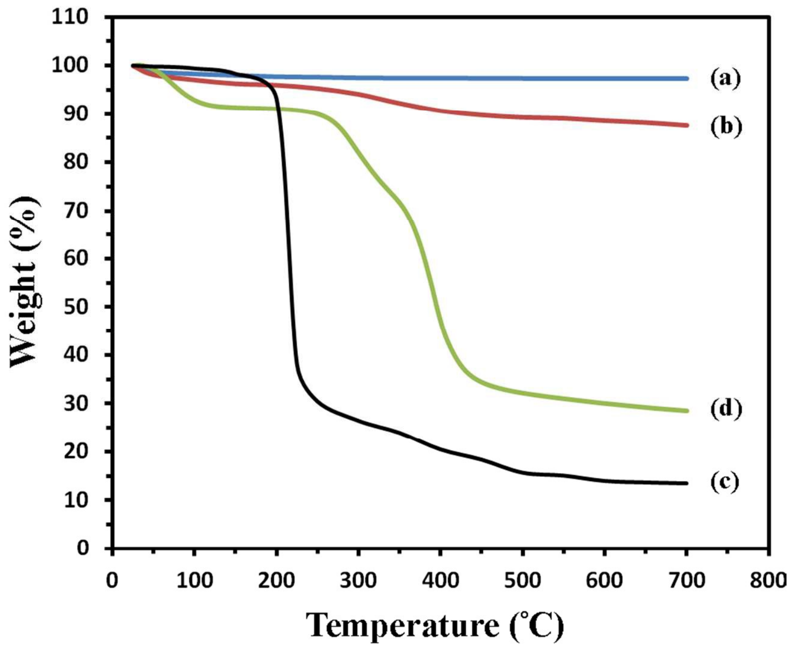


Fig. 6 TGA curves of Fe_3O_4@SiO_2 (a), Fe_3O_4@SiO_2@MPS (b), pure starch (c) and MNP@SPAAm/Cu (d).

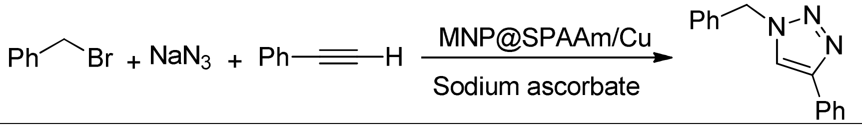
Catalytic performance of MNP@SPAAm/Cu

The catalytic activity of the prepared catalyst in multicomponent cycloaddition of alkyl halides, sodium azide and terminal alkynes was then examined. The reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen as the control reaction and the effect of different experimental conditions on yield of the reaction was investigated.

The results of optimization experiments are listed in Table 1. It can be seen that in the absence of any catalyst, no significant amount of product was obtained even at 70 °C (Entries 1,2). The same result was observed in the case of using just MNPs or MNP@SPAAm, and the reaction yield was very low, indicating MNPs and MNP@SPAAm do not have any catalytic activity in this reaction (Entries 3,4). In the presence of 5 mg (0.8 mol%) of MNP@SPAAm/Cu, the reaction yield was increased to 99% in 30 min at 50 °C (Entry 5). However, the reaction was slower at room temperature and only 80% yield was obtained after

2 h (Entry 6). Completion of the reaction at room temperature required longer times up to 8 h (Entry 7). The effect of the amount of the catalyst on yield of the reaction was also investigated. Decreasing the amount of MNP@SPAAm/Cu to 0.5 mol% did not change the yield of the reaction (Entry 8). However, further decreasing of the amount of MNP@SPAAm/Cu to 0.3 and 0.1 mol% reduced rate of the reaction, and only 73 and 66% yield were obtained after 1 h (Entries 9,10). Thus, 0.5 mol% was chosen as the optimum amount of MNP@SPAAmCu. In other experiments, the reaction performed in the presence of small amounts of catalyst and the results showed that in longer reaction times only 0.01 mol% of catalyst gave 89% yield (Entries 11,12). The reaction was also performed in different solvents such as H_2O/t-BuOH (3:1), t-BuOH, CH_3CN, CH_3OH and toluene (Entries 13-17). However, the best result was obtained in pure water or water/alcohol mixture due to NaN_3 dissolves in water. Based on the results obtained here, the reaction of alkyl halides, sodium azide and alkynes in H_2O at 50 °C in the presence of 0.5 mol% MNP@SPAAm/Cu was considered as optimum experimental condition for further experiments.

Table 1 Optimization of the reaction conditions for the synthesis of 1,4-disubstituted 1,2,3-triazoles[a]



Entry	Catalyst	Cat. Amount (mol%)	*T* (°C)	Time (h)	Solvent	Yield (%)[b]
1	-	-	50	7	H_2O	-
2	-	-	70	8	H_2O	12
3	MNPs	100 mg	50	7	H_2O	27[c]
4	MNP@SPAAm	100 mg	50	7	H_2O	7
5	MNP@SPAAm/Cu	0.8	50	0.5	H_2O	99
6	MNP@SPAAm/Cu	0.8	r.t	2	H_2O	80
7	MNP@SPAAm/Cu	0.8	r.t	8	H_2O	97
8	MNP@SPAAm/Cu	0.5	50	0.5	H_2O	99
9	MNP@SPAAm/Cu	0.3	50	1	H_2O	73
10	MNP@SPAAm/Cu	0.1	50	1	H_2O	66
11	MNP@SPAAm/Cu	0.1	50	10	H_2O	94
12	MNP@SPAAm/Cu	0.01	50	24	H_2O	89
13	MNP@SPAAm/Cu	0.5	50	0.5	H_2O/t-BuOH	99
14	MNP@SPAAm/Cu	0.5	50	1	t-BuOH	46
15	MNP@SPAAm/Cu	0.5	50	1	CH_3CN	32
16	MNP@SPAAm/Cu	0.5	50	2	CH_3OH	68
17	MNP@SPAAm/Cu	0.5	50	3	Toluene	10

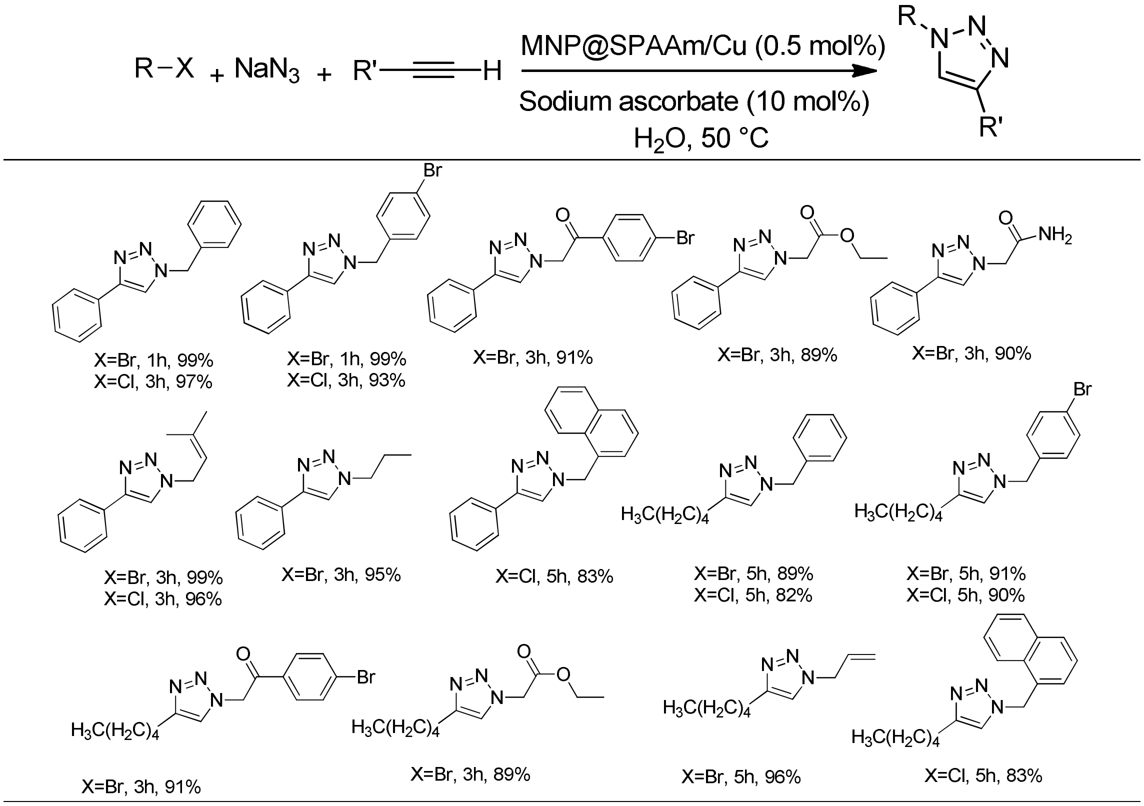
[a] Reaction condition: Phenyl acetylene (1 mmol), benzyl bromide (1 mmol), sodium azide (1.3 mmol), sodium ascorbate (10 mol%), solvent (2 ml).

[b] Isolated yield

[c] A mixture of isomers.

The activity of the catalyst in multicomponent cycloaddition reaction of sodium azide and various alkyl halides and alkynes were then investigated using optimized experimental conditions obtained previously. The structure of the alkyl halides and alkynes used as substrates and the results of the experiments are shown in Table 2. All reactions were proceeded easily and the corresponding 1,2,3-triazoles were produced with satisfactory yields. The results show that the prepared catalyst is very efficient in synthesis of various 1,2,3-triazole compounds.

Table 2 Cycloaddition reaction of different alkyl halides and alkynes catalyzed with MNP@SPAAm/Cu[a].



[a] Reaction condition: alkyl halide (1 mmol), NaN_3 (1.3 mmol), alkyne (1 mmol), H_2O (2 mL).

[b]Isolated yield.

Reusability of the catalyst

Reusability is an important feature of the catalyst which should be examined in catalytic reactions. The reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen as model reaction and the reusability of MNP@SPAAm/Cu in this reaction was tested. After completion of the reaction, the catalyst was readily separated by using a magnet, washed with ethanol (2×25 mL) and dried at 50 °C and used for next run. This process was repeated for ten runs of reactions and the results are shown in Fig. 7. It can be seen that high yields of the reactions were obtained even after ten cycles of reaction. However, the time required for completion of the reaction was slightly increased. It is also observed that turnover number (TON) of the catalyst did not changed significantly. However, turnover frequency (TOF) of the catalyst decreased after 6 cycles which resulted from increasing in reaction times. It is notable, that the increasing of the reaction time is attributed to loss of catalyst mass during the separation process. High catalytic activity and high loading of the catalyst along with simple separation, recyclability and reusability of MNP@SPAAm/Cu make it cost effective and environmentally friendly.

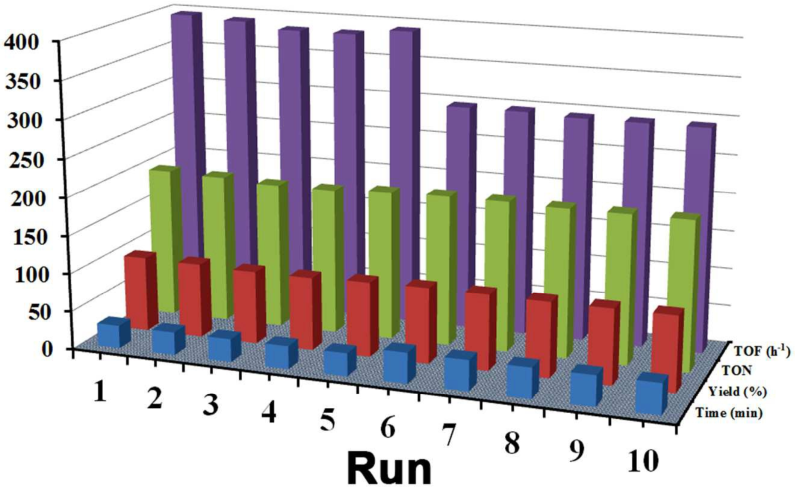


Fig. 7 Recycling experiment.

The structure of the recycled catalyst was investigated by FTIR spectroscopy and was compared with that of the fresh catalyst. Fig. S1 shows that FTIR spectra of both fresh and recycled catalyst are almost similar. Moreover, ICP-OES shows that there are no significant changes in copper content of the recycled catalyst and loading of copper after 10 cycles was 1.46 mmol g^{-1}. The results confirm that the catalyst is stable and its structure and composition did not change even after ten times recycling.

In order to investigate the leaching of the catalyst, the reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen as the model reaction and performed under optimized condition given in Table 1. The reaction was stopped after half of the reaction time and the catalyst was separated from the reaction mixture by using a magnet. The remaining mixture (without catalyst) was left to stir for another period of half the reaction time. As is shown in Fig. 8, no more products were produced after removal of the catalyst indicating there is no significant leaching of copper ions. Moreover, based on the results of ICP-OES, no free copper ions were detected in the reaction mixture which confirms that the leaching of catalyst is negligible.

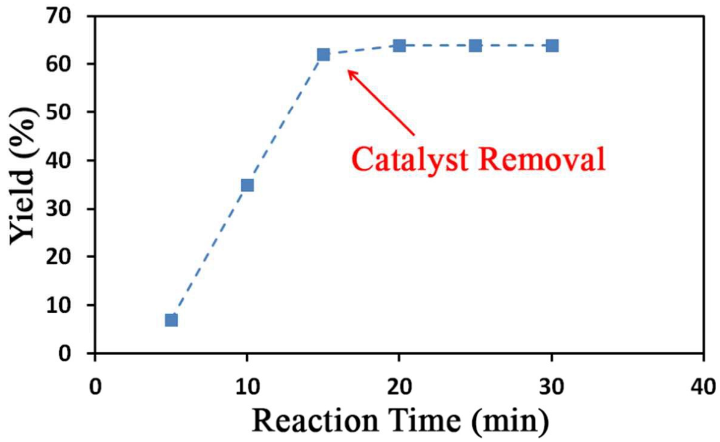
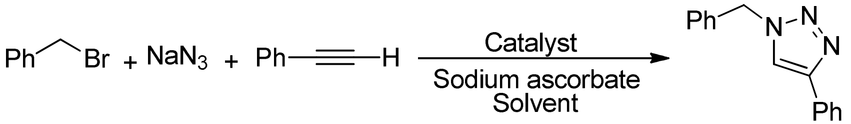


Fig. 8 Leaching experiment.

Comparison with other catalysts

The catalytic performance of MNP@SPAAm/Cu was then compared with that of some other catalysts used for Huisgen cycloaddition of azides and alkynes. The reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen as the model reaction and the data obtained from some catalysts reported recently are summarized in Table 3. It is observed that in most cases the yield of the reactions is high. However the process introduced in this study, is a green approach in which the reaction is performed in water at mild temperature and is completed in short time. The catalyst is partly composed of starch which as a non-toxic natural polymer makes the catalyst more biodegradable and environmentally friendly. Because of its magnetic properties, the catalyst can also be easily and rapidly separated from the reaction mixture by using a magnet. Moreover, the loading of the catalyst prepared here is very high which in turn decreases the amount of catalyst required for the reaction. Due to high loading of the catalyst, only a small amount of catalyst can precede the reaction effectively.

Table 3 The comparison of MNP@SPAAm/Cu with other catalysts reported for Huisgen cycloaddition.



Catalyst	Cu loading (mmol g^{-1})	Cat. Amount (mg(mol%))	Solvent	T (°C)	Time (h)	Yield (%)	Ref
Chitosan/Cu	0.80	50(0.4)	H_2O	r.t	4	99	28
Chitosan-coated Fe_3O_4/Cu	0.77	20(1.54)	CH_2Cl_2	r.t	12	92	22
Cu/SiO2	2.59	38.5(10)	H_2O	70	12	95	31
Hydroxyapatite/Cu (II)	0.1	200(2)	H_2O	50	8	97	32
Cu NPs/Activated carbon	0.3	17(0.5)	H_2O	70	3	98	33
Silica PEI/CuNPs	0.24	2(0.05)	DMSO	r.t	0.17	98	34
MNP@Triazole/Cu	0.51	10(0.5)	H_2O/t-BuOH	55	2	99	17
MNP@PILCu	1.87	4(0.7)	H_2O	50	2.5	95	24
Cu NPs/Graphite	0.77	6.5(0.05)	H_2O/CH_3OH	70	12	91	35
MNP@SPAAm/Cu	1.6	3.1(0.5)	H_2O	50	0.5	99	This study

Conclusion

We have successfully developed a green heterogeneous catalytic system for Huisgen cycloaddition by immobilization of copper ions on magnetic polymeric supports. The solid support was prepared by polymerization and grafting of AAm onto starch in the presence of functionalized Fe_3O_4 magnetic nanoparticles. The presence of starch makes the prepared catalyst more cost effective and eco-friendly. The loading level of copper ions on the cross-linked polymeric supports was 1.6 mmol g^{-1} and no significant loss of catalyst activity was observed. The prepared catalyst exhibits high catalytic activity in Huisgen cycloaddition of various azides and alkynes. 1,2,3-triazoles with good to excellent yields were synthesized by using the prepared catalyst. The catalyst was separated magnetically and reused for ten cycles of reaction without any significant loss of catalytic activity. Finlay, comparison of this protocol with other reported methods showed that the presented catalyst is used in lower weight percent. This aspect of catalyst is especially useful in large scale where a small amount of catalyst can produce large amounts of products.

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Graphical Abstract

Magnetic Starch Nanocomposite as a Green Heterogeneous Support for Immobilization of Large Amounts of Copper Ions

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