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FULL PAPER

Copper(I) oxide nanoparticles supported on magnetic casein as a bio-supported and magnetically recoverable catalyst for aqueous click chemistry synthesis of 1,4-disubstituted 1,2,3-triazoles

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Copper(I) oxide nanoparticles supported on magnetic casein (Cu_2O/Casein@Fe_3O_4NPs) has been synthesized as a bio-supported catalyst and was characterized using powder X-ray diffraction, transmission electron microscopy, energy dispersive X-ray and Fourier transform infrared spectroscopies, thermogravimetric analysis and inductively coupled plasma optical emission spectrometry. The catalytic activity of the synthesized catalyst was investigated in one-pot three-component reactions of alkyl halides, sodium azide and alkynes to prepare 1,4-disubstituted 1,2,3-triazoles with high yields in water. The reaction work-up is simple and the catalyst can be magnetically separated from the reaction medium and reused in subsequent reactions.

KEYWORDS
alkyne–azide cycloaddition, bio-supported catalyst, casein, copper(I) oxide nanoparticles, magnetically recoverable nanocatalyst

1 | INTRODUCTION

Click chemistry based on green chemistry has emerged as a fast and efficient approach for the design and implementation of environmentally benign processes. One of the most powerful click reactions is Huisgen 1,3-dipolar cycloaddition of an alkyne and an azide to afford 1,2,3-triazole derivatives. Although the 1,2,3-triazole structural moiety does not occur in nature, several members of the 1,2,3-triazole family have revealed interesting biological properties, such as anti-HIV activity,[1] antimicrobial activity against Gram-positive bacteria,[2] anti-allergic,[3] anti-convulsant[4] and β-lactamase inhibitory activity,[5] selective β3 adrenergic receptor agonism,[6] and so on.[7] Moreover, 1,2,3-triazoles have been used in industrial applications, such as in dyes, anticorrosive agents, photographic materials and so on.[8]

In 2002, the discovery of copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) by Sharpless and co-workers[9] and Meldal and co-workers[10] improved the regioselectivity of the Huisgen 1,3-dipolar cycloaddition reaction of azides and alkynes and provides a direct entry into 1,4-disubstituted 1,2,3-triazoles. CuAAC because of its unique click nature, namely no by-products, high yields, moderate reaction conditions and compatibility with water, has emerged as a promising synthesis approach.[11]

High regio-, chemo- and enantio-selectivity are some of the advantages of homogeneous catalysis, but the difficulty of catalyst separation from the final product creates economic and environmental barriers to broadening its scope. Removal of trace amounts of catalyst from the end product is essential since metal contamination is highly regulated, especially by the pharmaceutical industry. To overcome these problems, chemists and engineers have investigated a wide range of strategies; the use of heterogeneous catalyst systems appears to be the best logical solution.[12]

As is well known, nanoparticles with small sizes tend to aggregate in solution. To avoid uncontrolled growth or aggregation in the preparation of nanoparticles, stabilizers such as polymers, surfactants or small organic molecules are often used. The conjugation of nanoparticles with biomolecules such as proteins, DNA, enzymes, antibodies etc. has many different applications including catalysis, biosensing, targeted drug delivery and directed self-assembly leading to high-order nanoscale materials.[13] This conjugation affords long-term stability of the system and also introduces biocompatible functionalities into the nanoparticles for further biological application.[14]

Casein, a proline-rich globular protein which is readily available in milk, can be thought of as a block copolymer consisting of blocks with high levels of hydrophobic or hydrophilic amino acid residues. Thus, caseins are naturally self-assembled to form casein micelles with diameters ranging from 50 to 200 nm (average 150 nm) via a balance of attractive hydrophobic interactions and electrostatic repulsion in aqueous solution.[15]

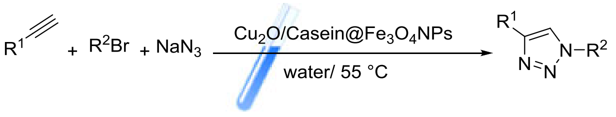
Functionalized magnetic nanocatalytic systems possess several advantages over conventional catalyst systems such as high surface area to volume ratio, reaction rates closer to homogeneous counterparts and being magnetically separable.

As part of our ongoing research programme on the development of new catalytic systems with emphasis on green and natural supports,[16] herein, we present a successful preparation of copper(I) oxide nanoparticles supported on magnetic casein (Cu_2O/Casein@Fe_3O_4NPs) which has excellent catalytic activity. One-pot three-component reactions of various alkyl halides, sodium azide and various alkynes were carried out under environmentally friendly conditions with excellent yields in short reaction times at room temperature (Scheme 1). To the best of our knowledge, the work presented is the first example to demonstrate the usefulness of casein as a support for copper(I) oxide nanoparticles and it is a novel catalyst with unique properties for Huisgen 1,3-dipolar cycloaddition for the preparation of 1,4-disubstituted 1,2,3-triazoles.

2 | EXPERIMENTAL

2.1 | Materials and methods

Casein was purchased from Merck (CAS 9000-71-9). Copper determination was carried out using inductively coupled plasma optical emission spectrometry (ICP-OES) with a Varian Vista PRO Radial. Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. Fourier transform infrared (FT-IR) spectra were recorded with a Bomem MB series FT-IR spectrophotometer. Scanning electron microscopy (SEM) observations were carried out with a TESCAN Vega instrument. All samples were sputtered with gold before observation. Transmission electron microscopy (TEM) was performed using a Philips CM-30 microscope with an accelerating voltage of 150 kV. Identification and quantification were carried out using a Varian model 3600 gas chromatograph (Varian Iberica, Madrid, Spain) equipped with a split/splitless capillary injection port and flame ionization detector. A CP-Sil-8 fused silica capillary column (25 m, 0.32 mm inner diameter and 0.52 mm film thickness) from Chrompack was employed. Thermogravimetric analysis (TGA) was carried out using an STA 1500 instrument at a heating rate of 10°C min^{-1} in air. Powder X-ray diffraction (XRD) data were collected with an XD-3 A diffractometer using Cu Kα radiation. Energy dispersive X-ray spectroscopy (EDX) was performed with a Philips XL-300 instrument.



SCHEME 1 Synthesis of 1,2,3-triazoles catalysed by Cu_2O/Casein@Fe_3O_4NPs

2.2 | Synthesis of Cu_2O/Casein@Fe_3O_4NPs

Casein (0.75 g) was mixed with 25 ml of deionized water and was stirred for 5 min. Then $FeCl_2·4H_2O$ (aq)/$FeCl_3·6H_2O$ (aq) (1:2) (0.65 g/1.75 g) which was dissolved in 2 ml of deionized water was added while the temperature of the mixture was increased to 80°C for 1 h. Ammonium hydroxide (25%) was added dropwise to adjust the pH of the solution to 8–9 (at this pH casein was dissolved) and then continually stirred for 1 h at 80°C. Subsequently, the reaction mixture was cooled to room temperature and $CuCl_2·2H_2O$ (0.09 g, 0.50 mmol) which was dissolved in 5 ml of water was added to it slowly. Then, the solution was neutralized with 0.5 M hydrochloric acid solution, ascorbic acid (50 ml, 0.05 M) was added, the temperature of the mixture was increased to 80°C and stirring was continued for another 24 h. Magnetic casein-supported copper(I) oxide was separated using an external magnet, washed with deionized water several times and once with ethanol, and then it was dried at 60°C to afford Cu_2O/Casein@Fe_3O_4NPs.

2.3 | Synthesis of magnetic casein (Casein@Fe_3O_4NPs)

Casein (0.75 g) was mixed with 25 ml of deionized water and was stirred for 5 min. Then $FeCl_2·4H_2O$ (aq)/$FeCl_3·6H_2O$ (aq) (1:2) (0.65 g/1.75 g) which was dissolved in 2 ml of deionized water was added while the temperature of the mixture was increased to 80°C for 1 h. Ammonium hydroxide (25%) was added dropwise to adjust the pH of the solution to 8–9 (at this pH casein was dissolved) and then continually stirred for 1 h at 80°C. Subsequently, the reaction mixture was cooled to room temperature and the solution was neutralized with 0.5 M hydrochloric acid solution. After 1 h, magnetic casein was separated using an external magnet, washed with deionized water several times and once with ethanol, and then it was dried at 60°C to afford Casein@Fe_3O_4NPs.

2.4 | General procedure for synthesis of 1,2,3-triazoles catalysed by Cu_2O/Casein@Fe_3O_4NPs

Alkyne (1 mmol), benzyl bromide (1 mmol) and sodium azide (1 mmol, 0.065 g) were added to a suspension of Cu_2O/Casein@Fe_3O_4NPs catalyst (0.43 mol%, 0.10 g) in water (5 ml). The reaction mixture was stirred for 2–8 h at 55°C. The progress of the reaction was followed by TLC (ethyl acetate–*n*-hexane). After the completion of the reaction, the mixture was cooled to room temperature and the catalyst was removed using an external magnet and washed twice with chloroform (6 ml) to separate the adsorbed organic compounds. Then the organic phase was combined and extracted twice with water. Finally the solvent was removed under vacuum to give the pure product. If necessary the products were purified by recrystallization. Selected NMR spectra may be found in the supporting information.

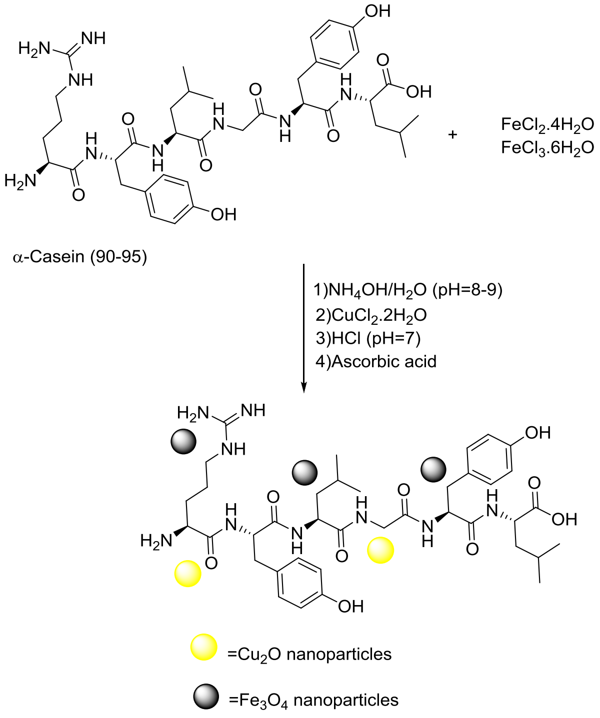
3 | RESULTS AND DISCUSSION

3.1 | Synthesis and characterization of Cu_2O/Casein@Fe_3O_4NPs

The synthesis of Cu_2O/Casein@Fe_3O_4NPs as a new catalyst was accomplished using the synthetic route shown in Scheme 2.

In order to evaluate the Cu content of the catalyst, it was treated with concentrated HCl–HNO_3 (3:1, *v*/v) to digest the metal complex and then analysed using ICP-OES. The results reveal that the content of Cu is 0.28 wt%.

FT-IR spectra of casein and Cu_2O/Casein@Fe_3O_4NPs are shown in Figure 1. The spectra of casein and Cu_2O/Casein@Fe_3O_4NPs show a band at 1557 cm^{-1}, corresponding to N—H bending vibrations of amide and a band at 1650 cm^{-1} assigned to the C=O stretch of peptide bond present in the casein molecules.[17] The FT-IR spectrum of Cu_2O/Casein@Fe_3O_4NPs exhibits a broad band at around 567–621 cm^{-1} corresponding to the stretching vibrations of the Fe—O and Cu—O bonds.[18]



SCHEME 2 Synthesis of Cu_2O/Casein@Fe_3O_4NPs catalyst

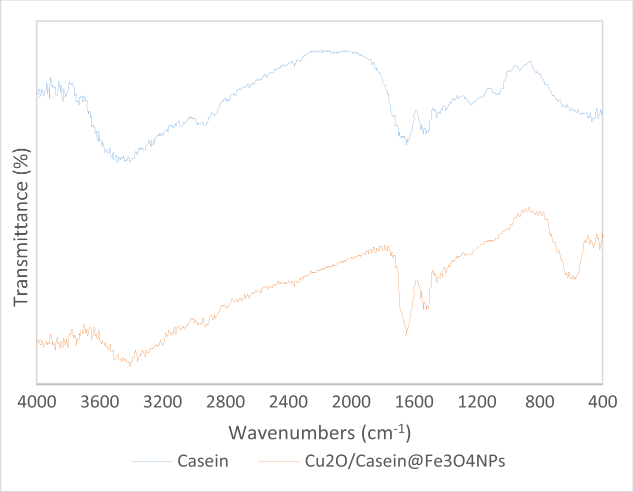


FIGURE 1 FT-IR spectra of casein and Cu_2O/Casein@Fe_3O_4NPs catalyst

SEM analysis (Figure 2(a)) was used to study the surface morphology of the Cu_2O/Casein@Fe_3O_4NPs catalyst. A homogeneous surface is observed. Figures 2(b) and (c) show TEM images of casein and the Cu_2O/Casein@Fe_3O_4NPs catalyst, respectively. TEM analysis of the catalyst shows the presence of particles with spherical morphology dispersed on the casein support with an average size range of 9–15 nm related to Cu_2O and Fe_3O_4 nanoparticles.

The EDX spectrum, which allows for detection of the chemical composition of the Cu_2O/Casein@Fe_3O_4NPs catalyst, is shown in Figure 3. The EDX spectrum shows peaks for Fe, Cu, O, C and N, which are the major constituents of Cu_2O/Casein@Fe_3O_4NPs.

The powder XRD patterns of Casein@Fe_3O_4NPs and Cu_2O/Casein@Fe_3O_4NPs are shown in Figure 4. For Casein@Fe_3O_4NPs, diffraction peaks at various angles (2θ) are in good agreement with the reported XRD pattern of Fe_3O_4NPs (JCPDF no. 03-0863).[19] For Cu_2O/Casein@Fe_3O_4NPs, all of the diffraction peaks match well with the normal characteristic diffractions of Fe_3O_4 and Cu_2O nanoparticles. The diffraction peaks at 30.34°, 35.40°, 43.42°, 57.19° and 62.86° correspond to the Fe_3O_4 nanoparticles (JCPDF no. 03-0863)[19] and those at 29.74°, 35.74° and 43.12° correspond to the Cu_2O nanoparticles (JCPDF no. 78-2076).[20]

Thermal stabilities of casein and Cu_2O/Casein@Fe_3O_4NPs were measured using TGA (Figure 5). The casein exhibits an initial weight loss starting at about 70°C and a weight loss at 220°C. When the temperature is above 500°C, casein is decomposed slowly and the total weight loss is about 96% at 900°C. In the TGA curve of the Cu_2O/Casein@Fe_3O_4NPs catalyst, at a temperature higher than 470°C a loss in weight of about 45% is observable; the remaining weight is related to the presence of Cu_2O and Fe_3O_4.

3.2 | Catalytic activity

To evaluate the efficiency of the newly synthesized catalyst, it was employed in 1,3-dipolar cycloaddition reactions

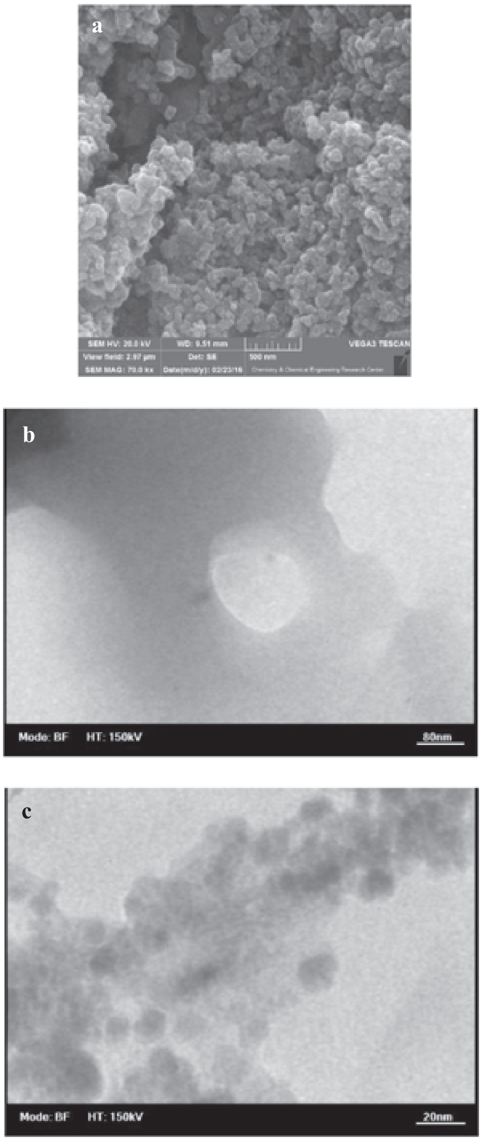


FIGURE 2 (a) SEM image of Cu_2O/Casein@Fe_3O_4NPs catalyst. (b) TEM image of casein and (c) TEM image of Cu_2O/Casein@Fe_3O_4NPs catalyst

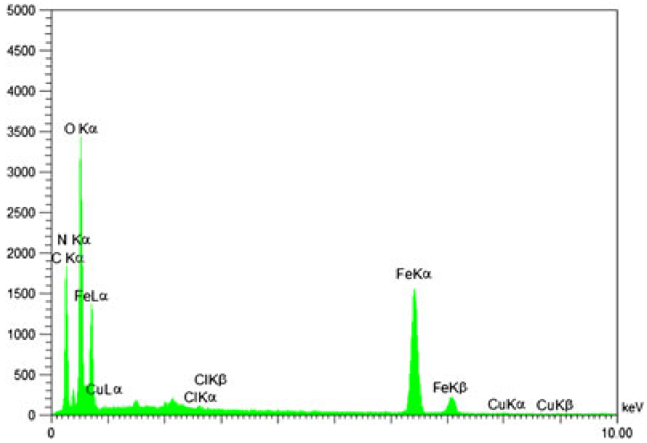


FIGURE 3 EDX spectrum of Cu_2O/Casein@Fe_3O_4NPs

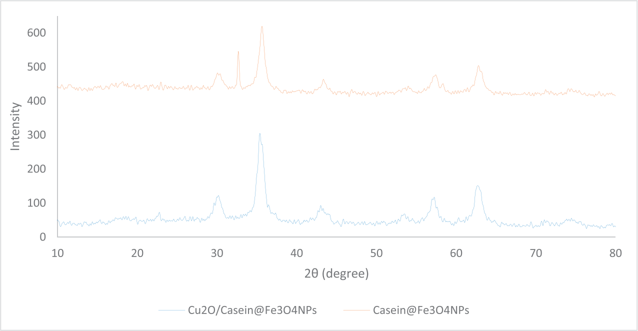


FIGURE 4 XRD patterns of Casein@Fe_3O_4NPs and Cu_2O/Casein@Fe_3O_4NPs

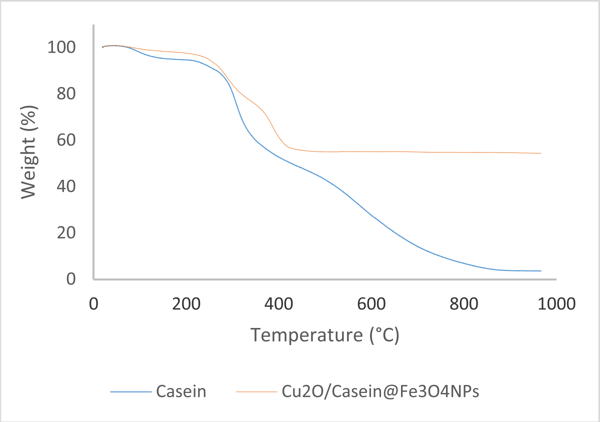


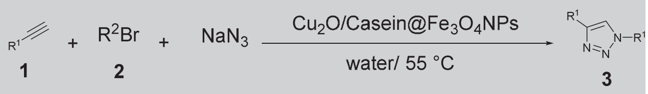
FIGURE 5 TGA curves obtained under air atmosphere

between terminal alkynes and organic azides in which the azides are generated *in situ* from corresponding halides and sodium azide.[21] As the starting point of our exploration, the reaction between phenylacetylene and benzyl bromide was chosen as a model reaction. The alkyne, benzyl halide and sodium azide were added to a suspension of Cu_2O/Casein@Fe_3O_4NPs as a heterogeneous catalyst (0.43 mol%, 0.1 g) in water. The reaction mixture was stirred for 2 h at 55°C, and then the mixture was cooled to room temperature and the catalyst was easily removed using an external magnet and washed twice with chloroform to separate the adsorbed organic compounds. Then the organic phase was combined and extracted. Finally the solvent was removed under vacuum to afford the pure 1,4-disubstituted 1,2,3-triazole in 100% yield (Table 1, entry 1).

For comparison, the model reaction was conducted in the presence of casein and Casein@Fe_3O_4NPs as catalysts for 2 h at 55°C in water, which gives both regioisomers, 1,4 and 1,5 cyclic adducts, in 1:1 ratio, and in 13 and 38% yield, respectively (Scheme 3).

Solvents define a major factor of the environmental performance of processes in the chemical industry and also have an impact on safety, cost and health issues. The idea of 'green' solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production.[22] Water as a potentially benign solvent was chosen for carrying out the synthesis of 1,2,3-triazoles and the reactions proceed smoothly to completion, and the products

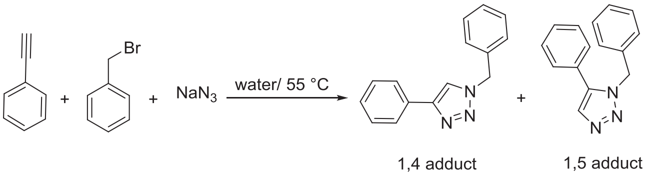
TABLE 1 One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from benzyl bromides, NaN_3 and alkynes catalysed by Cu_2O/Casein@Fe_3O_4NPs[a]



Entry	R^1	R^2	Time (h)	Yield (%)[b]
1	Ph	$PhCH_2$	2	98
2	Ph	$4\text{-}NO_2C_6H_4CH_2$	3	98
3	Ph	$3\text{-}IC_6H_4CH_2$	4	99
4	Ph	$4\text{-}BrC_6H_4CH_2$	4	100
5	Ph	$2\text{-}CH_3C_6H_4CH_2$	4	100
6	$CH_2N(Me)_2$	$PhCH_2$	2	100
7	$CH_2N(Me)_2$	$4\text{-}NO_2C_6H_4CH_2$	8	97
8	$HOC(Me)_2$	$PhCH_2$	2	100
9	$HOC(Me)_2$	$4\text{-}NO_2C_6H_4CH_2$	7	72
10	HOCHPh	$3\text{-}IC_6H_4CH_2$	5	70
11	HOCHPh	$4\text{-}NO_2C_6H_4CH_2$	5	95

[a] Reaction conditions: alkyne (1 mmol), benzyl bromide (1 mmol), sodium azide (1 mmol), Cu_2O/Casein@Fe_3O_4NPs (0.43 mol%, 0.10 g), H_2O (5 ml), 55°C.

[b] Isolated yield.



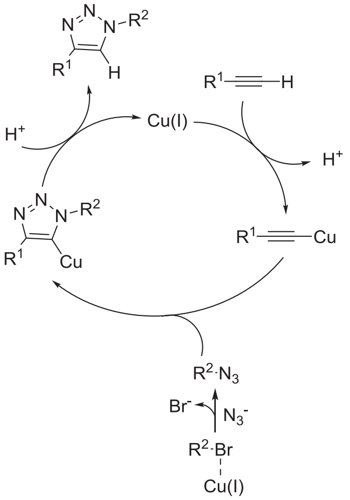
SCHEME 3 Screening of casein and Casein@Fe_3O_4NPs catalysts

are isolated in excellent yields. As a result, there was no need for solvent optimization.

To investigate the applicability of the prepared catalyst for 1,3-dipolar cycloaddition reactions, alkynes containing various functionalities and various benzyl halides were used. As evident from Table 1, all products are obtained in high yields. It is established that the triazole is formed in a completely regioselective manner, with no contamination by the 1,5-regioisomer. The results indicate that the electronic properties of benzyl halides affect the yields and longer reaction times are required for 3-iodobenzyl and 4-nitrobenzyl derivatives compared to other halides.

The proposed reaction mechanism is shown in Scheme 4. Organic azide is formed through the nucleophilic substitution reaction of the azide ion and benzyl bromide. The Cu(I) species reacts with an alkyne to give a copper acetylide. The 1,3-dipolar cyclization of the resulting Cu acetylide and an organic azide followed by the protonation provide the formation of a triazole and the regeneration of Cu(I) catalyst.[23]

The recyclability of the catalyst is a very significant factor. To determine recyclability of Cu_2O/Casein@Fe_3O_4NPs, a set of experiments was performed for the reaction of benzyl bromide, sodium azide and phenylacetylene using recycled Cu_2O/Casein@Fe_3O_4NPs catalyst (Table 1, entry 1). After carrying out the first cycloaddition reaction, the catalyst was easily removed using an external magnet and washed twice with chloroform to separate the adsorbed organic compounds, dried at 60°C and reused for subsequent reactions. The Cu_2O/Casein@Fe_3O_4NPs catalyst could be reused at least three times without any significant change in activity (Figure 6).



SCHEME 4 Proposed reaction mechanism

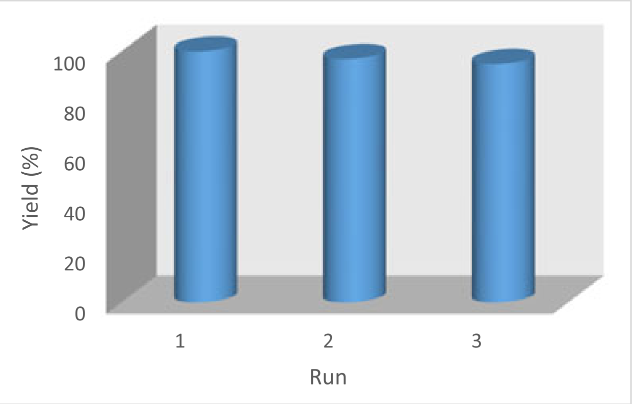


FIGURE 6 Successive runs using recovered Cu_2O/Casein@Fe_3O_4NPs catalyst

4 | CONCLUSIONS

The approach of this research is to introduce a new magnetically separable and easily recyclable heterogeneous copper(I) oxide bio-catalyst as a new and efficient catalyst with easy preparation, high catalytic activity and low cost for the generation of 1,4-disubstituted 1,2,3-triazoles in a completely regioselective manner in water. This work is the first example to demonstrate the usefulness of casein as a support for copper(I) oxide nanoparticles. Easy magnetic separation of the catalyst eliminates the requirement of catalyst filtration after completion of the reaction, which is an additional green attribute of this system.

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