

# Copper Nanoparticles Supported on Agarose as a Bioorganic and Degradable Polymer for Multicomponent Click Synthesis of 1,2,3-Triazoles under Low Copper Loading in Water

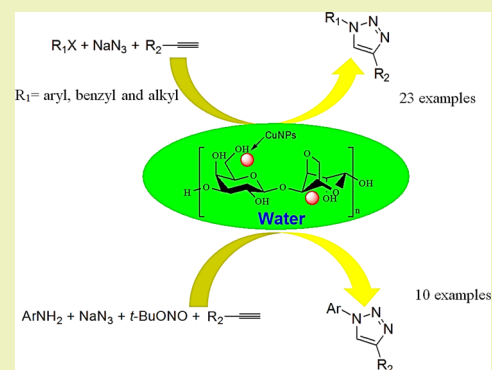
Mohammad Gholinejad\* and Neda Jeddi

Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), P.O. Box 5195-1159, Gava zang, Zanjan 45137-6731, Iran

## S Supporting Information

**ABSTRACT:** Agarose-supported copper nanoparticles (CuNPs@agarose) were prepared by immobilization of copper bromide on agarose followed by in situ chemical reduction. The new material was characterized by SEM, EDX, TEM, TGA, XRD, nitrogen adsorption–desorption, and solid UV–vis analysis. The catalytic activity of CuNPs@agarose was assessed in the three component click synthesis of 1,2,3-triazoles in water under low catalyst loading and mild reaction conditions. The easy synthesis and air-stable catalyst was recycled for five runs with small drops in catalytic activity.

**KEYWORDS:** Agarose, Copper nanoparticles, Click, Triazoles, Water



## INTRODUCTION

1,2,3-Triazole derivatives are important moieties because of their wide range of applications and biological activities such as anti-HIV,<sup>1,2</sup> activity against Gram-positive bacteria,<sup>3</sup> and selective  $\beta$ 3 adrenergic receptor agonist.<sup>4</sup> In addition, 1,2,3-triazole compounds have different applications in industry as dyes, corrosion inhibitors (of copper and copper alloys), photostabilizers, photographic materials, and agrochemicals.<sup>5</sup> A common method for the synthesis of 1,2,3-triazole compounds was the 1,3-dipolar Huisgen cycloaddition reaction of azides with terminal alkynes. However, using this method, a mixture of 1,4- and 1,5-disubstituted products were obtained. In addition, the reaction required a strong electron-withdrawing substituent either on azide or on alkyne under high temperature and prolonged period of reaction time.<sup>6</sup> The recent independent discovery by Meldal and Tornøe<sup>7</sup> and Sharpless<sup>8</sup> on the cycloaddition reaction of terminal alkynes with organic azides catalyzed by copper(I) complexes produced highly regioselective 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions.

Nowadays, environmental consciousness encourages the chemical community to the search for more environmentally sustainable chemical processes for chemical syntheses. For these purposes, development of new heterogeneous recyclable catalysts and the use of less toxic materials as solvents and reagents are two important challenging issues. The use of water as a cheap and safe solvent instead of expensive, flammable, and toxic organic solvents reduces environment damages caused by organic solvents. In addition, conducting the reactions in aqueous

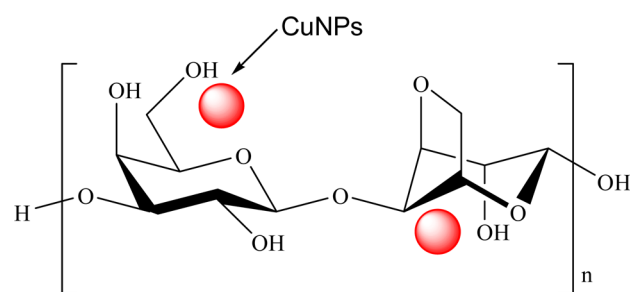


Figure 1. Pictorial presentation of CuNPs@agarose.

media caused easy phase separation of products because most of the organic compounds are not soluble in water.<sup>9–11</sup>

In recent years, several homogeneous copper catalysts have been employed for the click reaction of azides and alkynes.<sup>12–21</sup> Despite the significant efficiency of the reported homogeneous catalysts, they suffer from the difficulty of separating the copper catalyst from the products that are found in the building blocks of a wide range of natural and pharmaceutical products. In order to solve the problem, different heterogeneous copper catalysts have been introduced for the preparation of 1,2,3-triazoles. Examples of heterogeneous copper catalysts used for the click reaction include silica-supported nanocopper,<sup>22</sup> magnetite-supported

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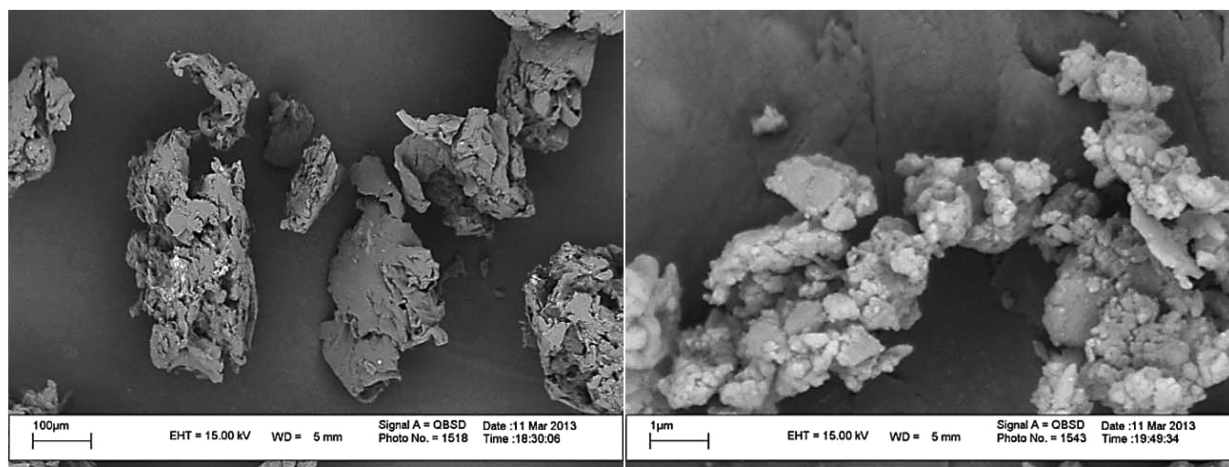


Figure 2. SEM images of CuNPs@agarose.

copper nanoparticles,<sup>23–25</sup> polymer-supported copper catalysts,<sup>26</sup> polyvinylpyrrolidone-coated copper nanoparticles,<sup>27,28</sup> Cu/C,<sup>29–35</sup> surfactant-assisted hydrothermal-synthesized Cu nanoparticles,<sup>34</sup> hetero-bimetallic Cu–Ni/C,<sup>37</sup> CuO,<sup>38,39</sup> Cu(II)-anchored functionalized mesoporous,<sup>40</sup> and melamine-formaldehyde resin-supported<sup>41</sup> copper nanoparticles. Even with simple handling of the heterogeneous catalysts, they are typically less effective than their homogeneous counterparts.

In recent years, there are growing interests in using different ecofriendly and biodegradable polymer supports as recyclable heterogeneous catalysts.<sup>42–47</sup> Recently, we have introduced agarose as a cheap and bioorganic ligand for palladium and its application in different carbon–carbon bond formation reactions.<sup>48–50</sup> Also very recently, synthesis of a chitosan-supported copper catalyst and its application in Huisgen 1,3-dipolar cycloaddition reactions in water was reported.<sup>51</sup> Now in this article, we have employed agarose as a cheap and degradable polysaccharide for support and stabilization of copper nanoparticles (CuNPs@agarose) and its application as an efficient catalyst in a multicomponent click coupling reaction in water (Figure 1).

## EXPERIMENTAL METHODS

**General.** All chemicals were purchased from Acros, Sigma-Aldrich, and Merck. Thin layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was carried out on silica gel 60 Merck (230–240 mesh) in glass columns (2 or 3 cm diameter). <sup>1</sup>H NMR spectra were recorded at 250 and 400 MHz, and <sup>13</sup>C NMR were recorded at 62.9 and 100 MHz in CDCl<sub>3</sub> using TMS as the internal standard. UV–vis spectra were recorded on a PerkinElmer, Lambda 25, UV–vis spectrometer. X-ray diffraction (XRD) patterns were recorded using a Philips X'pert PRO instrument. Thermogravimetric analysis was conducted from room temperature to 800 °C in an oxygen flow using a NETZSCH STA 409 PC/PG instrument. The structures of the prepared materials were observed by transmission electron microscopy (Philips CM-120).

**Preparation of Agarose-Supported Copper Catalyst.** Two grams of agarose was added to 200 mL of distilled water and was stirred for 12 h at 80 °C. In an additional flask, 0.2 mmol of CuBr salt was dissolved in 25 mL of water and then was added to an agarose hydrogel suspension. Then, 2 mmol of NaBH<sub>4</sub> as a reducing agent was added to the mixture, which was accompanied by a change in color from gray to green dark confirming the formation of copper nanoparticles. Then the mixture was cooled to room temperature, centrifuged, and dried in oven at 80 °C for 24 h. The content of the copper was determined by atomic adsorption analysis to be 0.1 mmol g<sup>-1</sup>.

**General Procedure for Click Reaction of Benzyl Halides with Sodium Azides and Alkynes Compounds with Cu/Agarose Catalyst.** CuNPs@agarose (0.05 mol %, 5 mg), alkyl halide (1.0 mmol), NaN<sub>3</sub> (1.5 mmol), and alkyne (1.5 mmol) were placed in a flask equipped with a magnetic stirring bar containing 2 mL of water under an air atmosphere. The reaction mixture was then heated at 40 °C for 8 h. After completion of the reaction, the mixture was cooled to room temperature and thoroughly washed with ethyl acetate to extract product. The organic solution was evaporated to afford the desired product in an almost pure state. Further purification, if it was necessary, was performed by using silica gel column chromatography eluted with *n*-hexane/EtOAc (10:2) to give the pure 1,2,3-triazole products in high to excellent yields.

**General Procedure for Click Reaction of Arenediazonium Salts with Sodium Azides and Alkynes Using CuNPs@agarose.** CuNPs@agarose (0.05 mol %, 5 mg), arenediazonium salt (1.0 mmol), NaN<sub>3</sub> (1.5 mmol), and alkyne (1.5 mmol) were placed in a flask equipped with a magnetic stirring bar containing 2 mL of water under air atmosphere. The reaction mixture was then heated at 40 °C under air for 8 h. Purification of the product was the same as the previous procedure for alkyl halides.

**General Procedure for One-Pot Click Reaction, Starting from Anilines.** Aniline (1.0 mmol), *t*-BuONO (3 mmol), NaN<sub>3</sub> (3 mmol), and alkyne (1.5 mmol) were added to a suspension of CuNPs@agarose (0.05 mol %, 5 mg) in 2 mL of a mixture of H<sub>2</sub>O and *t*-BuOH (1:1). The reaction mixture was then warmed to 40 °C and stirred for 12 h under air. Then, the reaction mixture was washed with ethyl acetate to extract the product. After evaporation of ethyl acetate, pure product was obtained using silica gel column chromatography eluted with *n*-hexane/EtOAc (10:2) to give the pure product.

**General Procedure for Recycling of Catalyst.** Recycling of the catalyst was performed upon the reaction of benzyl bromide, NaN<sub>3</sub>, and phenylacetylene. After completion of the reaction in the first run, the

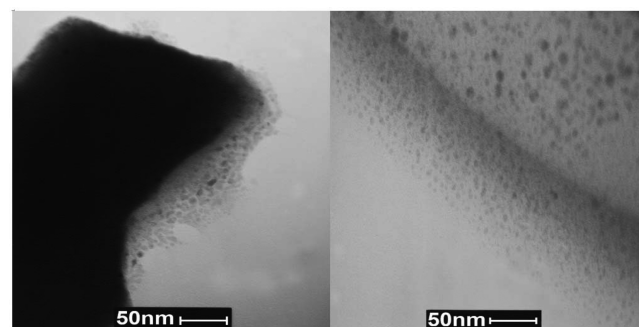


Figure 3. TEM images of CuNPs@agarose.

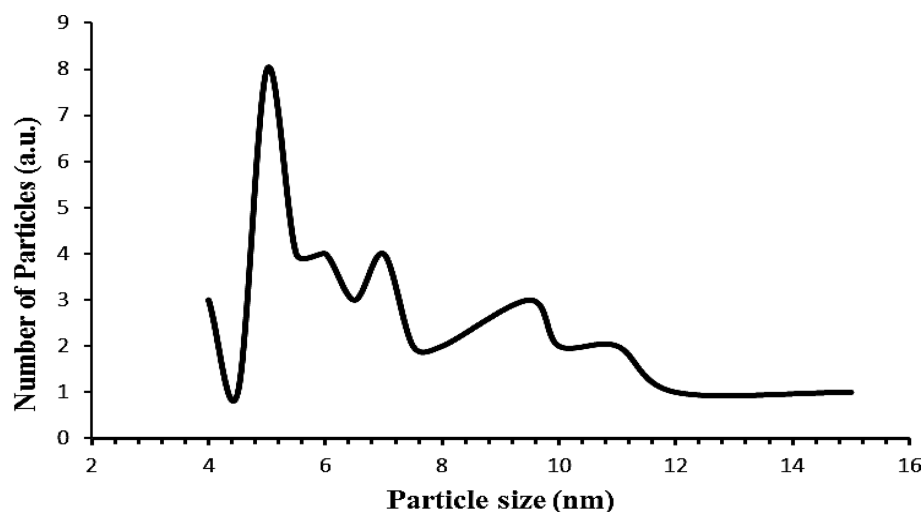


Figure 4. Particle size distribution plot obtained from TEM measurements determined for a randomly selected 60 nanoparticles.

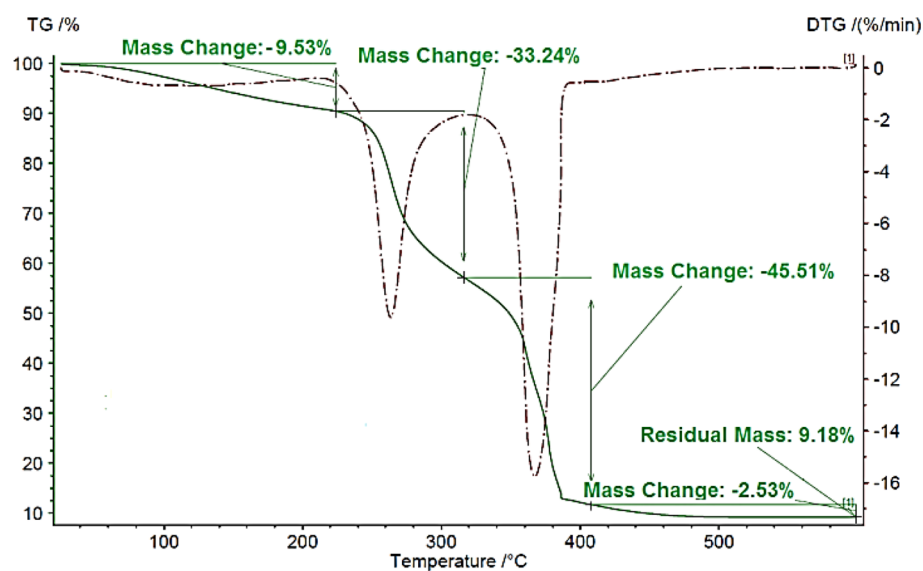


Figure 5. Thermogravimetric diagram of CuNPs@agarose.

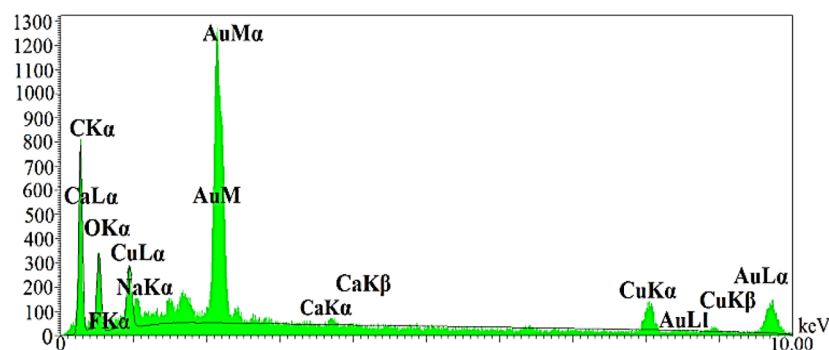


Figure 6. EDX spectrum of CuNPs@agarose.

reaction mixture was cooled to room temperature, and the mixture was washed with ethyl acetate to extract the organic product. Then, the residue was centrifuged, and the solid catalyst was washed with 5 mL diethyl ether and decanted. The resulting solid mass was reused for another batch of the similar reaction. This process was repeated for five consecutive runs.

## RESULTS AND DISCUSSION

The copper catalyst supported on agarose was readily prepared by dissolving and sonication of agarose in deionized water, and the addition of an aqueous solution of CuBr was followed by the addition of NaBH<sub>4</sub> as a reducing agent. On the basis of the atomic

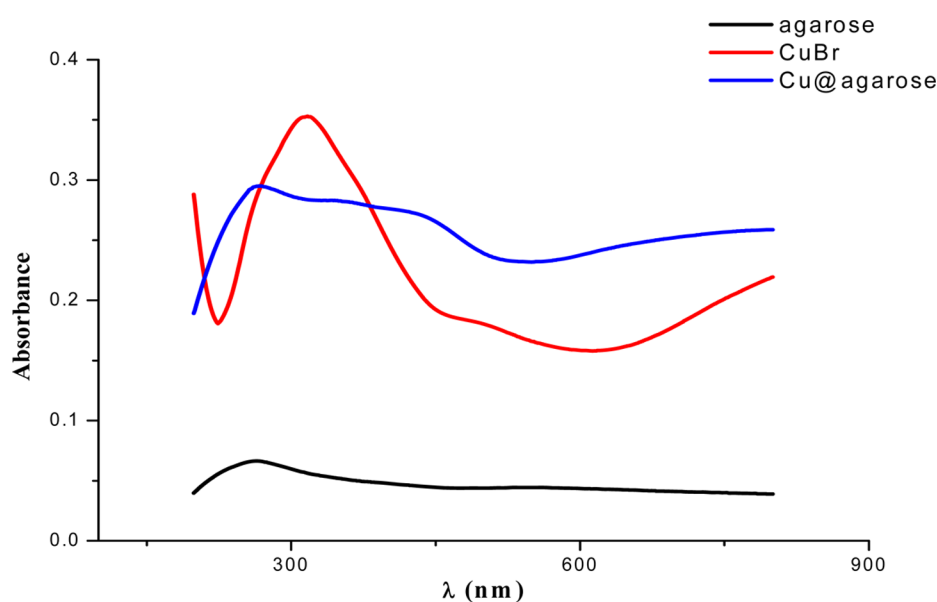


Figure 7. Solid UV-vis spectrum of CuNPs@agarose.

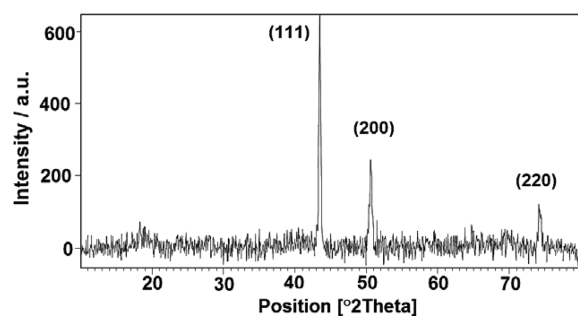
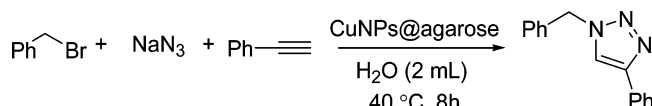


Figure 8. XRD pattern of the catalyst.

Table 1. Effect of Different Amounts of CuNPs@agarose for Reaction of Benzyl Bromide, Sodium Azide, and Phenylacetylene



entry	mol% of CuNPs	Isolated yield (%)
1	0.025	35
2	0.04	75
3	0.05	96

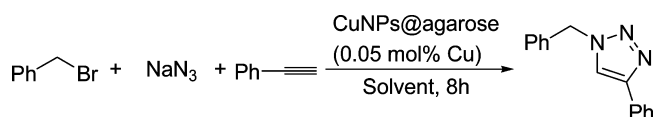
adsorption analysis, the content of copper in the prepared catalyst was found to be  $0.1 \text{ mmol g}^{-1}$ . SEM images of the catalyst showed dry gel-like structures of CuNPs @agarose catalyst (Figure 2).

Also, TEM images of catalyst confirm the formation of monodispersed and uniform nanoparticles (Figure 3).

Figure 4 shows the particle size distribution plot obtained from TEM measurements determined for randomly selected 60 nanoparticles in which it is clear that the major portions of the particles are located between 4 and 8 nm.

The thermogravimetric analysis (TGA) of the catalyst shows that the prepared composite has high thermal stability and negligible agarose leaching up to  $220^\circ\text{C}$  (Figure 5).

Table 2. Screening of Different Solvents for Reaction of Benzyl Bromide, Sodium Azide, and Phenylacetylene



entry	solvent	$T^\circ\text{C}$	isolated yield (%)
1	toluene	40	30
2	THF	40	15
3	$\text{H}_2\text{O}$	40	96
4	$\text{CH}_2\text{Cl}_2$	40	15
5	$\text{CH}_3\text{CN}$	40	trace
6	$\text{H}_2\text{O}$	25	81

EDX analysis of copper nanoparticles supported on agarose, which allows for detection of the copper species in the structure of the catalyst (Figure 6).

The complete reduction of copper in CuNPs@agarose was confirmed by solid UV-vis, in which the peak at 310 nm corresponding to CuBr disappeared upon reduction (Figure 7).<sup>52</sup>

The nitrogen adsorption-desorption isotherm of the catalyst exhibited type-III curves, which confirms the preservation of the polymeric structure<sup>53</sup> of the catalyst; the BET surface area was calculated to be  $15 \text{ m}^2 \text{ g}^{-1}$  (Figure S1, Supporting Information).

The X-ray diffraction (XRD) analysis of the catalyst confirms the formation of metallic copper nanoparticles in Bragg's reflections at  $2\theta = 43.5, 50.6, \text{ and } 74.3$ , which can be indexed as the (111), (200), and (220) planes of copper (Figure 8).<sup>20,26</sup>

The catalytic activity of the prepared catalyst was evaluated in 1,3-dipolar cycloaddition of azides and alkynes in water as an environmentally benign solvent. The reaction of benzyl bromide, sodium azide, and phenylacetylene was selected as a model reaction, and different reaction conditions such as solvent and amount of catalyst were investigated. The results indicated that using water as a solvent and 0.05 mmol of copper catalyst at  $40^\circ\text{C}$  was the best reaction condition as shown in Tables 1 and 2.

As shown in Table 3, benzyl bromide, 4-chlorobenzyl bromide, 4-nitrobenzyl bromide, benzyl chloride, and 2-(bromoethyl)-benzene reacted efficiently with sodium azide and alkynes, and

Table 3. Reactions of Alkyl Halides or Arenediazonium Salts with Sodium Azide and Different Alkynes in the Presence of Catalyst in Water

$$R^1X + NaN_3 + R^2 \equiv \xrightarrow[\text{H}_2\text{O (2 mL), 40 }^\circ\text{C, 8 h}]{\text{CuNPs@agarose (0.05 mol\% Cu)}} \begin{matrix} R^1 \\ \diagdown \\ \text{N} \\ \diagup \\ \text{N} \\ \diagdown \\ \text{N} \\ \diagup \\ R^2 \end{matrix}$$

Entry	R <sup>1</sup> X	R <sup>2</sup>	Product	Isolated yield (%) <sup>a</sup>	Entry	R <sup>1</sup> X	R <sup>2</sup>	Product	Isolated yield (%) <sup>a</sup>
1		Ph		96	13		Ph		88
2		Ph		95	14		Hexyl		84
3		Ph		97	15		Butyl		87
4		4-MeC <sub>6</sub> H <sub>4</sub> -		98	16		4-MeC <sub>6</sub> H <sub>4</sub> -		85
5		4-MeOC <sub>6</sub> H <sub>4</sub> -		95	17		4-MeOC <sub>6</sub> H <sub>4</sub> -		88
6		Butyl		98	18		Ph		82
7		Ph		97	19		Ph		85
8		Ph		95	20		Butyl		86
9		Ph		94	21		4-MeC <sub>6</sub> H <sub>4</sub> -		91
10		Ph		86	22		4-MeOC <sub>6</sub> H <sub>4</sub> -		90
11		Ph		82	23		Ph		48
12		Ph		79					

<sup>a</sup>Reaction condition: 1 mmol alkyl halides or arenediazonium salt, 1.5 mmol NaN<sub>3</sub>, 1.5 mmol alkyne, 0.05 mol % catalyst, and 2 mL H<sub>2</sub>O

corresponding triazole products were isolated in excellent yields (Table 3, entries 1–8). In addition, reactions of aliphatic alkyl bromides such as ethyl bromoacetate, 1-bromobutane,

1-bromohexane, and 1,3-dibromopropane proceeded well, and desired triazole products were obtained in high yields (Table 3, entries 9–12). Also, reactions of structurally different

**Table 4.** One-Pot Reaction of Aniline Derivatives with Sodium Azide and Alkynes in Presence of Catalyst and *t*-BuONO in Mixture of Water and *t*-BuOH

$$\text{ArNH}_2 + \text{NaN}_3 + \text{R}-\text{C}\equiv\text{C} \xrightarrow[\text{40 }^\circ\text{C, 12 h}]{\begin{array}{c} t\text{-BuONO} \\ \text{CuNPs@agarose} \\ (0.05 \text{ mol\% Cu}) \\ t\text{-BuOH-H}_2\text{O (1:1)} \end{array}} \text{Ar}-\text{N}=\text{N}-\text{C}(\text{R})=\text{N}$$

Entry	ArNH <sub>2</sub>	R	Isolated Yield(%) <sup>a</sup>
1		Ph	82
2		Butyl	79
3		Hexyl	77
4		4-MeC <sub>6</sub> H <sub>4</sub> -	83
5		Ph	86
6		4-MeC <sub>6</sub> H <sub>4</sub> -	86
7		4-MeOC <sub>6</sub> H <sub>4</sub> -	84
8		Butyl	81
9		Ph	80
10		Ph	82

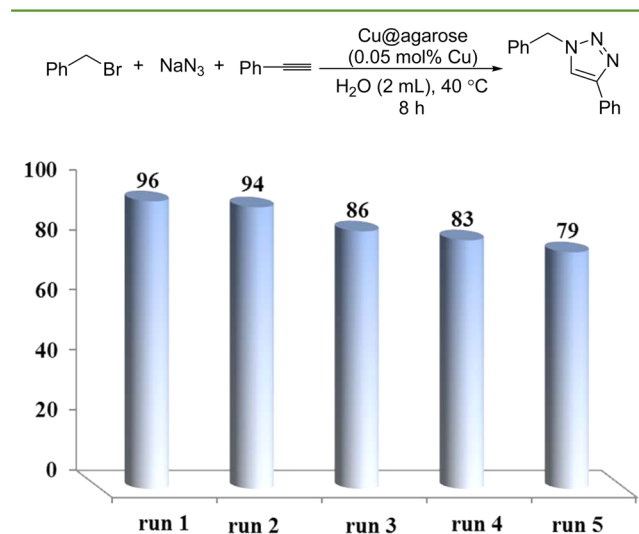
<sup>a</sup>Reaction condition: Aniline 1.0 mmol, *t*-BuONO<sub>3</sub> 3 mmol, NaN<sub>3</sub> 3 mmol, alkyne 1.5 mmol, catalyst 0.05 mol %, 2 mL of H<sub>2</sub>O, and *t*-BuOH (1:1)

arene-diazonium salts<sup>28</sup> containing both electron-donating and electron-withdrawing groups with sodium azide and alkynes proceeded well, and desired products were obtained in 82–91% isolated yields (Table 3, entries 13–22). We have also studied the reactions of phenylboronic acid with sodium azide and phenylacetylene under optimized reaction conditions. However, workup of the reaction afforded only 48% isolated yield of product, and the starting materials were isolated intact (Table 3, entry 23). In order to gain information about copper leaching because of the possibility of agarose swelling in water and weakening of the agarose–Cu nanoparticles interaction, after completion of reaction of benzyl bromide, sodium azide, and phenylacetylene, we have cooled reaction mixture to room temperature and used solution obtained from centrifugation of the reaction mixture for the another batch of reaction. However, the results showed that after 8 h, trace amounts of triazole as a

product (9%) was obtained. This result clearly showed negligible leaching of copper from support under the reaction conditions.

As the synthesis of arene-diazonium salt typically proceeds quantitatively and with minimal byproduct formation,<sup>54</sup> we have studied the one-pot click reaction of arene-diazonium salt formed in situ from the corresponding aniline derivatives, sodium azide, and alkynes in the mixture of water and *t*-BuOH. As depicted in Table 4, reactions of azides with alkynes in the presence of catalyst were performed efficiently via the one-pot conversion of aniline derivatives to diazonium salts by reaction of anilines with *t*-BuONO in the mixture of water and *t*-BuOH.<sup>28</sup>

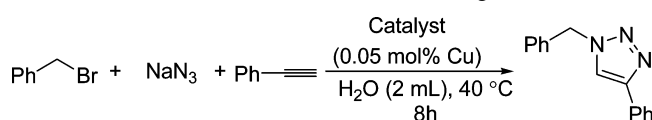
Finally, we have investigated the possibility of recycling of the catalyst. For this purpose, after completion of the reaction of benzyl bromide, sodium azide, and phenylacetylene, the reaction mixture was cooled to room temperature, and reaction product was isolated with ethyl acetate. The water residue, which contains copper nanoparticles on agarose hydrogel, was used for another batch of reaction and repeated for five runs with a small decrease in catalytic activity (Figure 9).

**Figure 9.** Recycling of catalyst for the reactions with benzyl bromide, sodium azide, and phenylacetylene.

The proposed mechanism for the reaction is the same as the known mechanism for the multicomponent click reaction. On the basis of common analogies and considerations, during the reaction, Cu(0) gets oxidized to Cu(I), and the reaction proceeded via formation of the Cu(I)–acetylide complex.<sup>20,26,40,55</sup> Also, XRD analysis of the recycled catalyst after the third run showed formation of Cu(I) species during the reaction (Figure S2, Supporting Information).

In order to get information about stability of the catalyst, TGA analysis of the recycled catalyst after the third run was studied. The results indicated that the catalyst is thermally stable up to 200 °C, and agarose as a support existed in the structure of the catalyst even after recycling (Figure S3, Supporting Information). Furthermore, the TEM image of the separated catalyst after the third run proved that the nanoparticles state was preserved within the reaction with small aggregation of particles (Figure S4, Supporting Information).

Finally, in order to show efficiency of the catalyst and particle size upon the reaction, we have compared the results of the catalytic activity of CuNPs@agarose with the catalyst generated in the absence of NaBH<sub>4</sub> as a reducing agent and with homogeneous CuBr under optimized reaction conditions (Table 5).

**Table 5. Comparison of Using CuNPs@agarose with Catalyst Generated in Absence of NaBH<sub>4</sub> and Homogenous CuBr**


entry	catalyst	isolated yield%
1	CuNPs@agarose	96
2	Catalyst generated in absence of NaBH <sub>4</sub>	75
3	CuBr	70

The results of Table 5 clearly support the positive effect of using agarose-supported Cu nanoparticles over bulk Cu(I) species in this reaction. It is worth mentioning that the SEM image of the copper catalyst generated in the absence of NaBH<sub>4</sub> showed extensive accumulation and formation of ununiform and bulk copper particles on the surface of agarose (Figure S5, Supporting Information). In Cu nanoparticles, probably the Cu(I) species, which existed in clusters of nanoparticles, performed as an active species in the reaction compared to the bulk CuBr catalyst.

## CONCLUSIONS

In conclusion, in this study for the first time, we have used agarose as a cheap and degradable polysaccharide for stabilization of copper nanoparticles. The new catalyst was characterized by SEM, EDX, TEM, TGA, XRD, nitrogen adsorption–desorption, and solid UV–vis analysis. The catalytic activity of CuNPs@agarose was assessed in the three component click synthesis of 1,2,3-triazoles in water under low catalyst loading and mild reaction conditions. The catalyst was recycled for five runs with small loss of catalytic activity.

## ASSOCIATED CONTENT

### Supporting Information

<sup>1</sup>H NMR, <sup>13</sup>C NMR, melting points of products, nitrogen adsorption–desorption isotherm of catalyst, and XRD, SEM, TEM, and TGA of catalyst. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [gholinejad@iasbs.ac.ir](mailto:gholinejad@iasbs.ac.ir)

### Notes

The authors declare no competing financial interest.

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