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DOI: 10.1039/C6RA13314B

Journal Name

ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Direct access to stabilized Cu^l using cuttlebone as a naturalreducing support for efficient CuAAC click reactions in water

Sara S. E. Ghodsinia,^a Batool Akhlaghinia,^{*a} Roya Jahanshahi^a

Cuttlebone@CuCl₂ has efficiently catalyzed the one-pot azidonation of organic bromides, followed by regioselective azidealkyne 1,3-dipolar cycloaddition (CuAAC) reaction to produce the corresponding 1,4-disubstituted 1,2,3-triazole derivatives in excellent yields, in water. Importantly, cuttlebone not only used for successful immobilization of CuCl₂ in order to its heterogenation, but also utilized as a natural-reducing platform which can reduce Cu^{II} to the click-active stabilized Cu^I. This mild three component synthetic approach avoids handling of hazardous and toxic azides, because of their in situ generation. Moreover, the catalyst has the advantages of being ligand-free, leaching-free, thermal stable, easy to synthesize from inexpensive commercially available precursors, environmentally friendly and recyclable for at least seven times without a significant decrease in its activity and selectivity.

1. Introduction

Copper(I)-catalyzed Huisgen1,3-dipolar cycloaddition of organic azides and alkynes (click reaction) which was pioneered by Sharpless and co-investigators,¹ has received impressive attention in green chemistry scope due to the mild reaction conditions, as well as the high efficiency involved.² Accordingly, a great deal of methods have prospered around this reaction to afford the corresponding 1,2,3-triazoles.³ These compounds are predominant building blocks of the numerous classes of nitrogen-containing heterocyclic compounds⁴ and are widely used as a powerful tool in several fields of chemistry such as pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, photostabilizers and photographic materials.⁵ In spite of providing excellent yields and good regioselectivity of the products obtained through the Cu(I)catalyzed click reaction, thermodynamic instability and also formation of undesired alkyne-alkyne coupling by-product restricted the use of Cu(I) catalysts, directly.⁶ Instead, the favorable approach is the in situ generation of Cu(I) species through the reduction of Cu(II) salts,⁷ oxidation of Cu(0) metals,⁸ and Cu(II)/Cu(0) comproportionation⁹ or using Cu(I) salts in the presence of bases and/or ligands which protect Cu(I) intermediates from oxidation and disproportionation, and hamper undesired sideproduct formation.¹⁰ However, most of the existing methods involve handling of unstable, toxic organic azides and using homogeneous catalysts which cannot be separated easily from the reaction media.^{8,11}

In this context, to promote the existing synthetic protocols, many efforts have been made on the heterogeneous copper based catalytic systems and the in situ generation of organic azides from suitable precursors which would avoid the difficulties associated with the hazardous and explosive nature of the azides. Using heterogeneous catalysts is accompanied with several advantages such as fast and efficient recyclability of the catalyst, as well as facile separation of the products. Consequently, the number of steps and time involved in the reaction strategy would be diminished. For this purpose, immobilization of Cu(I) species on various supports such as alumina,¹² polymers,¹³ Amberlyst,¹⁴ zeolites,¹⁵ activated charcoal,¹⁶ titanium dioxide,¹⁷ silica-supported *N*-heterocyclic carbene,¹⁸ clay,¹⁹ magnetic materials,²⁰ and aluminum oxyhydroxide nanofibers,²¹ has received a remarkable attention in the Huisgen1,3-dipolar cycloaddition. Additionally, solid supported Cu^{II} species as heterogeneous catalytic systems without employing any reducing agents or additives have been reported in alkyne-azide cycloaddition reaction.²² In accordance with our previous study on cuttlebone²³ and to continue our research interest in developing new efficient and environmentally benign heterogeneous catalysts,²⁴ herein, we are willing to report synthesis and characterization of cuttlebone@CuCl2 as an efficient heterogeneous catalyst for the first time (Scheme 1). The catalytic activity of this newly synthesized catalyst was proved for the onepot synthesis of 1,4-disubstituted 1,2,3-triazoles via a threecomponent reaction between terminal alkynes, organic bromides, and sodium azide, in water (see Scheme 2).



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DOI: 10.1039/C6RA13314B

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2. Experimental

2.1. Materials

All chemical reagents and solvents were purchased from Merck and Sigma-Aldrich chemical companies and were used as received without further purification. Cuttlebone was taken out from cuttlefish (*Sepia esculenta*),²⁵⁻²⁸ which is commonly found in saltwater beaches like Persian Gulf in Iran.

2.2. Instrumentation analysis

The purity determinations of the products and the progress of the reactions were accomplished by TLC on silica gel polygram STL G/UV 254 plates. The melting points of the products were determined with an Electrothermal Type 9100 melting point apparatus. The FT-IR spectra were recorded on pressed KBr pellets using an AVATAR 370 FT-IR spectrometer (Therma Nicolet spectrometer, USA) at room temperature in the range between 4000 and 400 cm⁻¹ with a resolution of 4 cm⁻¹, and each spectrum was the average of 32 scans. NMR spectra were recorded on a NMR Bruker Avance spectrometer at 400 and 300 MHz in CDCl₃ as solvent in the presence of tetramethylsilane as the internal standard and the coupling constants (J values) are given in Hz. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 Series instrument (furnace: 900 °C, oven: 65 °C, flow carrier: 140 mL min⁻¹, flow reference: 100 mL min⁻¹). Mass spectra were recorded with a CH7A Varianmat Bremem instrument at 70 eV electron impact ionization, in m/z (rel %). Elemental compositions were determined with an SC7620 Energy-dispersive X-ray analysis (EDX) presenting a 133 eV resolution at 20 kV. Surface analysis spectroscopy of the catalyst was performed in an ESCA/AES system. This system was equipped with a concentric hemispherical (CHA)

2.3. Pre-preparation of cuttlebone

In order to remove pollution on the surface of cuttlebone, it was powdered, washed with distilled water and dried at 100 $^{\circ}$ C, for 2 h.

2.4. Preparation of catalyst

In a round-bottom flask, cuttlebone (5.0 g) was mixed with $CuCl_2$ (1.5 g, 0.011 mol) in deionized water (50 mL). The mixture was stirred at room temperature for 10 h. The catalyst was filtered and washed with water and ethanol several times (to remove excess of copper salt), and then was dried at 50 °C for 12 h.

2.5. Typical procedure for preparation of 1-benzyl-4-phenyl-1,2,3-triazole

Catalyst 0.048 g (8.5 mol%) was added to a solution of phenyl acetylene (1 mmol), benzyl bromide (1 mmol) and sodium azide (1.2 mmol), in H_2O (5 mL). The reaction mixture was stirred at 40 °C and monitored by TLC until total conversion of the starting materials. After 5 min, the reaction mixture was cooled to room temperature. The catalyst was separated by simple filtration and washed with water, ethanol and EtOAc, successively and then was dried at 60 °C, for 3 h. Afterwards, water (10 mL) was added to the resulting reaction mixture, followed by extraction with EtOAc (3 × 15 mL). The recovered catalyst was used directly in the next cycle. The organic phase was washed with water and dried with Na₂SO₄. Solvent was removed under vacuum and the crude product was purified by a simple crystallization from ethanol to provide the corresponding triazole (1-benzyl-4-phenyl-1*H*-1,2,3-triazole) as a white solid (0.222 g, 95% isolated yield).

3. Results and Discussion

An extremely porous hard tissue in the cuttlefish (Sepia esculenta). which acts as a rigid buoyant tank in the animal is called "cuttlebone".²⁹ It is a natural material which has the multifunctional properties of high flexural stiffness, high porosity and compressive strength.³¹ Cuttlebone framework is an inorganic-organic composite consist of aragonite, protein and β -chitin.²⁹ The principal component of the organic matrix derived from the cuttlebone framework is β-chitin.²⁹ However, an attractive application of cuttlebone-derived organic matrix, that has not yet received much attention, is related to its application as a reducing agent for the preparation of metal nanoparticles and a scaffold for their assembly, which will lead to a new class of functional materials.²⁹ β -Chitin as the main component of the cuttlebone-derived organic matrix is a natural carbohydrate (polysaccharide) composed of poly[2-acetamido-2-deoxy-(1,4)-β-Dparallel arranged glucopyranose].29 Recently, carbohydrates (including oligosaccharides and polysaccharides) as monosaccharide. biodegradable, renewable natural materials, have been employed

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as stabilizers or reducing agents for the green providing of nanomaterials and nanocomposites.²⁹ Hence, cuttlebone can be used as a natural platform for immobilization of CuCl₂, which subsequently reduced Cu^{II} to the click-active stabilized Cu^I. Fascinatingly, the resulted Cu^I was long-term stabilized in the cuttlebone network. On the other hand, during the reaction, when the catalyst has been treated with sodium azide, Cu²⁺ has reduced to Cu¹⁺ oxidation state, much more than before.³⁰ Then, this newly synthesized heterogeneous catalyst was characterized by different techniques such as fourier transform infrared spectroscopy (FT-IR), energy-dispersive X-ray analysis (EDX), X-ray photoelectron spectrum (XPS) and inductively coupled plasma (ICP).

3.1. Characterization of catalyst

3.1.1. FT-IR spectroscopy

The FT-IR spectrum of the cuttlebone was shown in Fig. 1a. It is worth to note that the observed absorption bands for aragonite phases (calcium carbonate) in cuttlebone structure are related to the planar CO_3^{2-} ions. As can be seen, there are four main vibrational modes in the free CO_3^{2-} ions.³² The peak appearing at about 1082 cm⁻¹ is assigned to the symmetric stretching vibration of the carbonate ion. The peak positioned at about 857 cm⁻¹ is ascribed to out-of plane bending vibration of carbonate ion. Moreover, the asymmetric stretching vibration at about 1400-1500 $\rm cm^{-1}$ and the split in-plane bending vibration at about 700 $\rm cm^{-1}$ are clearly demonstrate the free CO_3^{2-} ions of the cuttlebone structure. Also, the FTIR spectrum of cuttlebone shows the absorption bands at 3448 and 3318 cm⁻¹, which are attributed to the OH and NH stretching vibrations of the β -chitin segment in cuttlebone, respectively. The absorption bands in the range of 2977–2855 cm⁻¹ were corresponded to the symmetric stretching vibrations of CH, CH₃ and the asymmetric stretching vibrations of CH₂ in the cuttlebone structure. Furthermore, the CH bending, CH₃ symmetric deformation and CH₂ wagging bands were appeared at 1384 to 1312 cm⁻¹. In the FTIR spectrum of cuttlebone@CuCl₂ (Fig.1b and c), the peaks positioned at 442, 453 and 428 cm⁻¹ are assigned to the Cu–Cl,³³ Cu–O^{33,24a} and Cu–N^{24a} stretching vibrations, respectively.

3.1.2. EDX analysis

Energy-dispersive X-ray analysis (EDX) indicates the presence of C, O, Ca, Cl and Cu elements in the cuttlebone structure (Fig. 2). This analysis confirms the successful immobilization of copper on the cuttlebone surface.

3.1.3. XPS Characterizations of the catalyst

Fig. 3 shows the high resolution narrow X-ray photoelectron spectra (XPS) for fresh catalyst and the 7th recovered catalyst. As observed in Fig. 3 binding energy peaks at 937 eV and 956.5 eV can be attributed to 2p3/2 and 2p1/2 spin-orbit split-doublets, respectively, which are characteristic of Cu in +2 oxidation state.^{30a,34} However, binding energy peaks at 934.6 eV and 954.6 eV can be attributed to 2p3/2 and 2p1/2 spin-orbit split-doublets, respectively, which are characteristic of Cu in +1 oxidation state.³⁴ These results led us to conclude that after the immobilization of



DOI: 10.1039/C6RA13314B

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Fig. 1 FT-IR spectrum of (a) Cuttlebone; (b) Catalyst; (c) 7th recovered catalyst.

 $CuCl_2$ on the cuttlebone as a reducing stabilizer support, Cu^{II} was partially reduced to Cu^{I} state and thus is present as Cu^{II}/Cu^{I} mixed valency dinuclear species, but with the predominance of Cu^{II} (Fig. 3a).

On the other hand, as proved by XPS analysis, it is evident that the treatment of catalyst with sodium azide during the reaction, leads to reduction of Cu^{2+} to Cu^{1+} oxidation state, much more than before. Thus, meanwhile the click reaction the dominant species would be Cu^{1+} (Fig. 3b).



Fig. 2 EDX analysis of the catalyst.



Peak	BE	FWHM	Height	Norm.	Rel.
Label/ID	(eV)	(eV)		Area	Area %
Cu⁺	934.63	2.81	25.4235	76.165	39.30%
Cu ²⁺	937	3.08	35.8022	117.419	60.70%

Fig. 3 (a) XPS spectrum of fresh catalyst.



Fig. 3 (b) XPS spectrum of 7th recovered catalyst.

3.2. Catalytic synthesis of 1,4-disubstituted 1,2,3-triazoles

After the successful preparation and full characterization of catalyst, to evaluate this novel synthesized catalyst efficiency, its



R¹ = Ph, 4-MeC₆H₄, 4-OMeC₆H₄, 4-*t*BuC₆H₄, 4-CIC₆H₄, 4-BrC₆H₄, 4-NO₂C₆H₄, 2-pyridinyl

 $R^2 = PhCH_2$, $p-ClC_6H_4CH_2$, $p-NO_2C_6H_4CH_2$, Allyl

Scheme 2. One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles using catalyst.

catalytic activity was examined for the mild one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles, by the reaction between terminal alkynes and the *in situ* generated substituted azides from their corresponding organic bromides, in water (Scheme 2).

Initially the 1,3-dipolar cycloaddition reaction between phenyl acetylene, benzyl bromide and sodium azide, was selected as a model reaction to optimize the different reaction conditions. The obtained results were represented in Table 1. The in situ generated azide from the reaction mixture of benzyl bromide and NaN₃ reacted well with phenyl acetylene and the desired 1-benzyl-4phenyl-1H-1,2,3-triazole was obtained through a one pot procedure. However, when the model reaction was performed at 100 °C in aqueous media, in the absence of any catalyst, no desired product was formed, even after a prolonged reaction time (Table1, entry 1). It was observed that the click reaction occurred smoothly in the presence of several different catalysts including cuttlebone, cuttlebone@Cu(SO₄)₂, CuCl₂, $Cu(SO_4)_2$, $Cu(OAc)_2$, cuttlebone@Cu(OAc)₂ and cuttlebone@CuCl₂.

Thermal evaluation of the reaction revealed that the higher the temperature, the greater the reaction progress. Among the different catalysts screened, cuttlebone@CuCl₂ in water, was found to be excellent for this tandem reaction. Other protic solvents such

Table 1. Catalyst optimization studies for one-pot synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole, under different reaction conditions.^a

Entry	Catalyst	Solvent	Temperature	Time	Isolated
			(°C)	(min)	Yield (%)
1	None	H ₂ O	100	15 h	0
2	Cuttlebone	H ₂ O	r.t	2 h	45
3	Cuttlebone	H ₂ O	100	30	65
4	Cu(SO ₄) ₂	H ₂ O	100	40	80
5	Cu(OAc) ₂	H ₂ O	100	20	89
6	CuCl ₂	H ₂ O	100	10	89
7	CuCl ₂	H ₂ O	r.t	60	70
8	Cuttlebone@Cu(SO ₄) ₂	H ₂ O	100	20	90
9	Cuttlebone@Cu(OAc) ₂	H ₂ O	100	10	95
10	Cuttlebone@CuCl ₂	H ₂ O	100	5	95
11	Cuttlebone@CuCl ₂	H ₂ O	r.t	40	72
12	Cuttlebone@CuCl ₂	MeOH	Reflux	30	75

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13	Cuttlebone@CuCl ₂	MeOH/H ₂ O (1:1)	60	30	87
14	Cuttlebone@CuCl ₂	THF	Reflux	60	Trace
15	Cuttlebone@CuCl ₂	CH ₃ CN	Reflux	60	20
16	$Cuttlebone@CuCl_2$	DMSO	100	60	Trace
17	Cuttlebone@CuCl ₂	Acetone	Reflux	60	25
18	Cuttlebone@CuCl ₂	Neat	100	30	70
19	Cuttlebone@CuCl ₂	H ₂ O	40	5	95
20	Cuttlebone@CuCl ₂	H ₂ O	50	5	95

 $^{\rm a}$ Reaction conditions: phenyl acetylene (1 mmol), benzyl bromide (1 mmol), NaN_3 (1.2 mmol), catalyst (0.048 g) in H_2O (5 mL).

as MeOH and a solution of MeOH/H₂O (1:1, v:v) have proved to be less suitable for such a click reaction (Table 1, entries 12,13). On the other hand, aprotic solvents like THF, CH₃CN, DMSO and acetone were ineffective for this transformation (Table 1, entries 14-17). Similarly, the improvement of the reaction was not promising by using neat condition (Table1, entry 18). The obtained results confirmed that cuttlebone@CuCl₂ catalyst renders a promising catalytic activity in water, at 40 °C, with enhanced regioselectivity towards the desired 1,4-disubstituted 1,2,3-triazole product (Table 1, entry 19).

Having identified cuttlebone@CuCl₂ as the most efficient catalyst for the Huisgen1,3-dipolar cycloaddition reaction in H_2O at 40 °C, as the optimized reaction conditions, the catalyst and also sodium azide amounts were next investigated for the representative phenyl acetylene, benzyl bromide and sodium azide reaction (Table 2). This reaction gives high yields of the corresponding 1-benzyl-4-phenyl-

1*H*-1,2,3-triazole, in the presence of 0.048 g (8.5 mol%) of the present catalyst and 1.2 mmol of sodium azide (Table 2, entry 2).

With the optimal conditions in hand, the scope of this methodology has been explored using a variety of organic bromides and terminal alkynes. The results are illustrated in Table 3. It was found that the electron-rich, electron neutral and electron-poor phenyl acetylenes reacted with organic bromides and NaN₃ successfully to provide the desired products in good to excellent yields. Aliphatic alkynes also underwent the successful coupling reactions with the *in situ* generated corresponding azide from the reaction mixture of benzyl bromide and NaN₃ (Table 3, entries 9, 10).

Moreover, 2-ethynylpyridine as a heteroaryl substituted acetylene was converted to the corresponding triazoles, efficiently (Table 3, entries 5, 15 and 20). In an attempt to develop the scope of our methodology, the model reaction was accomplished with a range of

substituted benzyl bromides (Table 3, entries 11-20). As it is evident from Table 3, in all cases the clean reactions were performed to produce the corresponding triazoles, smoothly. Afterwards, we focused our attention on using allyl bromide instead of benzyl bromide. Similarly, the Huisgen 1,3-dipolar cycloaddition reactions of terminal alkynes and allyl bromide were clean and high-yielding (Table 3, entries 21-24).

Also, to investigate the on water effect on the reaction progress of polar propargyl alcohol and 2-bromo ethanol, the model reactions were performed in the presence of catalyst (Table 3, entry 9 and 25). As can be observed, using polar alkynes and alkyl bromides reduced the reaction efficiency. Although, nonpolar organic compounds have more interactions together in the aqueous media and would increase the effective efficiency of the reaction, as well as reducing the reaction time as a result of their lack of solubility in water (water solvation effect), in contrast due to the solubility of propargyl alcohol and 2-bromo ethanol in the aqueous media, the efficiency of the corresponding reactions reduced.

As it was expected, by using this methodology in the reaction of sodium azide, benzyl or allyl bromides with different terminal alkynes, only one of the possible regioisomers was produced, through an efficient three-component click reaction.

All of the obtained triazoles were known and their physical (color, melting points) and spectral (mass spectrometry) data found to be identical with those of authentic compounds. The selected compounds were further identified by elemental analysis, FT-IR, ¹H NMR and ¹³C NMR spectroscopy, which compared with literature data. In the FT-IR spectra of the products, the disappearance of the absorption bands related to C=C and =C-H stretching bands (at about 2250-2100 and 3300 cm⁻¹, respectively) along with the appearance of the characteristic bands corresponding to the

Table 2 Copper-catalyzed azide–alkyne cycloaddition with different amounts of NaN $_3$ and catalyst. ^a

Entry	Catalyst (mol%)	NaN₃ (mmol)	Time (min)	Isolated Yield (%)
1	9.5	1.2	5	95

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2	8.5	1.2	5	95
3	7.5	1.2	15	90
4	6.5	1.2	20	80
5	10.5	1.2	5	95
6	8.5	1.1	10	70
7	8.5	1.4	5	95

 a Reaction conditions: phenyl acetylene (1 mmol) and benzyl bromid (1 mmol) in $H_{2}O$ (5 mL) at 40 °C.

Table 3. One-pot click reaction between a variety of acetylenes, organic bromides and sodium azide by using the present catalyst.



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4 NO₂ $O_2 N'$ ∕∕СН Ņ≓^N Br OH HO 9 60 __СН Ņ≤^N∖ B 10 65 _СН C N≃µ Br 11 CI 15 CH CI N= `Br CI 12 30 CH CI N≂v B 13 CI 40 OMe MeO CH Ņ≓^N CI B 14 CI 50 *t*-Bu t-Bu __СН CI Ņ=∕ B 55 CI 15 //СН O_2N Ņ≓^N Br 16 O_2N 25 //СН O_2N Ņ≓Ņ Br 17 O₂N 40 Ņ≓^N CH O_2N Br 18 O_2N 50 OMe MeO

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out-of plane bending vibrations of the =C–H in the triazole ring (at about 815 cm⁻¹), were document for the formation of 1,4disubstituted 1,2,3-triazoles. Moreover, the FT-IR spectra of all products show absorption bands at about 1293–1217 cm⁻¹ (due to N–N=N–) related to the triazole ring. Structural assignments of triazoles were made by comparison of the ¹H and ¹³C NMR spectra with those reported, previously. In fact, the click condensations were confirmed by the appearance of a singlet resonating at around 8.5–7.5 ppm in ¹H NMR spectra, which corresponds to the hydrogen on 5-position of triazole ring and corroborates the regioselective preparation of 1,4-disubstituted triazole regioisomers (*see ESI*).

To evaluate the regioselectivity of this click reaction towards the 1,4-disubstituted triazole regioisomers instead of 1,5-disubstituted triazole regioisomers, and since ¹HNMR and ¹³CNMR spectra could not conclusively distinguish between such two isomers, the structure of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (a) was investigated through the NOE technique.

Fig. 4 shows the NOESY ¹HNMR spectrum of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole. As it is evident from the spectrum, cross-peak is obtained due to the interaction between benzyl protons (H_b) and (H_x) of triazole ring (see the encircled area in Fig. 4). However, if the product was 1-benzyl-5-phenyl-1*H*-1,2,3-triazole (**b**), no cross-peak should have appeared due to the lack of spatial vicinity between H_x and H_b (lack of interaction between benzyl protons (H_b) and (H_x) of triazole ring). According to the results of NOESY ¹HNMR spectrum, it has been proved that 1-benzyl-4-phenyl-1*H*-1,2,3-triazole is the only isomer obtained from the click reaction in our study.

By analogy with our investigation and based on reports in the literature, ^{22b} a possible mechanism for the click synthesis of 1,4disubstituted 1,2,3-triazoles catalyzed by using the present catalyst is proposed in Scheme 3. The 1,2,3-triazole formation proceeds through the formation of copper acetylide (I), which then followed by the coordination of the *in situ* generated organic azide to the copper center of acetylide. Subsequently, Huisgen 1,3-dipolar

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Fig. 4 NOESY ¹HNMR spectrum of the 1-benzyl-4-phenyl-1*H*-1,2,3-triazole isomer in the presence of the catalyst.



cycloaddition reaction between organic azide and copper acetylide (I) leads to the formation of complex (II).

Finally, the desired 1,2,3-triazole was obtained by copper exchange with the acidic hydrogen which has been generated in the first step and then the re-generated catalyst re-enters the catalytic cycle. It is worth to note that, the formation of complex (II) would be proceed through an "on water" effect, because of the insolubility of organic azides and terminal acetylenes in aqueous media.^{22f,35} Further studies to elucidate the details of the mechanism are ongoing.

One of the principal advantages of a heterogeneous catalyst is its ease of separation and possible reusability in the further runs. Thus, the recyclability of the catalyst was examined in a one-pot synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole, under the optimized reaction conditions. The catalyst was separated easily from the reaction mixture by simple filtration, followed by washing with water, ethanol and EtOAc, successively. Afterwards, the catalyst

was dried at 60 $^\circ \rm C,$ for 3 h. The recovered catalyst was then utilized directly in the next cycle. The results revealed that this simple



Scheme 3. Plausible mechanism of one-pot CuAAC protocol using present catalyst.

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Fig. 5 Recycling of the catalyst, in the click synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole.

separation method could be repeated for seven consecutive runs and the recovered catalyst showed remarkably constant catalytic activity in all seven cycles (Fig. 5).

The copper content of freshly prepared cuttlebone@CuCl₂ which was acquired by inductively coupled plasma (ICP) was 1.77 mmol of Cu per 1.000 g of the catalyst, whereas ICP illustrates that the 7th reused cuttlebone@CuCl₂ contains 1.54 mmol of Cu per 1.000 g of 7th reused catalyst. It means that, the amount of leached metal from the surface of catalyst is very low.

To confirm the presence of contaminant copper ions in the reaction medium after extraction with organic solvent, ICP-OES technique was employed for the selected products including 1-allyl-4-(p-tolyl)-1H-1,2,3-triazole and 1-benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole, and the exact amounts of contaminant copper ions was measured (90 ppm; 75 ppm), in the reaction medium. Moreover, ICP-OES technique was employed for the isolated triazole compounds 1-allyl-4-(p-tolyl)-1H-1,2,3-triazole, including 1-benzyl-4-(4nitrophenyl)-1H-1,2,3-triazole, 1-benzyl-4-(4-(tertand butyl)phenyl)-1H-1,2,3-triazole (the exact amounts of contaminant copper ions was measured to be 43 ppm; 37 ppm; 46 ppm, respectively), and the minimum copper contamination was detected in the corresponding compounds. These results can rule out almost any contribution of leached copper ions in to the reaction medium, as well as the isolated triazole compounds, and confirms that the presented catalyst is heterogeneous.

As can be seen in the FT-IR spectrum of the 7th recovered catalyst (Fig. 1c), all of the characteristic peaks are well preserved in terms of shape, position and relative intensity.

These results demonstrate no significant changes have been occurred on the chemical structure of functional groups and the hydrogen bonding network of the catalyst.

The present catalyst was exhibited much more catalytic efficiency compared with some of the catalysts used for this transformation,

previously. To prove the superiority of the present catalyst over some of the reported catalysts in the literature, its catalytic activity in the synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole, was compared with various reported catalyst (Table 4). Although, other copper catalysts afford high yield of the product, some of these methods suffer from one or more of the following drawbacks, such as using organic solvents, 18, 36, 37 higher temperatures, 18, 24f, 37-41 certain and difficult conditions as mw irradiation^{39,41} or ballmilling,^{22d} and some additives or reducing agents³⁷ and require longer reaction times to achieve reasonable yields. However, compared to these catalysts, the present catalytic system, offered higher activity with lower amount of catalyst, without using any reducing agents or additives, under mild conditions for the synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole, in water (Table 4, bold in entries). These findings significantly confirm the high efficiency of the present catalyst in three-component click synthesis of the desired triazole.

4. Conclusion

In summary, cuttlebone@CuCl₂ as a novel and efficient heterogeneous catalyst was synthesized and characterized by different techniques such as, FT-IR, EDX, XPS, and ICP. The newly synthesized catalyst revealed a privileged catalytic efficiency towards the highly efficient and economical synthesis of 1,4disubstituted 1,2,3-triazoles, through a one-pot Huisgen 1,3-dipolar cycloaddition reaction. The present protocol involves a rapid formation of 1,4-disubstituted 1,2,3-triazoles via a shorter reaction pathway, as well as easy workup and also avoids the isolation of unstable and toxic azides, by using recyclable and reusable catalyst, in water as a green solvent. Mildness of the reaction conditions. compatibility with a wide range of substrates with high functional group tolerance, high yields of the products, ligand-free and leaching-free feature of the catalyst, along with its ease of preparation and handling, make this protocol very attractive and environmentally compatible process for the regioselective synthesis of a variety of 1,2,3-triazoles. Most importantly, this approach does not require additional reducing agent, since cuttlebone as a naturalreducing platform can reduce Cu^{II} to the click-active stabilized Cu^I, in the freshly prepared catalyst, which would be followed by more reduction of Cu^{II} species while the catalyst treated with NaN₃ during the reaction.

Acknowledgements

The authors gratefully acknowledge the partial support of this study by Ferdowsi University of Mashhad Research Council (Grant no. p/3/39490).

Table 4. Comparison of catalytic activity of the present catalyst with some other reported methods in the click reaction of phenyl acetylene, benzyl bromide and sodium azide.

Entry	Catalyst (mol%)	Reaction conditions	Yield (%)	Ref.	
1	Silica-APTS-Cu(I), ^a (5)	EtOH, 78 °C, 24 h	92	18	

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15	Cuttlebone@CuCl ₂ , (8.5)	H ₂ O, 40 °C, 5 min	95	Present study
14	Zn/C, (10)	DMF, 50 °C, 15 h ^h	91	44
13	Nanoporous Au/TiO ₂ , (2 mg)	H ₂ O, r.t, 20-30 min	91	43
12	CuT, ^g (40)	PEG ₂₀₀₀ , 70 °C, 6 h ^e	95	42
11	CuNP, ⁽ 1)	PEG ₂₀₀₀ , 70 °C, 0.5 h ^e	90	42
10	Cul, (1)	PEG ₂₀₀₀ , ^d 70 °C, 0.5 h ^e	97	42
9	Cu/SiO ₂ , (10)	H ₂ O, 70 °C, mw, 10 min	92	41
8	Copper nanoparticles on charcoal, (1)	H ₂ O, 100 °C, 0.6 h	91	40
7	MNP–CuBr, (1.46)	H ₂ O/PEG, 80 °C, mw, 0.3 h	96	39
6	CuFe ₂ O ₄ , (5)	H ₂ O, 70 °C, 3 h	93	38
5	MNPs@FGly, ^c (0.5)	H ₂ O/ <i>t</i> -BuOH; (3/1), 55 °C, 2 h	99	37
4	Cu NP, (5)	MeOH, r.t, 8 h	93	36
3	γ-Fe ₂ O ₃ @TiO ₂ -EG-Cu ^{II} , ^b (4)	H ₂ O, 50 °C, 5 min	94	22f
2	Cu/Al ₂ O ₃ , 10	Ball-milling, 1 h	92	22d

^{*a*} Copper(I) on 3-aminopropyl functionalized silica. ^{*b*} Cu^{II} immobilized on guanidinated epibromohydrin functionalized γ -Fe₂O₃@TiO₂. ^{*c*} Fe₃O₄-silica-coated@functionalized 3-glycidoxypropyltrimethoxysilane. ^{*d*} Polyethylene glycol of molecular weight 2000. ^{*e*} CuAAC between 3-azidopropanol and phenylacetylene for the synthesis of 1-(3-hydroxypropyl)-4-phenyl-1,2,3-triazole. ^{*g*} Copper turnings (CuT). ^{*b*} CuAAC between 4-nitrophenyl azide and phenylacetylene for the synthesis of 1-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazole.

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DOI: 10.1039/C6RA13314B

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Graphical Abstract

Direct access to stabilized Cu^I using cuttlebone as a green-reducing support for efficient CuAAC click reactions in water

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Cuttlebone@CuCl₂ as a highly active, versatile and green heterogeneous catalyst for the efficient preparation of 1,4disubstituted 1,2,3-triazoles through one-pot Huisgen 1,3-dipolar cycloaddition reaction in water, was investigated. This approach does not require additional reducing agent, since cuttlebone as a green reducing platform can reduce Cu^{II} to the clickactive stabilized Cu^{II} .