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One-pot three-component synthesis of 1,4-disubstituted 1*H*-1,2,3triazoles using green and recyclable cross-linked poly(4vinylpyridine)-supported copper sulfate/sodium ascorbate in water/*t*-BuOH system

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Abstract Cross-linked poly(4-vinylpyridine)-supported copper sulfate, $[P_4-VP]CuSO4$ as a green and recyclable, heterogeneous catalyst in the presence of sodium ascorbate (NaAsc), is reported for the regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles from benzyl halides, sodium azide and terminal alkyne in water/*t*-BuOH (1/1:V/V) at 70 °C. Various alkyl halides and benzyl halides, with electron-withdrawing groups as well as electron-donating groups, were used for synthesis of various 1,4-disubstituted-1,2,3-triazoles in high yields. The present procedure offers as short reaction time and simple reaction work up. This catalyst can be recovered by simple filtration and recycled several consecutive runs without any loss of its efficiency.

Keywords Polymer-supported copper sulfate \cdot 1,2,3-Triazole \cdot 1,3-Dipolar cycloaddition reaction \cdot Click chemistry \cdot Sodium azide

Introduction

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. 1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications [1] and biological activities such as anti-HIV activity [2], anticonvulsant [3], anti-allergic [4] and anti-microbial agents [5]. Recently, synthesis of 1,2,3-triazole derivatives and evaluation of their anticancer activity [6] and antibiotic activity [7] have been

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Department of Chemistry, College of Science, Yazd University, P. O. Box 89195-741, Yazd, Iran e-mail: makarimi@yazd.ac.ir reported. The most popular method for the synthesis of 1,2,3-triazole is Huisgen 1,3-dipolar cycloaddition reaction of azides with alkynes [1, 8-18], but this reaction suffered from a lack of selectivity yielding a mixture of the 1,4- and the 1,5-regioisomers. Furthermore, this transformation requires elevated temperature, typically in refluxing conditions and long reaction times to go to completion. Therefore, it is desirable to develop a new, convenient and regiospecific synthetic approach for the formation of triazoles.

The copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of organic azides and terminal alkynes (also called "click chemistry") resulting in the formation of only 1,4disubstituted 1,2,3-triazoles [9–17]. The sources of copper(I) are the most commonly used directly (e.g., CuI) [11– 17], or generated by in situ oxidation of a copper metal, reduction of a Cu(II) salts, and/or Cu(II)/Cu(0) [10], and the redox couple copper(II)/ascorbic acid in organic or organo-aqueous systems [8, 15–17]. Copper(I) salts have been less used because of their thermodynamic instability and the formation of undesired alkyne-alkyne coupling products is sometimes observed [11]. While the use of soluble Copper(I) salts complexes to promote this reaction is well established (high reactivity and high selectivity) [7, 8, 14]. Homogeneous catalysis is generally connected with the problem of separation (purity of the products), recovery and regeneration of the catalysts, low regioselectivity and long reaction times. In small-scale synthesis, these problems are solved by purification using chromatography accompanied by the loss of the catalysts, but for synthesis of industrial interest the costs of the catalyst materials are of importance. In addition to the separation problems, deactivations of the homogeneous catalysts by formation of inactive colloidal species are encountered at the comparatively high reaction temperature. The problems discussed

could be principally minimized by a heterogeneously catalvzed such as heterogeneous copper(I) catalysts based on silica [19–21], montmorillonite [22], copper nanoparticles [23, 24], zeolites [25], Cu in charcoal [26, 27] and polymer [28, 29], have been developed. Nitrogen-containing polymer is used to generate metal complexes with transition metal, in which nitrogen atoms are coordinative bounded to metal ions [30, 31]. There are a few polymer-supported copper catalysts reported in the literature for the synthesis of 1,2,3-triazole derivatives such as polymer-supported azide and copper(I) [32], copper iodide nanoparticles on poly(4-vinylpyridine) [33], polymer-supported copper(I) catalysts [34] and macroporous polymer-supported azide and nanocopper (I) [35]. The present paper also refers to the complexation between Cu^{2+} ions with poly(4vinylpyridine) cross-linked with 2 % divinyl benzene, [P₄-VP] 2 % DVB.

Although numerous applications of solid supported reagents and catalysts are reported in the literature [30-44], but, there are only a few reports in the literature based on polymer-supported copper ion [30-35].

In continuation of our studies on development of application of polymeric reagents and catalysts in organic transformations [38–44] herein, we wish to report an improved, fast and general convenient procedure for one-pot three-component synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles via cycloaddition of alkyl azides (that in situ generated from sodium azide and alkyl halides) to a terminal alkyne such as phenyl acetylene using [P₄-VP]CuSO₄/NaAsc in mixture of water/*t*-BuOH (1/1:v/v), at 70 °C.

Experimental

General

Chemicals were purchased from Fluka (Buchs, Switzerland), Aldrich (Milwaukee, WI) and Merck chemical companies. Poly(4-vinylpyridine) cross-linked with 2 % divinyl benzene (DVB), [P₄-VP] 2 % DVB was purchased from Fluka company (Buchs, Switzerland). The reactions were monitored by thin layer chromatography (TLC) using silica gel Poly Gram SIL G/UV 254 plates. All products were characterized by the comparison of their melting points, FT-IR, and ¹HNMR spectral data, with those of known samples and all yields referring to the isolated pure products. Melting points were determined with a Buchi melting point B-540 B.V. CHI apparatus. FT-IR spectra were obtained using a Bruker, Equinox (model 55) and NMR spectra were recorded on a Bruker AC 400, Avance DPX spectrophotometer at 400 MHz in CDCl₃ solutions. The excessive copper ions in the filtrate determination were carried out on a Buck Scientific atomic absorption spectrometer (SEM). SEM images were recorded using Jeol make T-300 Scanning Electron Microscope. The copper in $[P_4-VP]CuSO_4$ determination was carried out on a Buck Scientific atomic absorption spectrometer (Model 210 VGP, USA) with a hollow cathode lamp at a wavelength of 327.4 nm using air–acetylene flame.

Preparation of [P₄-VP]CuSO₄

Cross-linked poly(4-vinylpyridine) (1.00 g) was added to a 5 mL of 1 M aqueous solution of CuSO₄·5H₂O, and the mixture was slowly stirred for 24 h at room temperature. The blue polymer, [P₄-VP]CuSO₄, was filtered and the excessive copper ions in the complex were washed by deionized water $(3 \times 5 \text{ mL})$. It was then dried under vacuum in the presence of P₂O₅ at 40 °C overnight. The excessive copper ions in the filtrate determination were carried out on a Buck Scientific atomic absorption spectrometer (Model 210 VGP, USA) with a hollow cathode lamp at a wavelength of 327.4 nm using air-acetylene flame. The single-line flow-injection system consisting of peristaltic pump (Ismatic, MS-REGLO/ 8-100, Switzerland), and rotary injection valve (Rheodyne, CA, USA) with a loop of 100-µL capacity was used for the effective control of the amount of sample and reproducibility of the measurements. The absorbance time response was monitored on an x-t-chart recorder (L-250) and quantitative analysis was based on the measurement of the peak height of transient signals.

The amount of the Cu^{2+} ions in complex was obtained by difference of the amount of Cu^{2+} ions that used for loading of the polymer and the excess of remained in the filtrates and consequently, the capacity of the polymer was determined to be 1.5 mmol of Cu^{2+} ion g^{-1} of the polymer.

General procedure for synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles

To a solution of phenylacetylene (1.2 mmol), alkyl halide (1 mmol), and NaN₃ (1 mmol), in mixture of *tert*-butyl alcohol (3 mL) and water (3 mL) were added [P₄-VP]CuSO₄ (1.5 g) and sodium ascorbate (0.1 g). The resulting mixture was stirred at 70 °C for appropriate time as indicated in Table 2. The progress of reaction was monitored by TLC (*n*-hexane/ethyl acetate: 8/2). After completion, ethanol (8 mL) was added to the reaction mixture was filtered off and washed with hot ethanol. Solvent was removed under vacuum, and the residue was precipitated in water. The precipitate was dried at room temperature. For further purification, the solid was recrystallized in ethanol/water.

Regeneration of [P₄-VP]CuSO₄

The spent green colored polymer (1.00 g) was slowly stirred with ethanol for 24 h. The mixture was filtered and washed with hot ethanol, and dried under vacuum in the presence of P₂O₅ at 40 °C overnight. The regenerated polymer can be recovered several consecutive runs without significant loss of its efficiency.

Results and discussion

In preliminary experiments, we investigated the template reaction of sodium azide, alkyl halide, phenyl acetylene using [P₄-VP]CuSO₄/NaAsc system in a 1:1 (v/v) mixture of water and tert-butyl alcohol, and the reaction only gave the corresponding 1,4-disubstituted 1,2,3-triazoles in high yields. The process is experimentally simple and appears to have enormous scope. Although, a number of copper(I) sources can be used as catalyst for the synthesis of triazoles directly [11–17] but, copper(I) salts have been less used because of their thermodynamic instability and the formation of undesired alkyne-alkyne coupling products is sometimes observed [11]. Hence in this study, we used in situ reduction of Cu(II) salts, which are less costly and often purer than CuI salts (CuSO₄·5H₂O serves well). As the reductant, ascorbic acid and/or sodium ascorbate proved to be excellent (for a review of reactions of ascorbic acid with transition metals, see [45, 46] and references therein) for they allow preparation of a broad spectrum of 1,4-triazole products in high yields and purity. Comparison with an authentic sample established that the triazole was formed in a completely regioselective manner with no contamination by the 1,5-regioisomer. [P₄-VP]CuSO₄ was easily prepared in a one-step procedure as described in experimental section by stirring the suspension of $[P_4-VP]$ 2 % DVB in aqueous solution of CuSO₄·5H₂O. After filtration, the excessive copper ions in the filtrate determination were carried out on a Buck Scientific atomic absorption spectrometer (Model 210 VGP, USA) with a hollow cathode lamp at a wavelength of 327.4 nm using air-acetylene flame. The single-line flow-injection system consisting of peristaltic pump (Ismatic, MS-REGLO/8-100, Switzerland), and rotary injection valve (Rheodyne, CA, USA) with a loop of 100-µL capacity was used for the effective control of the amount of sample and reproducibility of the measurements. The absorbance time response was monitored on an x-t-chart recorder (L-250), and quantitative analysis was based on measurement of the peak height of transient signals. The amount of the Cu^{2+} ions in complex was obtained by different amount of selected Cu²⁺ for loading on polymer and the excess of remained in the filtrates after filtration and washing with hot ethanol, and consequently, the capacity of the polymer was determined to be 1.5 mmol of Cu^{2+} ion g^{-1} of the polymer. Our effort for preparing the oxidation state of copper sulfate on the spent polymer was not successful. Based on changing the blue color of catalyst to greenish species when the reaction was occurred, we proposed that Cu^{2+} ion in the [P₄-VP]CuSO₄ in the presence of NaAsc reduces to Cu^{1+} ion. Also, based on changing the color of the spent polymer in air to original color (blue), we proposed that Cu^{1+} ion oxidizes to Cu^{2+} ion with oxygen in the air. The process for the preparation of [P₄-VP]CuSO₄, the structure of P₄-VP] 2 % DVB and [P₄-VP]CuSO₄ is shown in Scheme 1, and the FT-IR spectra of [P₄-VP] 2 % DVB and [P₄-VP]CuSO₄ are compared in Fig. 1.

Direct evidence for the formation of the coordination complex can be obtained from the FT-IR of the support and complex. It is known that the C=N and C=C stretching frequencies in vinylpyridine polymers shifts to higher frequencies upon complexation with metal ions. Belfiore et al. [47] have observed displacements in the stretching band of the poly(4-vinylpyridine) ring and related this to the formation of coordination compounds formed with the metal and the polymer. The wavenumber increases according to the force of interaction with the metallic ion. Hasik et al. [48] discussed the possibility for the formation of a coordination bond in the poly(4-vinylpyridine)-Pd²⁺ (PVP-Pd²⁺) complex, and found a new vibration bond at $1,612 \text{ cm}^{-1}$. In our case, the frequency of C=N and C=C stretch in the support was seen at 1,597 and 1,414 cm^{-1} for C=N and C=C stretching, respectively. These peaks suffer shift towards higher wave numbers at 1,616 and 1,449 cm⁻¹, respectively, when $[P_4-VP]$ 2 % DVB was treated with aqueous solution of CuSO₄ and [P₄-VP]CuSO₄ complex was formed. This interaction increases the stiffness of the associated ring and, consequently, more energy is required to deform the aromatic cycle, reflected at higher frequencies. On the other hand, the specific characteristics of the stretching bands of the SO₄²⁻ anion and S–O vibrations of SO₄²⁻ groups in FT-IR spectrum of [P₄-VP]CuSO₄ complex appeared between 900 and $1,300 \text{ cm}^{-1}$ (1,120) and 610 cm^{-1} , respectively, that are absent in FT-IR spectrum of [P₄-VP] 2 % DVB copolymer (Fig. 1). The obtained results are supported by Belfiore et al. [47], Hasik et al. [48], Li [49], Wu et al. [50], and Santana et al. [51]. In this work, we also studied the scanning electron microscopy (SEM) of [P₄-VP] 2 % DVB and $[P_4-VP]CuSO_4$. The SEM of $[P_4-VP]$ 2 % DVB (a) and [P₄-VP]CuSO₄ (b) is shown in Fig. 2. [SEM photographs of (a) and (b) at $2,710 \times$ magnification]. It is seen from the Fig. 2 that the surface of the polymer is distinctly altered in supported catalysts (b) and with comparison of particle size diameter of $[P_4-VP] 2 \% DVB (a) (7.7 \mu m)$ with $[P_4-VP]CuSO_4$ (b) (14.2 µm) can be concluded that chelating occurred between pyridine pendant group of [P₄-VP] 2 %



Wavenumber cm-1

DVB chain with $CuSO_4$ and sandwiched between two polymer chain of $[P_4-VP] 2 \%$ DVB. Also, as Fig. 2 reveals no definite size particles are observed in $[P_4-VP] 2 \%$ DVB (a) with uniform morphology.

This polymeric catalyst with NaAsc, catalyzed Huisgen 1,3-dipolar cycloaddition reaction between phenylacetylene and alkyl azides that in situ generated from sodium azide and alkyl halides. Since organic azides are often Fig. 2 Scanning electron microscopy (SEM) images of a [P₄-VP] 2 % DVB, and b [P₄-VP]CuSO₄







unstable to heat and light, the in situ preparation recommends a great choice to their use and handling. All alkyl azides were prepared in situ and subjected to multicomponent click cyclization with phenylacetylene. A variety of alkyl halides were also subjected to one-pot three-component reaction for synthesis of 1,4-disubstituted 1,2,3-triazoles under heterogeneous conditions (Scheme 2).

To exploit a method for preparation of 1,2,3-triazole derivatives, the reaction of 4-nitrobenzyl bromide, phenylacetylene and sodium azide in the presence of [P₄-VP]CuSO₄/NaAsc via a 1,3-dipolar Huisgen cycloaddition reaction was chosen as a model reaction. This reaction is known to give high yields of triazoles with homogeneous catalysts. The model reaction behavior was studied under a variety of conditions, and the results are summarized in Table 1. First we began to test in acetonitrile, methylene chloride, ethanol and water as solvents. Unluckily, we did not get good results at room temperature with various amounts of heterogeneous catalysts and reagents with each of solvents after 4 h. Therefore, the reaction was followed at various solvent systems such as H₂O/t-BuOH, H₂O/i-PrOH, H₂O/EtOH, H₂O/THF and H₂O/CH₃CN and it was found that the solvent plays a significant role in terms of reaction rate, isolated yield, and selectivity. H₂O/t-BuOH clearly stands out as the solvent of choice with its fast reaction rate, high isolated yield and selectivity. As can be seen from Table 1, THF and CH₃CN afforded low yield (entry 17, 18), while the mixed solvent $H_2O/alcohol$ achieved high yield (entries 5, 15 and 16) which is one of the most popular solvent system used for click reaction. In these solvent systems, sodium azide and sodium ascorbate were dissolved in water and alkyl halide and phenyl acetylene were dissolved in organic solvent t-BuOH. The reaction between 4-nitrobenzyl bromide, phenylacetylene and sodium azide in the presence of 1.50 g of $[P_4-$ VP]CuSO₄ and 0.10 g of sodium ascorbate furnished the 1,4-disubstituted triazole product in 93 % isolated yield after stirring for 95 min at 70 °C. Also during our optimization studies, it was found that, 1/1.2/1 molar ratios of 4-nitrobenzyl bromide/phenyl acetylene/NaN₃ in the above conditions were the best to achieve the highest yield of the product (Table 1, entry 5). Then the amount of catalyst, [P₄-VP]CuSO₄ and reducing agent (NaAsc) were examined. As Table 1 reveals (entries 5 and 11-14) the best result was obtained when the reaction took place in the presence of 1.50 g of [P₄-VP]CuSO₄ and 0.10 g of NaAsc (Table 1, entry 5), for multicomponent click cyclization. Furthermore, [P₄-VP]CuSO₄, in the absence of a reducing agent, was also evaluated, and negative results were observed (Table 1, entry 10).

We then applied these conditions for synthesis of various 1,4-disubstituted-1H-1,2,3-triazoles, and the results are summarized in Table 2. Various alkyl or benzyl halides with both electron-donating and -withdrawing substituents were subjected to the same reaction conditions to furnish the corresponding 1,2,3-triazole derivatives. When benzyl

Table 1 Optimization of the reaction conditions for model substrate (after 95-min stirring)	Entry	MS (mmol) ^a	NaN ₃ (mmol)	PA (mmol) ^b	Catal (g) ^c	NaAsc (g) ^d	RT (°C) ^e	Solvent (v/ v = $1/1$)	Yield $(\%)^{f}$
at 70 °C using [P ₄ -VP]CuSO ₄ /	1	1	1	1	1.50	0.10	70	Water/t-BuOH	75
NaAsc to furnish the corresponding 1,2,3-triazole derivatives	2	1	1.5	1	1.50	0.10	70	Water/t-BuOH	75
	3	1	2	1	1.50	0.10	70	Water/t-BuOH	75
	4	1	1	1.5	1.50	0.10	70	Water/t-BuOH	75
	5	1	1	1.2	1.50	0.10	70	Water/t-BuOH	93
	6	1.5	1	1.2	1.50	0.10	70	Water/t-BuOH	42
	7	1	1	1.2	1.50	0.10	70	Water/t-BuOH	52
	8	1	1	1.2	1.50	0.10	70	Water/t-BuOH	93
	9	1	1	1.2	1.50	0.10	rt	Water/t-BuOH	38
	10	1	1	1.2	1.50	_	70	Water/t-BuOH	_
	11	1	1	1.2	1.50	0.20	70	Water/t-BuOH	93
	12	1	1	1.2	1.50	0.05	70	Water/t-BuOH	48
^a MS model substrate (4-	13	1	1	1.2	2.00	0.10	70	Water/t-BuOH	93
 nitrobenzylbromide) ^b PA phenyl acetylene ^c Catalyst, [P4-VP]CuSO4 ^d Sodium ascorbate ^e RT reaction temperature ^f Isolated yield 	14	1	1	1.2	1.50	0.10	70	Water/t-BuOH	61
	15	1	1	1.2	1.50	0.10	70	Water/i-PrOH	92
	16	1	1	1.2	1.50	0.10	70	Water/EtOH	92
	17	1	1	1.2	1.50	0.10	70	Water/THF	20
	18	1	1	1.2	1.50	0.10	70	Water/CH ₃ CN	32

bromide and benzyl chloride were compared for the synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazol product, we observed that benzyl bromide reacted faster with higher isolated yield (see Table 2, entries 9 and 10). This result was also observed when 4-nitrobenzyl bromide and 4-nitrobenzyl chloride were used (entries 7 and 8). This can be attributed to this fact that bromide is a better leaving group than chloride in reaction with NaN₃ for the formation of the corresponding benzyl azide intermediates. This new, simple method can be successfully applied for the synthesis of a wide range of 1,4-disubstituted-1H-1,2,3triazoles starting from the corresponding alkyl halides such as substituted benzyl bromide, substituted benzyl chloride, 1-chloromethyl naphthalene (Table 2, entry 13) and 2-phenylethyl bromide (Table 2, entry 14). As expected, the halide-leaving group and the electronic and steric effects of substituted benzyl halides also play a significant role in terms of reaction rate and isolated yield. As Table 2 reveals, using benzyl halides with electron-donating groups at 4-position of the ring, results in bout higher isolated yields and shorter reaction times (see entries 3 and 8) but, when benzyl halides with a substituent group at 2-position of the ring steric effect were observed and result in bout lower yields and longer reaction times (see entries 2 and 7).

This polymeric catalyst is used in one-pot three-component reaction, its main advantage over non-polymericsupported catalyst is its insolubility in the reaction medium and consequently its easier work up by a simple filtration. An important point concerning the use of heterogeneous catalysts is its lifetime, particularly for industrial and pharmaceutical applications. The leaching of active species from heterogeneous catalysts in solution is a crucial question to identify whether the active centers are solid surfaces or dissolved catalyst complexes. In this study, we used the cross-linked poly(4-vinylpyridine)-supported copper sulfate that does not dissolve in any solvent. The reaction occurred on the surface of the pores of the polymer. One reason for the observed different reaction times in different solvents perhaps could be the swelling of the reagent in the proper solvent. Hence, instead of leaching of the catalyst reusability of the catalyst was studied. The results obtained with [P₄-VP]CuSO₄ that was recycled for the chosen model reaction for six runs are shown in Fig. 3. The original [P₄-VP]CuSO₄ gave similar results concerning the recovery of the heterogeneous catalyst. As Fig. 3 reveals, when the polymer was reused after six runs under identical conditions and in the same reaction times, the isolated yield of the product was decreased only a few percent (4 %).

Our mechanistic proposal for the catalytic cycle is shown in Scheme 3. Cu^{2+} ion, in the [P₄-VP] CuSO₄ (blue species) in the presence of NaAsc reduced to Cu¹⁺, and its color was changed to greenish species that catalyzed the reaction. The spent polymer oxidized to Cu²⁺ in the presence of air and its color returned to original color (blue). It begins unexceptionally with the formation of the copper(I) acetylide (I) [52], which proceeds in addition to in situ generated alkyl azides (from sodium azide and alkyl halide) via the intriguing six-membered copper-containing intermediate (II) [53]. Finally, by cyclization, formation of

Entry	Substrate	Product	Time (min)	Yield (%)	M.p.(°C)		
					Found	Lit [References]	
1		Cl N Ph	105	88	141–143	_	
2	Cl NO ₂	NO _N NO _n	135	69	145–147	_	
3	Me	Me	30	95	108–110	110[27]	
4	Cl		85	93	107–108	_	
5	Cl		125	90	84–86	-	
6	Br		35	96	153–154	152–152.5 [27], 150–151 [19], 152–152.5 [33]	
7	O ₂ N-Cl		130	79	158–159	156–157 [27], 140–142 [19], 140–141 [33]	
8	O ₂ N-Br		95	93	158–159	156–157 [27], 140–142 [19], 140–141 [33]	
9			60	77	129–130	129–129.5 [27], 128–130 [19], 128–129 [33]	
10	Br		40	91	129–130	129–129.5 [27], 128–130 [19], 128–129 [33]	
11	MeCl	Me N Ph	45	94	96–97	109–110 [19], 110 [33]	

Table 2	Preparation of 1,4-disubstituted-1H-1,2,3-triazole from	om benzyl halide	s/NaN ₃ /phenyl acety	lene catalyzed by	P ₄ -VP]CuSO ₄ /NaAsc in
water/t-I	BuOH (1/1) at 70 °C				

Table 2 continued

Entry	Substrate	Product	Time (min)	Yield (%)	M.p.(°C)		
					Found	Lit [References]	
12	F Cl	F N Ph	120	90	156–158	-	
13			135	75	128–129	-	
14	Br		95	89	138–140	139 [27]	

^a Yields refer to isolated and pure products



Fig. 3 Recovery studies: cycloaddition of 4-nitrobenzyl bromide, phenylacetylene and sodium azide successively catalyzed by the same recovered $[P_4-VP]CuSO_4$ under the same reaction conditions as for the initial run

intermediate (III) occurred that is converted to 1,4-disubstituted 1H-1,2,3 triazole product by proton abstraction from reaction media (Scheme 3).

The solid products were easily recrystallized from a mixture of ethanol/water (1:3 v/v). The 1,2,3-triazole derivatives products were characterized by FT-IR; ¹H- and ¹³C NMR spectroscopy and physical properties were compared with the literature values of known compounds. Click condensations were confirmed by the appearance of a singlet in the region of 8–8.5 ppm in ¹H NMR spectra, which corresponds to the hydrogen on 5-position of triazole ring and confirms the regioselective synthesis of 1,4-disubstituted triazole regioisomers. Selected spectral data of some 1,4-disubstituted 1*H*-1,2,3-triazole products are

given below, and the FT-IR and ¹H NMR spectra of 1-(4-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole product are given in Figs. 4, 5, 6.

1-(3,5-Dichlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole

(**Table 2, entry 1):** White solid, m.p. = 141–143 °C; FT-IR (neat) v (cm⁻¹) = 3,089, 1,466, 1,425, 1,400, 1,255, 1,224, 1,206, 1,140, 1,080, 1,046, 1,030, 977, 890, 838, 816, 777, 763, 689, 547, 514; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 5.55 (s, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.42–7.49 (m, 4H), 7.73 (s, 1H), 7.83 (d, J = 7.2 Hz, 2H).

1-(2-Nitrobenzyl)-4-phenyl-1H-1,2,3-triazole (Table **2, entry 2):** Yellow solid, m.p. = 145–147 °C; FT-IR (neat) v (cm⁻¹) = 3,091, 1,609, 1,527, 1,463, 1,340, 1,222, 1,205, 1,074, 1,049, 977, 863, 791, 762, 730, 687, 600; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 6.02 (s, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.96 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H).

1-(4-Methylbenzyl)-4-phenyl-1H-1,2,3-triazole

(**Table 2, entry 3):** White solid, m.p. = 108–110 °C; FT-IR (neat) v (cm⁻¹) = 3,120, 1,609, 1,516, 1,483, 1,463, 1,445, 1,348, 1,223, 1,188, 1,134, 1,076, 1,047, 974, 913, 832, 762, 691, 540, 511, 478; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 2.28 (s, 3H), 5.46 (s, 2H), 7.11–7.15 (m, 4H), 7.23 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.56 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H).

1-(3-Chlorobenzyl)-4-phenyl-1*H***-1,2,3-triazole (Table 2, entry 4):** White solid, m.p. = 107–108 °C: FT-IR (neat) ν (cm⁻¹) = 3,083, 1,575, 1,462, 1,435, 1,342, 1,222,

Scheme 3 Proposed catalytic cycle for P₄-VP]CuSO₄- catalyzed ligation



Fig. 4 The FT-IR spectrum of 1-(4-chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole

1,078, 1,046, 973, 912, 888, 864, 840, 760, 692, 511; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 5.58 (s, 2H), 7.21 (d, J = 6.8 Hz, 1H), 7.33-7.36 (m, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.72 (s, 1H), 7.84 (d, J = 7.2 Hz, 2H).

1-(2-Chlorobenzyl)-4-phenyl-1*H***-1,2,3-triazole (Table 2, entry 5):** White solid, m.p. = 84–86 °C; FT-IR (neat) v (cm⁻¹) = 3,123, 1,573, 1,463, 1,356, 1,277, 1,220, 1,082, 1,046, 977, 915, 812, 750, 692; 1H NMR (400 MHz, CDCl₃) δ (ppm) = 5.74 (s, 2H),7.24 (d, *J* = 7.6 Hz, 1H), 7.28–7.37 (m, 3H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.48 (d, *J* = 6.4 Hz, 1H), 7.80 (s, 1H), 7.84 (d, *J* = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 51.45, 119.81, 125.74, 127.66, 128.22, 128.83, 129.94, 130.25, 130.27, 130.49, 132.57, 133.44, 148.19.

1-(4-Bromobenzyl)-4-phenyl-1*H***-1,2,3-triazole (Table 2, entry 6):** White solid, m.p. = 153–154 °C; FT-IR (neat) v (cm⁻¹) = 3,126, 1,589, 1,484, 1,461, 1,435, 1,324, 1,216, 1,182, 1,073, 1,048, 1,013, 917, 849, 808, 763, 694, 515, 490; ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 5.56 (s, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H).

1-(4-Nitrobenzyl)-4-phenyl-1*H***-1,2,3-triazole** (Table **2, entries 7, 8-12):** Yellow solid, m.p. = 158–159 °C; FT-IR (neat) v (cm⁻¹) = 3,081, 1,519, 1,647, 1,350, 1,222, 1,110, 1,078, 1,045, 861, 802, 763, 732, 690, 510; ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 5.74 (s, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.45–7.49 (m, 4H),



Fig. 5 ¹H NMR spectrum of 1-(4-chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole



Fig. 6 The expanded ¹H NMR spectrum of 1-(4-chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole

7.80 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 8.27 (d, J = 8.6 Hz, 2H).

1-Benzly-4-phenyl-1H-1,2,3-triazole (Table 2, entries 13, 14): White solid, m.p. = 129–130 °C; FT-IR (neat) ν (cm⁻¹) = 3,141, 1,606, 1,493, 1,468, 1,450, 1,360, 1,222, 1,139, 1,072, 1,044, 970, 922, 807, 768, 730, 695, 586, 506, 479; ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 5.61 (s, 2H), 7.37–7.45 (m, 8H), 7.72 (s, 1H), 7.85 (d, J = 7.7 Hz, 2H). **1-(3-Methylbenzyl)-4-phenyl-1H-1,2,3-triazole**

(Table 2, entry 15): White solid, m.p. = 96–97 °C; FT-IR (neat) v (cm⁻¹) = 3,119, 3,091, 1,608, 1,483, 1,463, 1,436, 1,446, 1,221, 1,191, 1,077, 1,050, 976, 882, 825,

768, 746, 699, 596, 511, 464, 436; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 2.37 (s, 3H), 5.56 (s, 2H), 7.14 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.30–7.35 (m, 3H), 7.42 (t, J = 7.6 Hz, 2H), 7.68 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H).

1-(2-Chloro-6-fluorobenzyl)-4-phenyl-1*H***-1,2,3-triazole (Table 2, entry 16):** White solid, m.p. = 156–158 °C; FT-IR (neat) v (cm⁻¹) = 3,129, 1,608, 1,579, 1,484, 1,459,1,430, 1,352, 1,248, 1,218, 1,179, 1,155, 1,128, 1,078, 1,043, 976, 950, 912, 853,824, 795, 763, 691, 473;¹H NMR (400 MHz, CDCl₃) δ (ppm) = 5.80 (s, 2H), 7.13 (t, *J* = 8.4 Hz, 1H), 7.30–7.37 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.78 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H). **1-(Naphthylmethyl)-4-phenyl-1***H***-1,2,3-triazole**

(**Table 2, entry 17):** White solid, m.p. = 128-129 °C; FT-IR (neat) v (cm⁻¹) = $3,119, 3,089, 1,602, 1,511, 1,483, 1,462, 1,432, 1,396, 1,341, 1,217, 1,194, 1,168, 1,081, 1,044, 976, 913, 940, 776, 725, 692, 624, 595, 539; ¹H NMR (400 MHz, CDCl₃) <math>\delta$ (ppm) = 5.95 (s, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.27(t, J = 7.2 Hz, 2H), 7.40–7.47 (m, 4H), 7.44 (s, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.82-7.86 (m, 2H), 7.94 (t, J = 5.6 Hz, 1H).

1-(2-phenylethyl)-4-phenyl-1*H***-1,2,3-triazole** (Table **2, entry 18):** White solid, m.p. = 138–140 °C; FT-IR (neat) v (cm⁻¹) = 3,082, 3,028, 1,606, 1,483, 1,456, 1,371, 1,223, 1,196, 1,048, 974, 911, 845, 764, 734, 695, 519; 1H NMR (400 MHz, CDCl₃) δ (ppm) = 3.28 (t, J = 7.2 Hz, 2H), 4.66 (t, J = 7.2 Hz, 2H), 7.16 (d, J = 6.4 Hz, 2H), 7.30–7.36 (m, 4H), 7.43 (t, J = 7.4 Hz, 2H), 7.49 (s, 1H), 7.79 (d, J = 6.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 36.82, 51.76, 119.91, 125.70, 127.15, 128.08, 128.75, 128.81, 128.86, 130.67, 137.08, 147.

Table 3 represents the efficiency of the introduced method in comparison with some of the reported methodologies [7, 8, 10, 18, 19, 27, 32, 33, 35]. The superiority of this work is that the catalyst is recoverable and reusable many times without significant loss of their activity. However, the yield of the product in our procedure is comparable with reported methods. The reaction time in the present method is shorter than in the previously reported methods for homogeneous catalyst [7, 8] or in the absence of catalyst [18]. This can probably be attributed to the local concentration of Cu²⁺ ion species inside the pores of the polymer.

The advantages to use this polymer-supported copper sulfate in comparison with $CuSO_4 \cdot 5H_2O$ [15–17] are recovery and regeneration of the catalysts, high regiose-lectivity, short reaction times and very simple reaction work up. In addition, there is a current research and general interest in heterogeneous systems because such systems are important in industry and developing technologies [54].

Entry	Reaction conditions	Time (h)	Isolated yield (%)	References
1	NaN ₃ /Nano Cu(I) on charcoal/H ₂ O, 100 °C	0.5-8	72–91	[27]
2	NaN ₃ /Silica supported CuI/H ₂ O, 25 °C	10-20 min	85–92	[19]
3	IRA-400 N ₃ /Amberlyst A21CuI,EtOH, reflux	1-2	70–92	[35]
4	NaN ₃ /Cu(0)/CuSO ₄ /t-BuOH/H ₂ O, MW	10-15 min	84–93	[10]
5	IRA-910 N ₃ /Amberlyst A21CuI/ CH ₃ CN, reflux	1-1.75	78–92	[32]
6	NaN ₃ /P ₄ VPy-CuI/Water, reflux	15-45 min	75–89	[33]
7	NaN ₃ /CuSO ₄ .5H ₂ O/Na ascorbate/Na ₂ CO ₃ / L-proline/DMSO/65 °C	24	14–96	[7]
8	NaN ₃ /CuSO ₄ .5H ₂ O/Na ascorbate/Na ₂ CO ₃ /DL-proline/DMSO/H ₂ O (1/1)/60 °C ^a	24	52–98	[8]
9	NaN ₃ /DMF/60-130 °C ^b	3-18		[18]
10	NaN ₃ /[P ₄ -VP]CuSO ₄ /NaAsc/t-BuOH/H ₂ O	0.5-2.25	75–96	Present work

Table 3 Evaluation of the introduced methodology in comparison with some of the previously reported methods

^a When $CuSO_4 \cdot 5H_2O$ is used, for synthesis of 1,2,3-triazoles, copper azide that is explosive when dry is formed, and an additional step for its separation via extraction is needed

^b In this method, the obtained sodium bromide and iodide are partially soluble in DMF and hinder the isolation of the desired reaction products, and the mixture of 1,4- and 1,5-disubstituted-1*H*-1,2,3-triazoles is prepared in nearly equal amounts

Conclusions

In conclusion, we have developed an efficient and one-pot three-component method for [3 + 2] cycloaddition of in situ generated organic azides (from sodium azide and alkyl halide) with terminal alkyne for the synthesis of 1,4disubstituted 1,2.3-triazoles using reusable polymer-supported copper sulfate catalyst/NaAsc. The present method has the advantages of operational simplicity, mild reaction conditions, ready availability, fast reaction rates, and simple reaction work up. The spent polymeric catalyst can be recovered and reused several times without significant loss of their activity.

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