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PVC-supported ethylenediamine-copper(II) complex: a heterogeneous, efficient, and eco-friendly catalyst for multi-component synthesis of 1,2,3-triazoles by reaction of propargyl bromide, aromatic azides, and amines in water

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Abstract The PVC-supported ethylenediamine-copper(II) complex (PVC–EDA–Cu^{+2}) has provided a highly efficient, active, and reusable heterogeneous catalyst for click chemistry. In this work, the PVC–EDA–Cu^{+2} catalyst is readily prepared by the reaction of PVC, ethylenediamine, and $CuCl_2{\cdot}2H_2O$ in water. The structure of the catalyst is then characterized via different analytical tools. This catalytic system shows a high activity in the multi-component synthesis of 1,4-disubstituted 1,2,3-triazoles by the click reaction of propargyl bromide, aromatic azides, and amines at room temperature. The advantages of this method are high reaction yield, short reaction time, and capability of recovering and reusing the catalyst. In addition, water, as a green medium, is used not only in the synthesis of 1,2,3-triazoles but also in the preparation of the catalyst. A number of new 1,2,3-triazole derivatives are also screened against two Gram-positive and Gram-negative bacterial strains.

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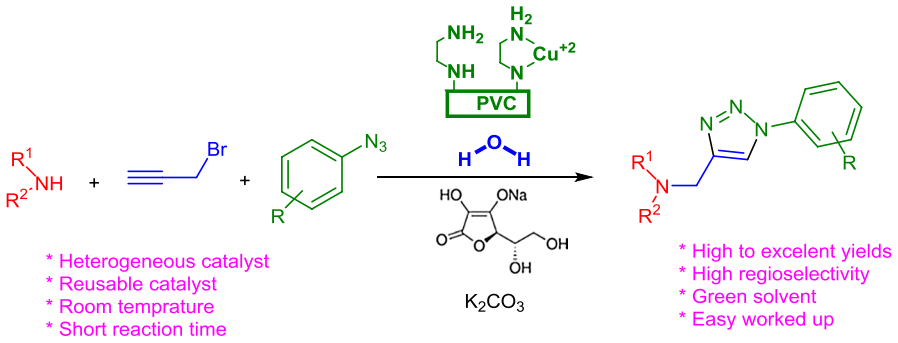
Graphical Abstract



Keywords PVC · Ethylenediamine 1,2,3-triazole · Multi-component reaction · Propargyl bromide · Aromatic azide

Introduction

The concept of "click chemistry" refers to a type of reaction that is fast, easy to use, versatile, wide in scope, modular, and stereospecific. It generates little by-product that can be removed without chromatography. In addition, the reaction proceeds under green conditions using readily available and inexpensive starting materials [1]. The copper-catalyzed azide–alkyne cycloaddition reaction is broadly known as the azide/alkyne "click" reaction [2]. A significant copper-catalyzed reaction is 1,3-dipolar cycloaddition, in which organic azides and terminal alkynes exclusively afford 1,4-disubstituted 1,2,3-triazoles in a regioselective manner [3–6].

1,2,3-Triazoles are an important class of organic compounds. They have enormous applications in various research fields such as synthetic organic chemistry [7–9] and material chemistry [10–12], and have biological activities [13, 14] such as the anticancer, anti-inflammatory, antitubercular, anti-allergic, antibacterial, and anti-HIV properties [15, 16].

Among the transition metal complexes, copper(II) complexes have been known as efficient catalysts in a variety of chemical reactions due to their being relatively inexpensive, having high selectivity, and use in numerous industrial applications [17–19]. Also, copper(I)-catalyzed azide/alkyne cycloaddition reactions have been developed for the regioselective synthesis of 1,2,3-triazoles [20–26]. Simple Cu(I) salts such as CuI, CuBr, and CuOTF are directly used in these cycloaddition reactions. Due to the instability of Cu(I) species, these active species can be generated in situ by the reduction of the Cu(II) salts such as $CuBr_2$, $CuSO_4$, and $Cu(OTf)_2$ by sodium ascorbate [27]. This method is extremely efficient, although it suffers from some serious troubles including the toxic effects of copper impurities on biological systems [28] and copper contamination of the desired isolated products. Heterogeneous catalysts have recently attracted considerable attention due to advantages such as lrger surface area

(resulting in higher loading of the active sites), easy recovery and reusability, low cost, and operational simplicity [29, 30]. Heterogeneous copper-based catalysts have been used effectively for the synthesis of 1,2,3-triazoles. Some examples of copper species immobilized on various supports such as zeolites [31], polymers [32], silica [33], activated charcoal [34], alumina [35], and titanium dioxide [36] have been reported. However, immobilization of Cu(I) salts on supports mostly suffers from the inherent thermodynamic instability of Cu(I) ions, which results in their easy oxidation to Cu(II) ions and/or disproportionation to Cu(0) and Cu(II). Moreover, the use of copper(I) iodide has been avoided in many cases to prevent the homocoupling oxidative reaction of acetylenes (Glaser-type reaction) [37, 38]. The by-products of this reaction are usually difficult to be separated from the desired products, and copper acetylide formed is a potentially explosive reagent. To overcome the above-mentioned problems, and as a consequence of our efforts in the development of efficient new catalytic systems for useful synthetic organic transformations [39–42], we wish to report here an efficient three-component synthesis of 1,2,3-triazoles in the presence of the ethylenediamine copper(II) complex on PVC as a novel heterogeneous catalyst.

Experimental

General

All the reagents used were supplied from Sigma, Aldrich, and Merck. IR spectra were obtained as potassium bromide pellets in the range of 400–4000 cm^{-1} on a Shimadzu Model 470 spectrometer. FT-IR spectra were obtained on a Bomem MB series spectrometer. NMR spectra were recorded on Bruker 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectrometers. Elemental analyses were performed using a Thermo Finnigan Flash EA micro-analyzer. Metal analyses were performed by inductively coupled plasma–atomic emission spectrometry (ICP-AES). Morphology of the catalyst was determined using a Hitachi (Japan) model s4160 scanning electron microscopy (SEM) at an accelerating voltage of 15 kV. Mass spectra were recorded on a 5975C spectrometer, manufactured by Agilent.

Synthesis of PVC–EDA

PVC (1 g) and ethylenediamine (0.6 mol) were added to a 50-mL round-bottomed flask equipped with a magnetic stirrer containing H_2O (20 mL). The reaction mixture was stirred for 24 h at 80 °C. The resulting precipitate was filtered, washed thoroughly (in turn) with H_2O and EtOH, and then dried.

Synthesis of PVC–EDA–Cu^{2+}

A mixture of PVC–EDA (1 g) and $CuCl_2{\cdot}5H_2O$ (0.002 mol) in water (20 mL) was stirred for 12 h at 80 °C. The reaction mixture was filtered, and the resulting precipitate was washed thoroughly (in turn) with H_2O and EtOH, and then dried.

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

A mixture of an amine (1 mmol), propargyl bromide (1 mmol), and K_2CO_3 (2 mmol) in H_2O (4 mL) was stirred at room temperature for 15 min. After consuming the starting materials (monitored by TLC), an aromatic azide (1 mmol), PVC–EDA–Cu^{+2} (0.1 g), and sodium ascorbate (10 mol%) were added to the reaction mixture. Upon completion of the reaction (monitored by TLC), the precipitate formed was filtered, washed thoroughly with H_2O, dried, and completely extracted with hot EtOH. The solvent was evaporated, and the crude product obtained was crystalized in a mixture of EtOH and H_2O.

4-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)morpholine (4c)

Mp, 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55–2.60 (m, 4H, $2CH_2$), 3.70–3.75 (m, 4H, $2CH_2O$), 3.78 (s, 2H, CH_2N), 7.76 (t, J = 8.1 Hz, 1H. ArH), 8.11 (s, 1H, CH of triazole), 8.20 (dd, J = 8.1, 1.2 Hz, 1H, ArH), 8.29 (dd, J = 8.1, 1.2 Hz, 1H, ArH), 8.60 (t, J = 2.1 Hz, 1H. ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.5, 53.6, 66.8, 115.1, 120.8, 123.1, 125.9, 131.0, 137.8, 145.9, 148.9 ppm; IR (KBr): $\tilde{\nu}$ = 3150, 2950, 2800, 1620, 1520 (NO_2), 1445, 1345 (NO_2) cm^{-1}; ESI–MS: *m/z* 289 (M^+).

***N*-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)aniline (4f)**

Mp, 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 4.23 (br., 1H, NH), 6.69 (d, J = 8.1 Hz, 2H. ArH), 6.74 (d, J = 7.2, 1H, ArH), 7.18 (t, J = 7.8 Hz, 2H, ArH), 7.27 (d, J = 8.1 Hz, 2H. ArH), 7.45 (d, J = 8.1 Hz, 2H, ArH), 7.83 (s, 1H, CH of triazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 40.0, 113.2, 113.7, 118.1, 120.0, 120.5, 139.3, 129.5, 130.2, 134.8, 138.9, 147.6 ppm; IR (KBr): $\tilde{\nu}$ = 3400 (NH), 3150, 2900, 1600, 1460 cm^{-1}; ESI–MS: *m/z* 264 (M^+).

***N*-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)aniline (4g)**

Mp, 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.23 (br, 1H, NH), 4.59 (s, 2H, CH_2), 6.73 (d, J = 8.1 Hz, 2H. ArH), 6.79 (d, J = 7.2, 1H, ArH), 7.24 (t, J = 7.6 Hz, 2H, ArH), 7.40–7.50 (m, 2H, ArH), 7.63 (d, J = 7.6 Hz, 1H, ArH), 7.78 (s, 1H, ArH), 7.90 (s, 1H, CH of triazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.0, 113.2, 118.3, 118.5, 119.7, 120.7, 128.8, 129.4, 130.8, 135.6, 137.9, 147.4 ppm; IR (KBr): $\tilde{\nu}$ = 3300 (NH), 3100, 2950, 1600, 1480 cm^{-1}; ESI–MS: *m/z* 284 (M^+).

1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperidine (4h)

Mp, 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.48 (m, 2H, CH_2), 1.52–1.63 (m, 4H, $2CH_2$), 2.45–2.55 (m, 4H, $2CH_2N$), 7.95 (d, J = 8.8 Hz, 2H, ArH), 8.05 (s, 1H, CH of triazole), 8.39 (d, J = 8.8, 1.2 Hz, 2H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 25.9, 54.0, 54.5, 120.3, 120.6, 125.5, 141.3,

146.8, 147.1 ppm; IR (KBr): $\tilde{\nu}$ = 3150, 2950, 2750, 1600, 1520 (NO_2), 1460, 1340 (NO_2) cm^{-1}; ESI–MS: *m/z* 287 (M^+).

1-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperidine (4 j)

Mp, 77–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.50 (m, 2H, CH_2), 1.562–1.65 (m, 4H, $2CH_2$), 2.45–2.55 (m, 4H, $2CH_2N$), 7.38–7.43 (m, 1H, ArH), 7.47 (t, J = 7.8, 1H, ArH), 7.63–7.69 (m, 1H, ArH), 7.79–7.82 (m, 1H, ArH), 7.95 (s, 1H, CH of triazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 25.9, 54.1, 54.4, 118.3, 120.7, 128.6, 130.8, 135.5, 138.0, 146.14 ppm; IR (KBr): $\tilde{\nu}$ = 3150, 2950, 2750, 1600, 1460 cm^{-1}; ESI–MS: *m/z* 276 (M^+).

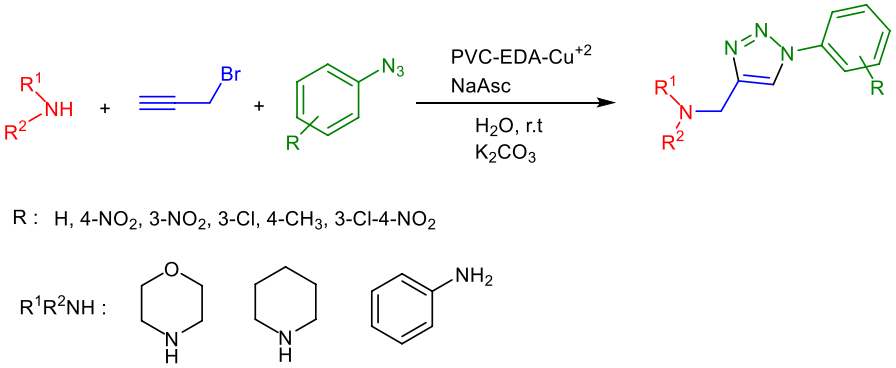
Antibacterial assay

The antibacterial activity of the 1,4-disubstituted 1,2,3-triazoles **4a**, **4d**, **4e**, **4f**, **4h**, and **4i** were evaluated using the well-diffusion method. First, the nutrient agar and nutrient broth cultures were prepared according to the manufacturer's instructions, and incubated at 37 °C. After incubation for an appropriate amount of time, a suspension of 30 µL of each bacterium was added to each nutrient agar plate. Cups (5 mm in diameter) were cut in the agar using a sterilized glass tube. Each well received 30 µL of a test compound at a concentration of 1000 µg/mL in DMSO. Then, the plates were incubated at 37 °C for 24 h, after which time, the inhibition zone was measured; the values were expressed in millimeters (mm). The antibacterial activity of each 1,2,3-triazole was compared with tetracycline as the standard drug. DMSO was used as the negative control.

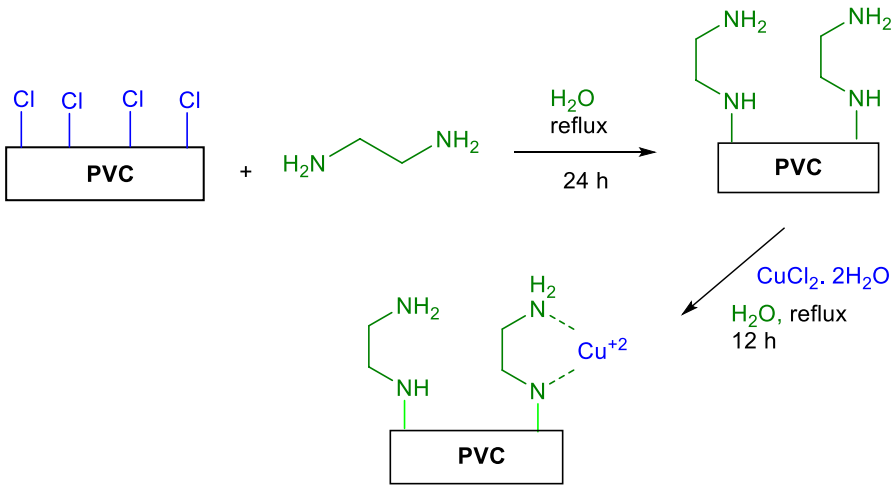
Results and discussion

The use of an amine-modified organic polymer catalyst for organic synthesis has been recently reported [43–45]. The reaction of PVC with ethylenediamine as solvent or in organic solvents at elevated temperatures or prolonged reaction times afforded reddish-brown crosslink polymers [46–49]. However, PVC-supported ethylenediamine ligands have recently been prepared under the above-mentioned condition; surprisingly, this has been reported without cross-linking formation [44]. In this work, we prepared PVC-supported ethylenediamine ligands without cross-linking as a light-yellow powder in water. This amine-functionalized PVC was subsequently reacted with copper(II) chloride dihydrate in water, affording the PVC-supported ethylenediamine-copper(II) complex. This heterogeneous and reusable catalyst was successfully employed for the synthesis of 1,4-disubstituted 1,2,3-triazoles from the reaction of propargyl bromide, aromatic azides, and amines in water (Scheme 1).

The catalyst was prepared by a simple procedure from commercially available starting materials. The synthesis of the PVC-supported ethylenediamine-copper(II) (PVC-EDA-Cu^{+2}) catalyst is shown in Scheme 2.



Scheme 1 Synthesis of 1,4-disubstituted 1,2,3-triazoles by reaction of propargyl bromides, amines, and aromatic azides in the presence of a PVC-supported ethylenediamine-copper(II) complex



Scheme 2 Synthesis of PVC-supported ethylenediamine copper(II) complex from PVC, ethylenediamine, and $CuCl_2{\cdot}2H_2O$

PVC was functionalized by molecules to give a polymer carrying an ethylenediamine ligand (PVC-EDA). The reaction was performed using PVC and an excess amount of ethylenediamine in water. The subsequent reaction of this functionalized polymer with copper(II) chloride dihydrate in water afforded the PVC-EDA-Cu^{+2} complex as a novel catalyst for the synthesis of 1,2,3-triazoles. To verify the formation of the functionalized polymer and its corresponding Cu(II) complex, FT-IR spectra were recorded separately at each preparation stage. The C–H vibrational stretching bands of PVC were observed at 2974 and 2912 cm^{-1} (Fig. 1).

In the functionalized polymer, the NH and NH_2 stretching and bending vibration bands of the immobilized ligand were observed at 3313, 3425, and 1550 cm^{-1}.

Complexation of the copper(II) ions with polymer-supported ethylenediamine, demonstrated by the creation of an additional band at 520 cm^{-1}, was characterized by the stretching vibration of the Cu–N bond. In addition, the NH and NH_2 stretching vibrations of the immobilized ligands shifted to 3367 and 3436 cm^{-1}, respectively. These shifts to higher frequencies in the polymer-supported copper complex suggest the coordination of the ligands to the metal ions. Scanning electron micrographs were recorded for a single bead of pure PVC and the polymer-anchored complex in order to observe the morphological changes. As expected, the pure PVC bead had a smooth and flat surface, while the anchored complex showed roughening of the top layer (Fig. 2).

Furthermore, successful functionalization of the polymer was confirmed by elemental analysis. According to the results obtained, the N content of the polymer was found to be 5.29% (1.88 mmol ligand/g), which indicated that only 11.8% of total

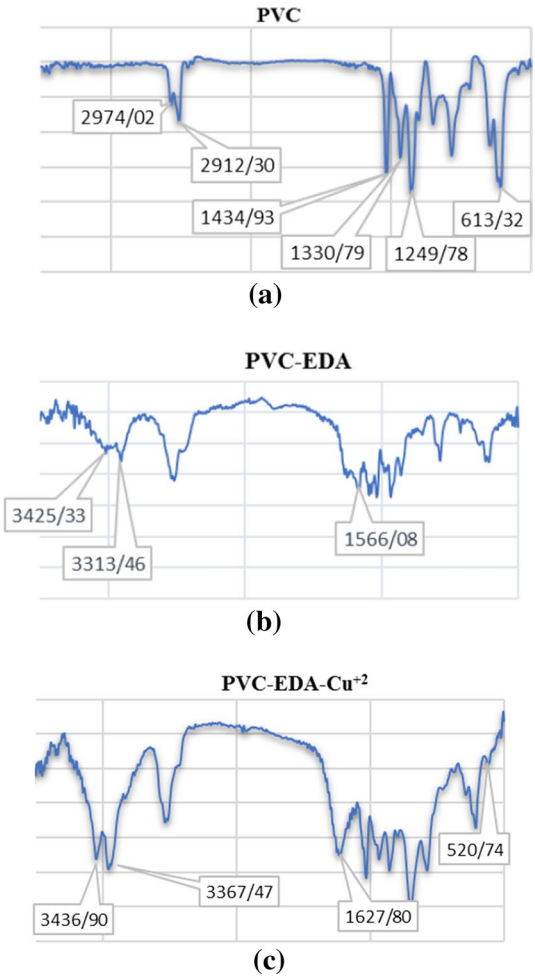


Fig. 1 FT-IR spectra for PVC (**a**), PVC–EDA (**b**), and PVC–EDA–Cu^{2+} (**c**)

chlorine was substituted by amine. The metal loading of the polymer-supported copper complex, determined using ICP-AES, was found to be 1.69% (0.25 mmol/g).

After the synthesis and characterization of the catalyst, the catalytic activity of the PVC–EDA–Cu^{+2} complex in the click reaction was studied. To optimize the reaction conditions for the synthesis of 1,2,3-triazoles, the reaction of propargyl bromide, morpholine, and 3-nitrobenzene azide was used as a model reaction to study the effects of various parameters on the reaction (Table 1). When the reaction was performed with propargyl bromide (1 mmol), morpholine (2 mmol) and 3-nitrobenzene azide (1 mmol) in H_2O (3 mL) as the solvent, in the presence of 2.5 mol% of the catalyst and 5 mol% of sodium ascorbate, an 80% reaction yield was obtained (Table 1, entry 11).

In this reaction, we used two equiv. of morpholine, one as reactant and the other as base. The reaction was significantly influenced by the nature of the base employed. Among the bases tested, K_2CO_3 proved to be the most efficient one, giving a cleaner product and an excellent reaction yield (Table 1, entries 1–6). The effects of the solvent and the amount of the catalyst used were also studied. We screened EtOH, CH_3CN, acetone, CH_2Cl_2, toluene, and water in the presence of an organic or inorganic base. Among the solvents tested, water was found to be the most suitable. Increasing or decreasing the amount of copper catalyst prolonged the reaction time and decreased the reaction yield. The optimum reaction conditions for the multi-component synthesis of 1,2,3-triazoles was 2.5 mol% of PVC–EDA–Cu(II) and 5 mol% of sodium ascorbate in the presence of K_2CO_3 at room temperature in

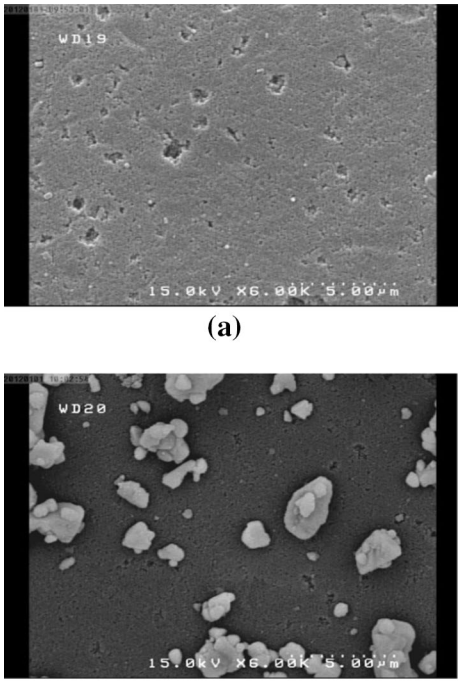
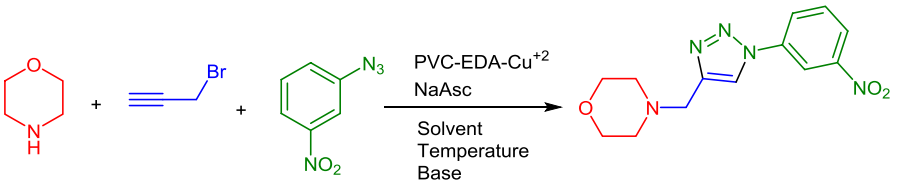


Fig. 2 SEMs for PVC (**a**) and PVC–EDA–Cu^{2+} (**b**)

Table 1 Optimization reaction of propargyl bromide, 3-nitrobenzene azide, and morpholine using different bases and solvents



Entry	Solvent	Base	Catalyst loading (mol%)	*T* (°C)	Time (min)	Yield (%)
1	H_2O	K_2CO_3	2.5	RT	30	91
2	H_2O	K_2CO_3	2.5	50	30	90
3	EtOH	K_2CO_3	2.5	RT	30	85
4	EtOH/H_2O(1:1)	K_2CO_3	2.5	RT	30	88
5	Acetone	K_2CO_3	2.5	RT	60	80
6	CH3CN	K_2CO_3	2.5	RT	60	75
7	CH2Cl2	Et_3N	2.5	RT	60	70
8	Toluene	K_2CO_3	2.5	RT	60	50
9	THF	K_2CO_3	2.5	RT	60	65
10	H_2O	Et_3N	2.5	RT	30	60
11	H_2O	Morpholine	2.5	RT	60	80
12	EtOH	Morpholine	2.5	RT	60	75
13	EtOH/H_2O (1:1)	Morpholine	2.5	RT	60	85
14	Acetone	Morpholine	2.5	RT	60	80
15	CH3CN	Morpholine	2.5	RT	60	60
16	H_2O	K_2CO_3	1.5	RT	30	70
17	H_2O	K_2CO_3	3.0	RT	30	88

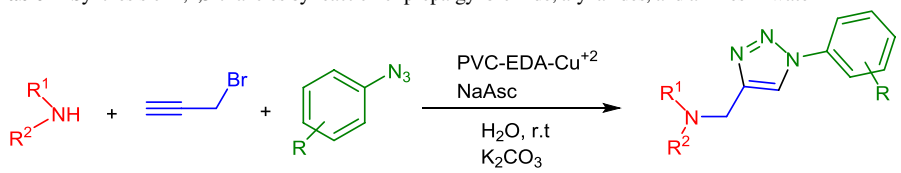
Reaction conditions: morpholine (1.0 mmol), propargyl bromide (1.0 mmol), 3-nitrobenzene azide (1 mmol), and PVC–EDA–Cu^{+2} in solvent

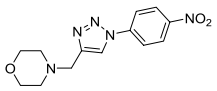
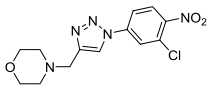
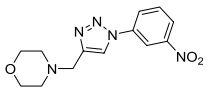
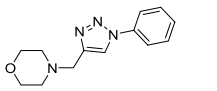
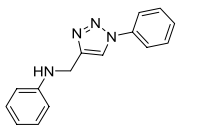
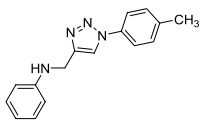
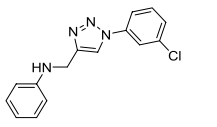
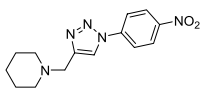
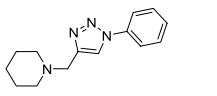
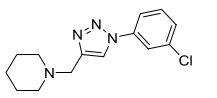
water (Table 1, entry 1). To study the scope of this protocol, reactions of a variety of aromatic azides and amines such as morpholine, piperidine, and aniline with propargyl bromide were run, and a library of substituted 1,2,3-triazoles was obtained (Table 2). Both the electron-withdrawing and electron-donating substituents on the aromatic azide were well tolerated. Methyl, nitro, and chloro produced the desired products with high reaction yields. The position of the substituent had no significant effect on the reaction yield.

The pure products were isolated by careful crystallization in EtOH/H_2O, avoiding tedious work-up and column chromatography for product purification. Structural assignments of the new compounds were based on the NMR spectroscopic data and mass analysis.

The reusability of the catalyst was also examined (Table 3, entries 1–4). After each run, the resulting precipitate was washed with water and then dried. Hot

Table 2 Synthesis of 1,2,3-triazoles by reaction of propargyl bromide, aryl azides, and amines in water



Entry	Product		Time (min)	Yield[a] (%)
1		**4a**	30	91 (32)[b]
2		**4b**	30	91
3		**4c**	30	93
4		**4d**	40	85 (32)
5		**4e**	50	88 (32)
6		**4f**	50	94
7		**4g**	40	86
8		**4h**	40	88
9		**4i**	40	85 (32)
10		**4j**	40	89

Reaction conditions: amine (1.0 mmol), propargyl bromide (1.0 mmol), aromatic azide (1 mmol), and PVC–EDA–Cu^{+2} (2.5 mol%) in H_2O

[a]Isolated yield

[b]Reference

ethanol was added to the solid, and the product was extracted. The residue (catalyst) was washed twice with hot EtOH and reused. This catalyst was reusable, although gradual decline in its activity was observed.

The synthesized compounds **4a**, **4d**, **4e**, **4f**, **4h**, and **4i** were screened for their in vitro antibacterial activity against Gram-positive and Gram-negative bacterial strains including *Micrococcus luteus* (*M. luteus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Bacillus subtilis* (*B. subtilis*) using the well-diffusion method (Table 4). Tetracycline and DMSO were used as positive and negative controls, which showed no activity against these bacterial strains.

The antibacterial activity of the synthesized compounds was screened at a concentration of 1000 µg/mL in DMSO. The values were expressed in millimeters (mm). According to the results tabulated in Table 4, compound **4f** was inactive against all three bacterial strains, compounds **4h** and **4i** possessed antibacterial activities against *P. Aeruginosa* and *M. luteus*, and only compound **4i** was active against all three bacterial strains. Moreover, the antibacterial activity of compound **4d** against *P. aeruginosa* was comparable to the standard drug, tetracycline.

Table 3 Condensation of amines, propargyl bromide, aromatic azides, and PVC–EDA–Cu^{+2} using recycled catalysts

Entry	Number of cycles	Yield[a] (%)
1	1	90
2	2	87
3	3	86
4	4	74
5	5	71

Reaction conditions: amine (1.0 mmol), propargyl bromide (1.0 mmol), aromatic azide (1 mmol), recycled catalyst (2.5 mol%), 10 min

[a]Isolated yield

Table 4 Antibacterial activities of selected compounds (1000 µg mL^{-1}) as inhibition zone in mm

Entry	Compound	*P. aeruginosa*	*M. luteus*	*B. subtilis*
1	**4h**	8	9	–
2	**4i**	9	8	9
3	**4d**	12	–	8
4	**4f**	–	–	–
5	**4e**	–	–	7
6	**4a**	–	10	–
7	DMSO	–	–	–
8	Tetracycline	13	41	15

Conclusion

We have developed an efficient, clean, and environmentally friendly procedure for the synthesis of 1,2,3-triazoles via the multi-component reaction of propargyl bromide, aromatic azides, and amines in water at room temperature in good-to-excellent yields. This protocol utilizes the PVC-supported copper(II) complex as a heterogeneous catalyst, in mild reaction conditions, and does not require tedious work-up and column chromatography for product purification. The other advantages of this method are short reaction time, using water as a green solvent, and the capability of recovery and reuse of the catalyst.

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