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Porous copper catalyzed click reaction in water⁺

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1,2,3-Triazoles were synthesized in water using a cheaper, simple and easily recyclable heterogeneous porous Cu catalyst *via* one-pot multi component reaction. The catalyst can be recycled five times without significant loss of its catalytic activity.

The copper-catalyzed azide-alkyne cycloaddition (CuAAC), also known as a "click reaction", has become one of the most important reactions for the preparation of 1,2,3-triazoles.¹ This important reaction has found a wide range of applications in organic synthesis, bio- and medicinal chemistry, and materials science.² Most AAC protocols call for a homogeneous Cu(1) source - either by direct addition of a Cu(I) salt, or by in situ reduction of Cu(II) by sodium ascorbate.³ In recent years, due to their efficient recyclability and facile separation of products, immobilized catalysts have attracted much attention in economical and environmentally benign chemical processes. In an effort to find immobilized copper catalysts, Cu(0) on charcoal,⁴ Cu(0) nanoparticles,⁵ or Cu(0) nanoporous⁶ as well as microwave irradiated Cu turnings7 have also successfully demonstrated activity for this reaction. The development of heterogeneous immobilized catalysts that are inexpensive, easily available, easy to handle, reusable, and have high efficiencies for this purpose still remains a major challenge. On the other hand, most of the reported CuAAC studies are on twocomponent (organic azide and alkyne) reaction systems; the organic azides need to be synthesized in advance, and the potential hazards of organic azides especially in the isolation or the purification process can be problematic. It is thus desirable to develop an efficient one-pot methodology that uses

alkyl halides and sodium azide for direct cycloaddition with alkynes, alkyl halides, and sodium azide using porous copper. Porous metals that have a large surface-to-volume ratio, are light weight, and exhibit excellent electrical-thermal conductivity have attracted much attention because of a wide range of applications in chemistry, mechanics, and nanotechnology.⁸ Porous copper, which has excellent structural characteristics and is basically harmless to the human body, was mostly used as filter material.

In an initial attempt to synthesize 1,2,3-triazoles using a copper catalyzed procedure, we have investigated the cycloaddition reaction of sodium azide (1 mmol) with benzyl bromide (1a) (1 mmol) and phenylacetylene (2a) (1 mmol) in water as solvent. Our catalytic system consists of commercially available sintered copper porous material. A systematic study was first undertaken to define the best reaction conditions, and the representative data obtained for the synthesis of 1,2,3-triazoles with porous copper catalysts having various pores are listed in Table 1. First of all, the reactions performed using porous copper (5 mol%) with a size of about ~5 μ m proceeded efficiently to form the corresponding triazole 3a in 96% isolated yield at 55 °C (Table 1, entry 1). Efficient cycloaddition was realized with significantly lower catalyst loading, although it required a longer reaction time (Table 1, entry 3). A large decrease in yield was observed using the copper catalyst with larger pores (Table 1, entries 4-6). Compared to other screened solvents such as acetonitrile, THF, DMF, ethanol, acetone, dioxane, and toluene, water appeared to be the best one (Table 1, entries 1 and 7-13).

With the optimal reaction conditions in hand, the scope of the copper-catalyzed synthesis of 1,2,3-triazoles was explored. The results are summarized in Table 2. In alkyl halides, benzyl chloride can serve as a good substrate to afford the triazole (Table 2, entry 2). Other aliphatic halides also reacted easily with sodium azide and alkynes affording **3k** and **3l** in high yields (Table 2, entries 12 and 13). Furthermore, to further analyze the possible electronic effects and to expand the scope of this method, acetylenes bearing aromatic groups of various

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Table 1 Catalyst screening in the synthesis of 3a^a

			Ph	
Bn—Br	+ Ph +	NaN ₃ $-$ cat. C	$\frac{cu}{c} \qquad \sum_{n \in \mathbb{N}} \frac{c}{n}$	N-Bn
1a	2a			3a
Entry	Cu catalyst size (mol%)	Solvent	Time (h)	Yield of 3a ^c (%)
1	~5 µm (5)	H ₂ O	29	96
2	$\sim 5 \mu m$ (10)	H_2O	10	95
3	$\sim 5 \ \mu m (1)$	H_2O	42	90
4	$\sim 15 \ \mu m \ (5)$	H_2O	29	87
5	$\sim 50 \ \mu m \ (5)$	H_2O	55	66
6	~150 µm (5)	H_2O	85	27
7	$\sim 5 \ \mu m (5)$	CH_3CN	30	10
8	$\sim 5 \mu m (5)$	DMF	53	28
9	$\sim 5 \ \mu m \ (5)$	EtOH	30	45
10	$\sim 5 \ \mu m \ (5)$	Acetone	30	59
11	$\sim 5 \ \mu m \ (5)$	THF	55	5
12	$\sim 5 \mu m (5)$	Dioxane	69	5
13	~5 µm (5)	Toluene	29	0
14^b	~5 µm (5)	H_2O	30	33

^{*a*} The reactions were performed with **1a** (1.0 mmol), **2a** (1.1 mmol), NaN₃ (2.0 mol), and Cu catalyst (1–10 mol%) in solvent at 55 °C. ^{*b*} rt. ^{*c*} Isolated yields.

Table 2 Cu Catalyzed synthesis of [1,2,3]-triazoles 3^a

R ¹ —2	X + R ²	: + I	NaN ₃ Cu (5 mol%) H ₂ O, 55 °C	R		^V ∼R ¹
1	2				3	
Entry	R ¹	x	R ²	Time (h)	3	Yield ^b (%)
1	Bn	Br	C_6H_5	29	3a	96
2	Bn	Cl	C_6H_5	25	3a	94
3	Bn	Br	$4-MeOC_6H_4$	20	3b	97
4	Bn	Br	$4-EtOC_6H_4$	26	3c	90
5	Bn	Br	$2,3-(MeO)_2C_6H_3$	39	3d	97
6	Bn	Br	$3,4-(MeO)_{2}C_{6}H_{3}$	33	3e	84
7	Bn	Br	3,4-(-OCH ₂ O-)C ₆ H ₃	28	3f	90
8	Bn	Br	3-FC ₆ H ₄	30	32	88
9	Bn	Br	$4-ClC_6H_4$	29	3ĥ	90
10	Bn	Br	$4 - C_5 H_{11} C_6 H_4$	37	3i	82
11	Bn	Br	$n-C_6H_{13}$	25	3i	92
12	$EtOOCCH_2$	Br	C_6H_5	49	3k	99
13	Et	Ι	C_6H_5	54	31	80
14	Bn	Br	$C_6H_5OCH_2$	30	3m	81
a Thor	contions word	porfe	rmod with 1 (1.0 mmo	1) 2 (1	1 mmol) NoN

^a The reactions were performed with 1 (1.0 mmol), 2 (1.1 mmol), NaN₃ (2.0 mol), and Cu catalyst (5 mol%) in H₂O at 55 °C. ^b Isolated yields.

electron densities were also studied. Alkynes not only with an electron-donating group but also with an electron-withdrawing group on the benzene ring all gave good isolated yields of the expected adducts (Table 2, entries 3–10). Under the same reaction conditions, alkyl alkyne 2j and propargyl derivative **2m** were catalyzed, affording triazoles **3j** and **3m** in excellent yields (Table 2, entries 11 and 14).

Moreover, we attempted recycling of porous copper; the reuse investigation was performed in the model click reaction of benzyl bromide, sodium azide and phenylacetylene with 5 mol% of a porous copper catalyst for 29 h. After the completion

Table	3	Recv	clina	of	catal	vsts ^a
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Entry	1	2	3	4	5	6
$\operatorname{Yield}^{b}(\%)$	96	95	100	99	98	94

^{*a*} The reactions were performed with **1a** (1.0 mmol), **2a** (1.1 mmol), NaN₃ (2.0 mol), and Cu catalyst (5 mol%) in H_2O at 55 °C for 29 h. ^{*b*} Isolated yields.

of the first reaction, simple filtration of the reaction mixture, the catalyst was washed with water and methanol and reused without further purification. A new reaction was then performed with fresh reactants, under the same conditions. We showed that the catalyst can be reused five times without any loss of activity. Examples of the reaction carried out using the recovered catalyst are presented in Table 3. The yields of triazole **3a** were basically similar to those observed using a fresh non-recycled copper catalyst.

In conclusion, a very efficient, sustainable and green procedure for the one-pot synthesis of triazoles has been developed using a cheaper, commercially available and easily recyclable heterogeneous porous Cu catalyst in water. The copper catalyst could be recycled in five subsequent reactions without the loss of the reaction efficiency. A wide range of alkynes and alkyl halides can be tolerated, giving the corresponding triazoles in good yields.

Experimental section

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded on a Bruker Avance spectrometer in CDCl₃ with Me₄Si as an internal standard. Data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet), coupling constant (Hz) and integration. Infrared spectra (IR) were obtained on a FT-IR spectrometer; absorptions were reported in cm⁻¹.

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

To a reactor containing alkyne (1.1 mmol), alkyl halide (1.0 mmol), sodium azide (2.0 mmol) and H_2O (4 mL) porous Cu (0.05 mmol) was added. The mixture was then sealed and stirred at 55 °C until the reaction was completed as judged by TLC. Then the reaction mixture was dissolved in ethyl acetate. The mixture was filtered and the recovered Cu catalyst was washed with water and methanol with no further purification before reuse. The water layer was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography to give the pure product.

1-Benzyl-4-phenyl-1H-1,2,3-triazole (3a)

M.p. 122–124 °C (lit.⁹ 122–124 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.83–7.81 (m, 2H), 7.68 (s, 1H), 7.43–7.38 (m, 5H), 7.34–7.31 (m, 3H), 5.59 (s, 2H).

1-Benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (3b)

M.p. 138–140 °C (lit.¹⁰ 143–144 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 8.7 Hz, 2H), 7.59 (s, 1H), 7.41–7.38 (m, 3H), 7.34–7.32 (m, 2H), 6.95 (d, J = 8.7 Hz, 2H), 5.58 (s, 2H), 3.85 (s, 3H).

1-Benzyl-4-(4-ethoxyphenyl)-1H-1,2,3-triazole (3c)

White solid, M.p. 139–140 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.9 Hz, 2H), 7.58 (s, 1H), 7.43–7.36 (m, 3H), 7.33–7.32 (m, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.58 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.08, 148.16, 134.78, 129.17, 128.79, 128.09, 127.07, 123.07, 118.67, 114.83, 63.54, 54.27, 14.82; IR (KBr, cm⁻¹): 3446.07, 3088.43 1618.74, 1502.85, 1452.96, 1251.06, 1176.28, 1116.37, 1046.27, 921.80, 815.85, 717.24. HRMS (ESI) calcd for C₁₇H₁₇N₃O: 280.1450 (M + H)⁺, found 280.1421.

1-Benzyl-4-(2,3-dimethoxyphenyl)-1*H*-1,2,3-triazole (3d)

White solid, M.p. 89–90 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 7.88 (dd, J = 8.0, 1.4 Hz, 1H), 7.40–7.35 (m, 3H), 7.32–7.30 (m, 2H), 7.16 (t, J = 8.0 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 5.61 (s, 2H), 3.89 (s, 3H), 3.75 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.93, 145.75, 143.50, 135.00, 129.04, 128.59, 127.84, 124.72, 124.50, 122.95, 119.63, 111.98, 59.71, 55.86, 54.05; IR (KBr, cm⁻¹): 3444.01, 3166.52, 2988.13, 1583.30, 1584.73, 1342.74, 1269.69, 1231.95, 1102.12, 1044.88, 997.70, 842.93, 790.41, 722.18, 669.84. HRMS (ESI) calcd for C₁₇H₁₇N₃O₂: 296.1399 (M + H)⁺, found 296.1368.

1-Benzyl-4-(3,4-dimethoxyphenyl)-1H-1,2,3-triazole (3e)

White solid, M.p. 118–122 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.61 (s, 1H), 7.48 (s, 1H), 7.41–7.38 (m, 3H), 7.35–7.30 (m, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.59 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.40, 149.19, 148.21, 134.80, 129.17, 128.79, 128.06, 123.66, 118.85, 118.20, 111.43, 109.09, 56.04, 55.99, 54.26; IR (KBr, cm⁻¹): 3442.17, 2992.97, 1636.46, 1508.22, 1440.17, 1365.58, 1263.19, 1238.00, 1172.33, 1143.77, 1025.90, 861.00, 816.48, 718.42. HRMS (ESI) calcd for C₁₇H₁₇N₃O₂: 296.1399 (M + H)⁺, found 296.1387.

4-(Benzo[d][1,3]dioxol-5-yl)-1-benzyl-1H-1,2,3-triazole (3f)

White solid, M.p. 145–146 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.57 (s, 1H), 7.41–7.39 (m, 3H), 7.34–7.32 (m, 3H), 7.29 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 5.58 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 148.23, 147.34, 134.48, 128.99, 128.62, 127.91, 124.57, 119.25, 118.72, 108.50, 106.25, 101.07, 54.26; IR (KBr, cm⁻¹): 3452.83, 3144.33, 2909.83, 1636.65, 1488.03, 1452.29, 1384.16, 1283.31, 1239.78, 1037.85, 694.15. HRMS (ESI) calcd for C₁₆H₁₃N₃O₂: 280.1086 (M + H)⁺, found 280.1057.

1-Benzyl-4-(3-fluorophenyl)-1*H*-1,2,3-triazole (3g)

M.p. 107–109 °C (lit.¹¹ 109–110 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.68 (s, 1H), 7.58–7.53 (m, 2H), 7.44–7.32 (m, 6H), 7.04–7.00 (m, 1H), 5.60 (s, 2H).

1-Benzyl-4-(4-chlorophenyl)-1*H*-1,2,3-triazole (3h)¹²

M.p. 130–132 °C; ¹H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.66 (s, 1H), 7.42–7.38 (m, 5H), 7.33 (d, J = 8.6 Hz, 2H), 5.60 (s, 2H).

1-Benzyl-4-(4-pentylphenyl)-1*H*-1,2,3-triazole (3i)

White solid, M.p. 92–94 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, J = 8.1 Hz, 2H), 7.62 (s, 1H), 7.39–7.35 (m, 3H), 7.30–7.29 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.56 (s, 2H), 2.60 (t, J = 7.6 Hz, 2H), 1.63–1.60 (m, 2H), 1.34–1.30 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.33, 143.12, 134.78, 129.12, 128.84, 128.73, 128.02, 127.91, 125.63, 119.15, 54.20, 35.69, 31.44, 31.03, 22.51, 14.00; IR (KBr, cm⁻¹): 3447.27, 3090.57, 2924.43, 1637.17, 1495.09, 1455.23, 1436.61, 1414.22, 1345.62, 1220.42, 1047.93, 977.40, 817.38, 716.63. HRMS (ESI) calcd for C₂₀H₂₃N₃: 306.1970 (M + H)⁺, found 306.1943.

1-Benzyl-4-hexyl-1*H*-1,2,3-triazole (3j)

M.p. 52 °C (lit.¹³ 51–53 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.35 (m, 3H), 7.25–7.27 (m, 2H), 7.19 (s, 1H), 5.50 (s, 2H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.68–1.62 (m, 2H), 1.36–1.27 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

Ethyl 2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (3k)

M.p. 92–93 °C (lit.¹¹ 80–81 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.93 (s, 1H), 7.88–7.86 (m, 2H), 7.46–7.43 (m, 2H), 7.38–7.35 (m, 1H), 5.22 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

1-Ethyl-4-phenyl-1*H*-1,2,3-triazole (3l)

M.p. 53–55 °C (lit.¹⁴ 59–61 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.86–7.84 (m, 2H), 7.78 (s, 1H), 7.46–7.43 (m, 2H), 7.36–7.33 (m, 1H), 4.48 (q, *J* = 7.4 Hz, 2H), 1.62 (t, *J* = 7.4 Hz, 3H).

1-Benzyl-4-(phenoxymethyl)-1H-1,2,3-triazole (3m)

M.p. 120–121 °C (lit.¹⁵ 119–121 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 1H), 7.41–7.37 (m, 3H), 7.31–7.28 (m, 4H), 7.00–6.97 (m, 3H), 5.54 (s, 2H), 5.20 (s, 2H).

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