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Nano-copper catalyzed three-component reaction to construct 1,4-substituted 1,2,3-triazoles



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ABSTRACT

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Keywords: Copper nanoparticles Phenylacetylene Cycloaddition Click chemistry Multicomponent reaction obtained regioselectively by this one-pot strategy. Nano copper can be reused at least three times without significant deactivation. © 2014 Elsevier Ltd. All rights reserved.

Three-component reaction of alkyl halides, sodium azide with terminal alkynes can be catalyzed by

nano-copper particles under ambient conditions. A series of 1,4-disubstituted-1,2,3-triazoles were

At the dawn of the 21st century, green catalysis, including using highly efficient catalyst, clean solvent, multicomponent reaction, and recoverable reaction system, has become a hot topic in chemical transformations and has been paid more attention by researchers.^{1,2}

In many transition metals, copper has been used as catalyst in organic synthesis for many decades.³⁻⁶ The discovery of Cu(I)-catalyzed azide-alkyne cycloaddition yielding selectively 1,4-disubstituted-1,2,3-triazoles is a very important advance in the chemistry of triazoles.^{7,8} As we know, 1,2,3-triazoles are important building blocks of nitrogen heterocyclic compounds and have been widely used in pharmaceuticals, agro chemicals, dyes, photographic materials, corrosion inhibition, etc.⁹ 1,2,3-Triazoles are also associated with a wide range of biological properties such as magnetic resonance imaging, drug delivery, and biomolecular sensors.¹⁰ Two routes are generally adopted for the synthesis of substituted 1,2,3-triazoles. One is copper catalyzed [3+2] cycloaddition of organoazides with alkynes. However, methods for the preparation of organic azides are rather limited.¹¹ Moreover, it needs two-step reactions, special reagents, even strictly oxygen, and water-free conditions to obtain the aimed products via organic azides.^{12–15} In order to overcome the disadvantages of the above two-step reactions, one pot, three-component reaction of alkyl halides, sodium azide, and alkynes is developed recently by using copper catalysts such as Cu_2O ,¹⁶ CuI,^{17,18} CuSO₄,^{19–21} CuBr (PPh₃)₃,²² CuFe₂O₄ nanoparticles,¹ and polymeric imidazole-Cu(II).²³ Supported Cu(0) nanoparticles were also used as a catalyst in this reaction, such as Cu–Fe bimetals for two-component reaction,²⁴ Cu/SiO₂,²⁵ Cu/C,²⁶ and polymer capped Cu/Cu₂O²⁷ for three-component reaction. Copper nanoclusters have already been











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Table 1

Screening of the catalyst for the three-component click reaction^a



 $^{\rm a}$ Reaction conditions: phenylacetylene (0.5 mmol), benzyl bromide (0.6 mmol), NaN_3 (0.6 mmol), catalyst (0.025 mmol), methanol (2 mL), r.t. $^{\rm b}$ Isolated yield.

. . ^c Catalyst (0.01 mmol).
 ^d Catalyst (0.05 mmol).

Table 2			
Cu NP catalyzed cycloaddition of	phenylacetylenes	, benzyl halides	, and sodium azide

Entry	Alkyne	Benzyl halide	Product	Time (h)	Yield ^b (%)
1	<hr/>	Br		8	93
2	<hr/>	CI		10	86
3	<hr/>	F		12	82
4	<hr/>	O ₂ N-Br		14	71
5	<hr/>	Me		12	88
6	Me-	Br	Me N=N N	12	90
	Me	F-CI	Me F		
7			N N N N N N N N N N N N N N N N N N N	12	80
	Me	0 ₂ N	Me Me NO ₂		
8		ВГ		16	69
			Me		
9	Me-	Me-CI	Me Ne Me	12	81

(continued on next page)

Table 2 (continued)

Entry	Alkyne	Benzyl halide	Product	Time (h)	Yield ^b (%)
10	F-	Br		12	72
11	F-	Me		12	77
12	F-	F		14	55
13 ^c	H ₂ N	Me	Me Ne Ne	14	82

^a Reaction conditions: phenylacetylenes (0.5 mmol), benzyl halides (0.6 mmol), NaN₃ (0.6 mmol), Cu NPs (0.025 mmol), methanol (2 mL), r.t.

^a Reaction conductor, ^b Isolated yield.
 ^c Yield was calculated with 4-methylbenzyl chloride as benchmark.

Table 3

Cu NP catalyzed cycloaddition	of phenylacetylenes,	alkyl bromides,	and sodium	azide ^a

Entry	Alkyne	Alkyl bromide	Product	Time (h)	Yield ^b (%)
1		Br		14	69
2		Br		14	62
3		Br		14	56
4		Br		14	58
5	Me-	Br		14	56
6	Me	Br	Me N=N	14	60
7	Me-	Br	Me	14	59
8	Me-	Br	Me	14	60
9	F	Br	F N N	16	55
10	F	Br	F N=N N=N	16	66
11		Br	N=N N	14	85

^a Reaction conditions: phenylacetylenes (0.5 mmol), alkyl bromides (0.6 mmol), NaN₃ (0.6 mmol), Cu NPs (0.025 mmol), methanol (2 mL), r.t. ^b Isolated yield.

 Table 4

 Reusability of Cu NPs

Cycle	Yield (%)	
Native	93	
1	91	
2	88	
3	87	

documented as a catalyst for the reaction of organic azides with alkynes.²⁸ However, to date, no literature was involved in Cu nanoparticle (NP) catalyzed three-component reaction without the use of any support and stabilizer. Herein, we report a simple and efficient three-component [3+2] cycloaddition of organic halides, terminal alkynes, and sodium azide to yield 1,4-disubstituted-1,2,3-triazoles catalyzed by Cu NPs under ambient conditions.

The Copper nanoparticles were prepared by reducing copper sulfate pentahydrate with hydrazine hydrate in ethylene glycol. This method gives a stable Cu NPs with a narrow particle size distribution that can be kept for several months in air. SEM micrograph showed that the average dimension of Cu NPs was around 18–23 nm (Fig. 1).

In our initial study, we chose benzeneacetylene, benzyl bromide, and sodium azide to optimize the reaction conditions.

The results are shown in Table 1. We found that all of Cu(I) and Cu(II) salts could effectively catalyze the click reaction of benzeneacetylene, benzyl bromide, and sodium azide to obtain 1-benzyl-4phenyl-1*H*-1,2,3-triazole exclusively in good yields in methanol at room temperature (Table 1, entries 1–5). When Cu NPs were used, excellent yield (93%) was achieved at the same amount of catalysts (5 mol %, Table 1, entry 6). However, when commercially available Cu powder was explored, only 45% yield was given (Table 1, entry 7). This illustrates that the particle size and surface properties played an essential role in this transformation. Then we studied the loading of Cu NPs and the results show that 5 mol % of Cu NPs is the optimized dosage (Table 1, entries 6, 8 and 9). It is noteworthy that the side-product of 4-phenyl-1*H*-1,2,3-triazole and the isomer of 1-benzyl-5-phenyl-1*H*-1,2,3-triazole were not found in the three-component reaction.

Under the optimized conditions, different substituted phenylacetylenes and benzyl halides were used in this click reaction and an array of 1,4-disusbstituted 1,2,3-triazoles were synthesized smoothly in good to excellent yields.²⁹ These results are presented in Table 2. Phenylacetylenes and benzyl halides containing hydrogen and electron-donating groups at the aryl ring worked well under these conditions, producing the corresponding products in good to excellent yields. Phenylacetylenes and benzyl halides bearing



Scheme 1. Exploration of the reaction process.



Scheme 2. Proposed mechanism.

electron-withdrawing groups could also obtain corresponding products in relatively low yields.

It is interesting that when electron-rich 4-methylphenylacetylene and electron-deficient benzyl halides were used in this cycloaddition reaction, 1,2,3-triazoles with an alkynyl substituent at 5-position were obtained in good yields (Table 2, entries 7 and 8). The results are in accord with literature reported,¹⁶ which might result from an oxidizing addition of copper and reductive elimination subsequently under ambient conditions. When 3-aminophenylacetylene reacted with 4-methylbenzyl chloride and sodium azide, a novel product *N*,*N*-di(4-methylbenzyl) 1,2, 3-triazole was formed in 82% of yield (Table 2, entry 13).

Various alkyl bromides were subjected to the same reaction conditions to furnish the corresponding 1,2,3-triazole derivatives and the results are listed in Table 3. The yields were moderate in general. The length of alkyl chain did not manifestly affect the yield of the product. When bulky tert-butyl bromide was used, the yields were 55–69% (Table 3, entries 1, 5, and 9). This shows that steric hindrance of alkyl bromides has also no significant effect on the reaction. Unfortunately, aliphatic alkynes gave no designed product under the same conditions.

At last, the reusability of Cu NPs was examined by the model reaction of phenylacetylene, benzyl bromide, and sodium azide and the results are given in Table 4. It can be showed that after three recycles, the product yield was still up to 87%, which indicates that Cu NPs have high catalytic activity and stability in our experimental conditions (Table 4).

In order to clarify the mechanism of this multicomponent reaction, we conducted two stepwise control experiments as shown in Scheme 1. The result showed that the yield of 1-benzyl-4-phenyl-1,2,3-triazole of this two-step process was slightly inferior to three-component reaction (85% of Scheme 1, Eq. 1 vs 93% of Table 2, entry 1). But, is it possible that phenyl acetylene clicked with sodium azides to get 4-phenyl-1,2,3-triazole and then underwent a N-alkylation with alkyl halides? Unfortunately, no target molecule was formed under the same reaction conditions (Scheme 1, Eq. 2). Therefore, we think that the one-pot, three-component reaction is virtually a two-step procedure. Organic halides firstly reacted with sodium azide to obtain organic azides, and then further converted into final products with alkynes catalyzed by nano copper.

Based on the above control experiments, a possible mechanism was proposed in Scheme 2. Alkynes are converted to alkynyl copper(I) in the presence of Cu NPs first. Then, intermediate (I) reacts with organic azides formed in situ by click chemistry to yield the key intermediate (II). Intermediate (II) is further transformed into 1,4-disubstituted 1,2,3-triazoles or 5-alkynyl-1,4-disubstituted 1,2,3-triazoles via intermediate (III).

In conclusion, we have developed a simple and highly efficient one-pot method to synthesize complex 1,2,3-triazoles regioselectively from organic halides, terminal alkynes, and sodium azide. The reactions were performed under ambient conditions in methanol at room temperature, using Cu NPs as catalysts. Simple operation, air atmosphere, easy separation, and reusability of Cu NPs are the salient features of this method.

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Supplementary data

Supplementary data (the ¹H NMR, ¹³C NMR, IR, MS spectroscopic data, elemental analysis and NMR spectra of all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.114.

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- 29. General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles: Sodium azide (0.6 mmol), organic halides (0.6 mmol), and phenylacetylenes (0.5 mmol) were added into a suspension of 0.025 mmol of Cu NPs in methanol (2 ml). The reaction mixture was stirred at room temperature for completion monitored by TLC. Then the solution was filtered by suction and the solvent was evaporated under reduced pressure. The residue was passed through flash column chromatography on silica gel to give the pure products. The characterization data of representative products are as follows. 4-Phenyl-5-(2-phenylethynyl)-1-propyl-1H-1,2,3-triazole: white solid, mp 85–86 °C; ¹H NMR (400 MHz, CDCl₃) δ = 1.06–1.10 (t, 3H), 2.09–2.15 (m, 2H), 4.51–4.54 (t, 2H), 7.41–7.54 (m, 6H), 7.62–7.64 (m, 2H), 8.25–8.27 (d, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 148.00, 131.81, 130.70, 129.91, 128.95, 128.92, 128.75, 126.45, 121.78, 117.44, 102.08, 75.79, 51.06, 23.57, 11.41; MS (EI) m/z (%) 287 $[M]^{\ast};$ IR (KBr, $cm^{-1}):$ 3062, 2852, 1620, 1478, 1359, 755, 690; Anal. Calcd for C₁₉H₁₇N₃ (287.36): C 79.41, H 5.96, N 14.63, Found C 79.37, H 5.91, N 14.60. 1tert-Butyl-4-(4-fluorophenyl)-1H-1,2,3-triazole: white solid, mp 141-142 °C; ¹H NMR (400 MHz, CDCl₃) δ = 7.96 (s, 1H), 7.82–7.86 (m, 1H), 7.30 (s, 2H), 7.16–7.21 (t, 2H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ = 160.09, 131.33, 127.49, 127.41, 115.67, 115.45, 30.25, 29.27; MS (EI) *m*/*z* (%) 163 [M]⁺; IR (KBr, cm⁻¹): 3040, 2853, 1611, 1367, 1238, 773, 687; Anal. Calcd for C₁₂H₁₄FN₃ (219.26): C 65.73, H 6.44, N 19.16, Found C 65.75, H 6.43, N 19.19.