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NANO-COPPER CATALYZED THREE-COMPONENT TANDEM CYCLOADDITION AND *N*-ALKYLATION REACTION FROM AMINOPHENYLACETYLENES, SODIUM AZIDE AND ALKYL HALIDES

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Abstract – Nano-copper catalyzed one-pot three-component method is realized from aminophenylacetylenes, sodium azide and alkyl halides via tandem 3+2 dipolar cycloaddition reaction and *N*-alkylation reaction. This synthetic process gave the product of 1-alkyl-4-(*N*-alkylaminophenyl)-1*H*-1,2,3-triazoles in good yields.

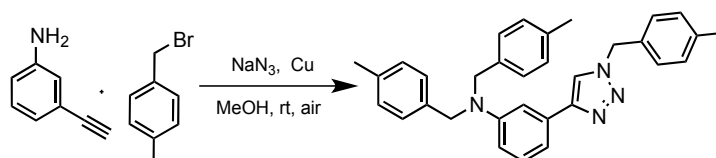
1,2,3-Triazoles are useful structural elements and have been widely used in pharmaceuticals, pesticides, materials and organic synthesis.¹ Thus, synthesis of 1,2,3-triazole derivatives is still an attractive project. After Cu-catalyzed azide-alkyne cycloaddition was found, it has been fully developed.² Different types of catalysts like nano-copper,³ CuI,⁴ CuFe₂O₄ nanoparticles,⁵ Cu₂O,⁶ CuSO₄⁷ can all efficiently catalyze this reaction. On the other hand, 1,2,3-triazole as a substrate to construct other derivatives has gradually attracted lots of interest, and this transformation was usually achieved by C—H functionalization⁸ and new C—N bond formation.⁹ However, some protocols needs noble metals, special reagents, water- and oxygen-free operation and multistep reactions, which will cause the cost increase and operation inconvenience.

As we all know, multicomponent reaction (MCR), as an environmentally friendly synthetic method, has many advantages for the synthesis of some structure-complex compounds.^{7d,10} With our continuous pursue of green chemistry on MCR¹¹ and PEG solvent,¹² we recently found that 4-methylbenzyl chloride not only participated the formation of the corresponding 1,4-disubstituted 1,2,3-triazole, but also occurred *N,N*-dialkylation of amino group on benzene ring of 3-aminophenylacetylene in the three-component reaction with sodium azide.^{3a}

The focus of this work is to develop a facile and highly efficient protocol for the synthesis of 1-alkyl-4-(*N*-alkylaminophenyl)-1*H*-1,2,3-triazoles by one-pot, three-component tandem reaction from aminophenylacetylene, sodium azide and alkyl halides.

Our initial investigation focused on the reaction of 3-aminophenylacetylene, sodium azide and *p*-methylbenzyl bromide as a template to optimize the conditions. The results are outlined in Table 1. Several copper compounds, copper powder and copper nanoparticles were firstly examined as catalysts of this reaction at room temperature in air. It is shown that when CuBr, CuCl₂ and CuSO₄·5H₂O were used as catalysts, the primary products were not expected 1-alkyl-4-(*N*-alkylaminophenyl)-1*H*-1,2,3-triazoles, but only 4-(3-aminophenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole with yields of 58%, 65% and 70%, respectively (Table 1, entries 1, 3 and 4). However, the reaction can be smoothly realized under the catalysis of CuI, CuO and Cu powder with low to moderate yields (Table 1, entries 2, 5 and 6). When the same amount of copper nano particles (Cu NPs)³ was used, it is surprised to find that the yield of 4-(3-(*N,N*-di(4-methylbenzyl)amino)phenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole as our target product can reach up to 87% (Table 1, entry 7). Then the amount of the catalyst was also examined. When the amount of Cu NPs was reduced from 10 mol% to 5 mol%, it is found that the yield of the product decreased significantly from 87% to 65%, and the yield was still not significantly improved even if the reaction time was prolonged to 24 hours (Table 1, entries 7-9). The effect of a base on this reaction was further explored. However the addition of K₂CO₃ just increased the yield slightly (Table 1, entry 10). So a base-free process with 10 mol% of Cu NPs as catalyst is determined. When decreasing the amount of 4-methylbenzyl bromide to 1.2 equivalent, the unique cycloaddition product was obtained; decreasing the amount of 4-methylbenzyl bromide from 3.6 to 2.4 equivalents, the mixture of cycloaddition product and *N,N*-dialkylated product was obtained. Furthermore, the yield of *N,N*-dialkylated product increased and the yield of cycloaddition product decreased with the increase of the amount of 4-methylbenzyl bromide (Table 1, entries 11 and 12). Therefore it is a tandem cycloaddition-*N*-alkylation reaction.

Table 1. Screening for the Optimal Conditions^a



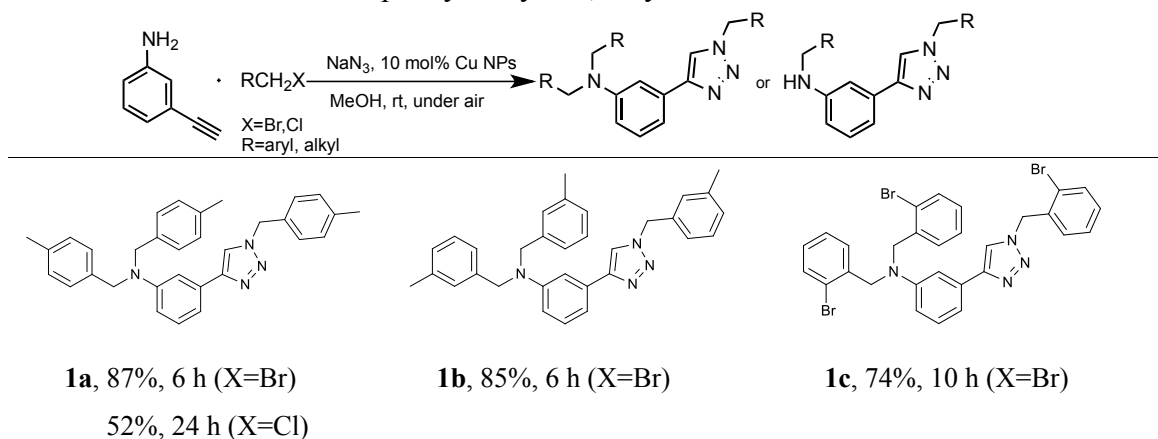
Entry	Catalyst	Isolated Yield(%)	Entry	Catalyst	Isolated Yield(%)
1	CuBr	—	7	Cu NPs	87
2	CuI	48	8 ^b	Cu NPs	65
3	CuCl ₂	—	9 ^{b,c}	Cu NPs	66
4	CuSO ₄ ·5H ₂ O	—	10 ^d	Cu NPs	89

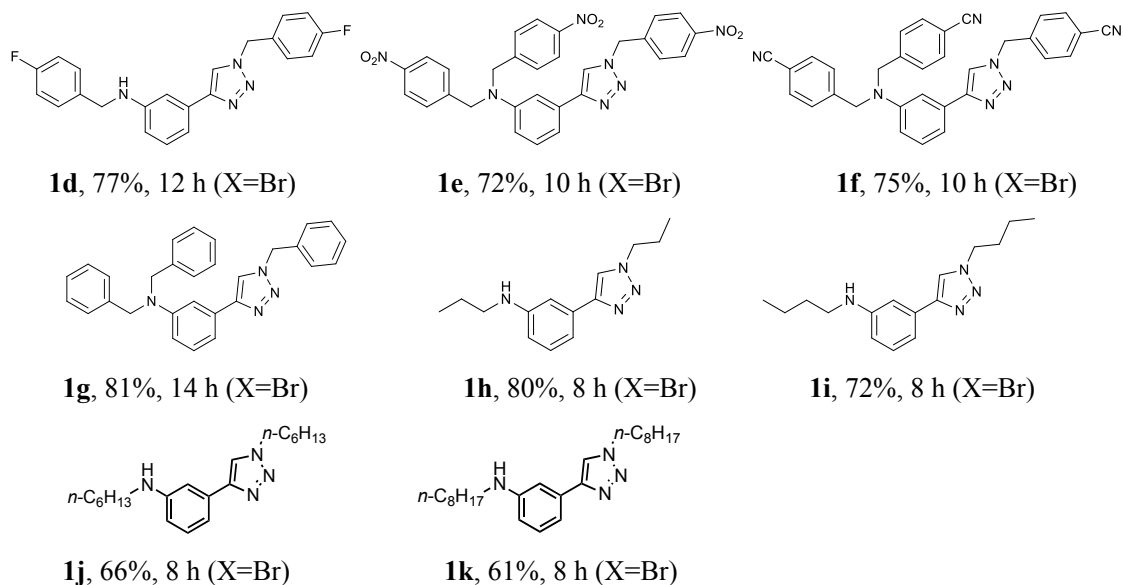
5	CuO	51	11 ^e	Cu NPs	trace (67)
6	Cu powder	24	12 ^f	Cu NPs	46 (32)

^a Reaction conditions: 3-Aminophenylacetylene (0.25 mmol), 4-methylbenzyl bromide (0.9 mmol), NaN₃ (0.3 mmol), catalyst (0.025 mmol), MeOH (1 mL), rt, 6 h. ^b Cu NPs (0.0125 mmol). ^c Reaction time is 24 h. ^d K₂CO₃ (0.75 mmol) was added. ^e 1.2 Equivalent of 4-methylbenzyl bromide was used and 67% of cycloaddition product was obtained. ^f 2.4 Equivalents of 4-methylbenzyl bromide was used and 32% of cycloaddition product was obtained.

With the optimum conditions in hand (Table 1, entry 7), the substrate scope was further extended to a broad variety of alkyl halides reacted with 3-aminophenylacetylene and NaN₃. The results are listed in Table 2. It is found that various substitutions on benzene ring of benzyl bromides were all well tolerated in this reaction with good product yields. When benzyl bromide was used, the yield of *N,N*-dibenzyltriazole is 81% (Table 2, **1h**). However, when methyl was attached to benzyl bromide, the yields of corresponding *N,N*-dibenzyltriazaoles increased to 87% and 85% in 6 hours for 4-methyl and 3-methylbenzyl bromide, respectively (Table 2, **1a** and **1b**). Compared with methyl, an electron-donating group, electron-withdrawing groups, such as Br, F, nitro and CN, provided lower yields (Table 2, **1c-f**). Different from other substituted benzyl bromides, 4-fluorobenzyl bromide generated *N*-monosubstituted product in the yield of 77% (Table 2, **1d**). When 4-methylbenzyl chloride was subjected to this reaction, the yield of *N,N*-disubstituted triazole decreased to 52% (Table 2, **1a**, X=Cl). It may be due to low reactivity of 4-methylbenzyl chloride. Chain bromoalkanes were also investigated. It is found that 1-bromopropane, 1-bromobutane, 1-bromohexane and 1-bromooctane can complete the reaction smoothly to form corresponding *N*-alkylation monosubstituted products in good yields (Table 2, **1h-k**). We think the reason of no formation of the tertiary amines is the low reactivity of chain alkyl bromide than that of benzyl bromide. Moreover, it is manifest that the reactivity of the brominated chain alkanes decreases with the chain lengthening. Iodobenzene was also used instead of alkyl halides to get the expected corresponding triarylamine, but only was 4-(3-aminophenyl)-1*H*-1,2,3-triazole obtained.

Table 2. Reaction results of 3-aminophenylacetylene, alkyl halides and NaN₃^a

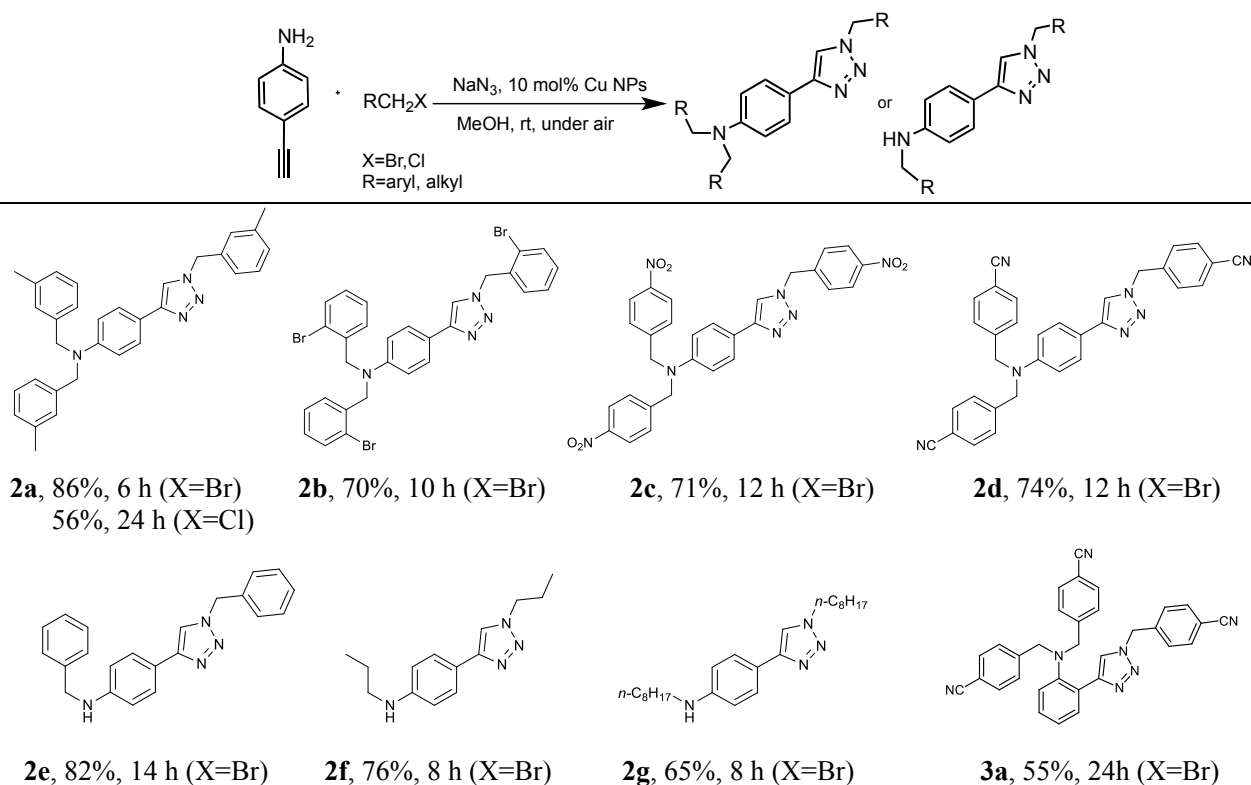




^a Reaction conditions: 3-Aminophenylacetylene (0.25 mmol), alkyl halide (0.9 mmol), NaN_3 (0.3 mmol), Cu NPs (0.025 mmol), MeOH (1 mL), rt, Isolated yield.

Subsequently, we replaced 3-aminophenylacetylene with 4-aminophenylacetylene and 2-aminophenylacetylene, and made the following expansion. Similar results were obtained and summarized in Table 3. Different substituents on the benzene ring of benzyl halides can be well compatible with this reaction to provide good yields in the range of 70%-86% (Table 3, **2a-e**).

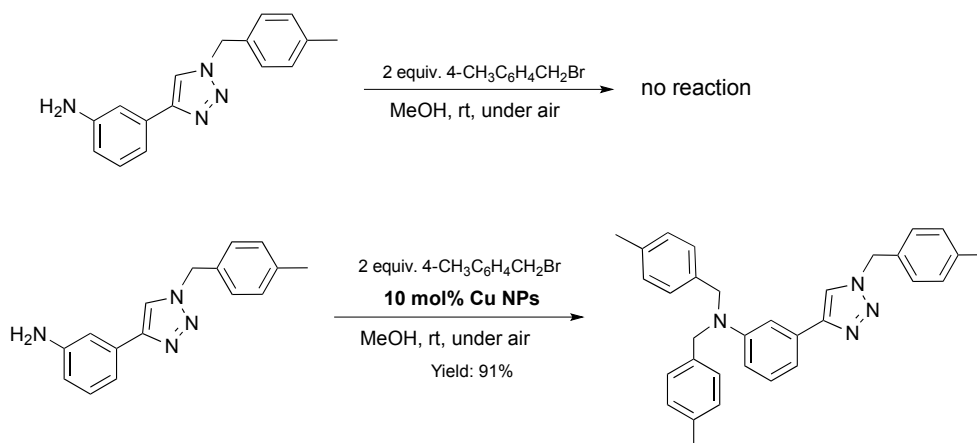
Table 3. Reaction results of 4-aminophenylacetylene/2-aminophenylacetylene, alkyl halides and NaN_3^a



^a Reaction conditions: 4-Aminophenylacetylene (0.25 mmol), alkyl halide (0.9 mmol), NaN_3 (0.3 mmol), Cu NPs (0.025 mmol), methanol (1 mL), rt, Isolated yield.

The reaction of 3-methylbenzyl chloride required longer reaction time to get only 56% yield under the same conditions (Table 3, **2e**). 1-Bromopropane and 1-bromooctane were also involved in this reaction and the corresponding *N*-monoalkyl substituted products were obtained in the yield of 76% and 65%, respectively (Table 3, **2f** and **2g**). Unfortunately, when 2-aminophenylacetylene is subjected to this reaction, only 4-cyanobenzyl bromide react with it in the presence of sodium azide to afford corresponding *N,N*-dibenzyltriazole after 24 hours (Table 3, **3a**). Other halogenated hydrocarbons, such as 4-methylbenzyl bromide, 2-bromobenzyl bromide, 4-nitrobenzyl bromide, 4-fluorobenzyl bromide and 1-bromobutane, can occur only Huisgen-cycloaddition reaction and can not obtain expected *N*-alkylated products, which may be mainly due to large steric hindrance of 2-aminophenylacetylene.

The possible reaction pathway is studied by some control experiments. The Huisgen-cycloaddition product of 3-aminophenylacetylene, 4-methylbenzyl bromide and NaN_3 was treated with 2 equivalents of 4-methylbenzyl bromide in methanol at room temperature. The results show that the *N*-alkylation did not occur without catalytic Cu NPs whereas the yield of *N,N*-dialkylated product was up to 91% in the presence of 10 mol% Cu NPs (Scheme 1). Obviously, Cu NPs play a catalytic role in Huisgen-cycloaddition as well as in the subsequent *N*-alkylation. The detailed mechanism is under investigation.



Scheme 1. Control experiments

In summary, a tandem one-pot, three-component protocol from aminophenylacetylenes, alkyl halides, and sodium azide to afford *N*-alkylated 1,4-substituted 1,2,3-triazoles is developed. The process includes one cycloaddition and two or three *N*-alkylation reactions occurred simultaneously without using any additional reagents except for copper nanoparticles as a catalyst in methanol. The reaction showed better atomic utilization and good regioselectivity.

EXPERIMENTAL

Typical Procedure for Cu NPs.^{3a} $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.01M) was mixed with 3 mL ethylene glycol (EG) solution of NaOH (0.005 M) and $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (0.015M) under magnetic stirring. After reacted under microwave irradiation at 616 W for 5 min, the mixture turned from blue to brick red. Then cooling to

room temperature, distilled water was added to the solution, filtered then the resulting solid was repeatedly washed with distilled water, EtOH and acetone. The resulting solid was placed in a vacuum oven and dried at 60 °C for 3 h and used directly. SEM micrograph showed that the average dimension of Cu NPs was around 18–23 nm.

General procedure for the synthesis of *N*-alkylated 1,4-disubstituted 1,2,3-triazoles. Sodium azide (0.3 mmol), benzyl halides (0.9 mmol), and aminophenylacetylene (0.25 mmol) were added into a suspension of 0.025 mmol of Cu NPs in MeOH (1 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 (EtOAc/hexane=1/10) on silica gel to give the pure products.

4-(3-(*N,N*-Di(3-methylbenzyl)amino)phenyl)-1-(3-methylbenzyl)-1*H*-1,2,3-triazole (1b): Yield: 85%, yellow solid, mp 135-137 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.51 (s, 1H), 7.27-7.09 (m, 14H), 6.72 (d, *J*=7.1, 1H), 5.48(s, 2H), 4.68 (s, 4H), 2.34 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 149.6, 148.6, 138.7, 138.3, 138.1, 134.6, 131.3, 129.5, 129.2, 128.8, 128.5, 128.4, 127.5, 127.3, 124.9, 123.7, 119.5, 114.2, 112.3, 109.4, 53.9, 53.8, 21.3. HRMS (ESI) calcd for C₃₂H₃₂N₄ (M + H)⁺: 473.2627; found 473.2700. IR (KBr, cm⁻¹): 690, 806, 889, 1086, 1184, 1380, 1459, 1496, 1608, 2851, 2918, 3020.

4-(4-(*N,N*-Di(3-methylbenzyl)amino)phenyl)-1-(3-methylbenzyl)-1*H*-1,2,3-triazole (2a): Yield: 86%, yellow solid, mp 133-134 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.49 (s, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 7.17-7.09 (m, 12H), 7.05(s, 1H), 6.68 (s, 1H), 5.47 (s, 2H), 4.61 (s, 4H), 2.33 (d, *J* = 19.6 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 149.6, 148.7, 138.5, 136.4, 135.3, 131.7, 131.4, 129.7, 129.6, 129.2, 128.0, 126.7, 119.4, 114.2, 53.9, 53.5, 21.0. HRMS (ESI) calcd for C₂₉H₂₃Br₃N₄ (M + H)⁺: 473.2627; found 473.2962. IR (KBr, cm⁻¹): 690, 749, 804, 1048, 1218, 1348, 1452, 1491, 1581, 2851, 2918, 3042.

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