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# A Convenient Preparation of 5-Iodo-1,4-disubstituted-1,2,3-triazole: Multicomponent One-Pot Reaction of Azide and Alkyne Mediated by CuI−NBS

Lingjun Li,[†,‡] Guisheng Zhang,*[,†] Anlian Zhu,[†] and Lihe Zhang*[,‡]

*College of Chemistry and Environmental Science, Henan Normal University, XinXiang 453007, P. R. China, and National Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100083, P.R. China*

*zgs6668@yahoo.com*

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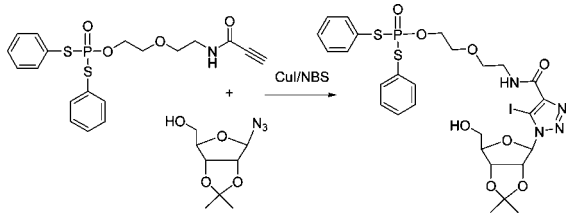


The system of CuI and NBS was found to provide both $I^+$ and $Cu^+$ for the first time. An efficient method for preparation of 5-iodo-1,4-disubstituted-1,2,3-triazole was achieved by multicomponent one-pot reaction of azides with alkynes in the presence of the novel CuI and NBS catalytic system. The high tolerance of various sensitive groups revealed the potential applications of this method in organic synthesis and drug discovery.

Although, the demand for new chemical materials and biologically active molecules continues to grow, chemists have hardly begun to explore the vast pool of potentially active compounds.[1] The emerging field of "click chemistry", a newly identified classification for a set of powerful and selective reactions, offers a unique approach to this problem.[2] The most powerful click reaction to date arguably is the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes to afford 1,2,3-triazoles.[2]

Currently, click chemistry has found applications in target-oriented synthesis,[3,4] building molecular library,[5,6] and biological conjugation.[7,8] A large number of biological active molecules have been discovered with this convenient chemical tool.[9–11] Possible reasons for the good biological activity of 1,2,3-triazole derivatives have been suggested.[4,10,12] One is that 1,2,3-triazoles can well mimic natural peptides and heterocycles in geometrical shape and interaction function.[12a,2c] Moreover, some recent research has begun to explore the activity of 5-substituted-1,2,3-triazole derivatives.[13] Therefore, diverse functionalities on the 5-position of 1,2,3-triazole will be another efficient method for exploring functional molecules.

A number of useful methodologies have been developed for the synthesis of 5-substituted-1,2,3-triazoles. These methods were summarized as follows: (1) specific 1,3-dipolar cylcoaddition between substituted alkynes and azides,[14,15] (2) substitution reactions based on the activity of 5-H in 1,2,3-triazoles,[16] and (3) substitution by trapping the carbon anion intermediates.[17] However, most current methods display very narrow structural diversity on both reactants and substituents. Thus, it is still a challenge to find new protocols for efficient preparation of 1,4,5-trisubstituted-1,2,3-triazole derivatives with diverse structure. Here, we report a convenient multicomponent one-pot method for efficient preparation of 1,4,5-trisubstituted-1,2,3-triazole

[†] Henan Normal University.
[‡] Peking University.

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(2) For reviews of click chemistry, see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B *Angew Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128–1137. (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H *Eur. J. Org. Chem.* **2006**, 51–68.
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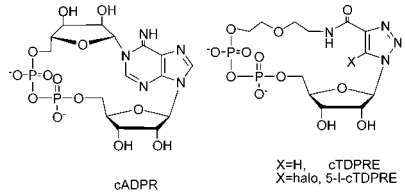
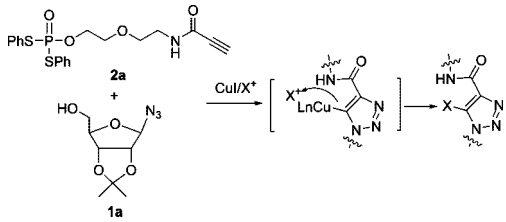



**FIGURE 1.** Structures of cADPR, cTDPRE, and 5-I-cTDPRE.

**TABLE 1. One-Pot Preparation of 5-Iodo-1,2,3-triazole under Different Conditions and Reagents**



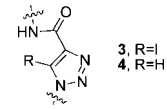

| catalyst system | solvent | $T$ (°C) | time (h) | yield[a] (%) |
|---|---|---|---|---|
| CuI/$I_2$[b] | THF | r.t. | 48 | |
| CuI/$I_2$[b] | $CH_3CN$ | reflux | 10 | |
| CuI/$I_2$[b] | $CH_3CN$ | r.t. | 48 | |
| CuI/$I_2$[b] | THF | reflux | 10 | |
| CuI/NIS[c] | THF | r.t. | 3 | 55 |
| CuI/NBS[d] | THF | r.t. | 3 | 90 |

[a] Isolated yields. [b] The mole ratio of alkyne, azide, CuI, and $I_2$ was 1:1.1:1.1:1.5. [c] The mole ratio of alkyne, azide, CuI, and NIS was 1:1.1:1.1:1.2. [d] The mole ratio of alkyne, azide, CuI, and NBS was 1:1.1:1. 1:1.2.

derivatives using a novel CuI and NBS system. The high tolerance of various sensitive groups revealed the potential applications of this method for the diverse modification on 1,2,3-triazoles.

Along with our research in cADPR binding protein with cADPR structural mimics, 5-halo-cTDPRE is designed on the basis of cTDPRE (Figure 1).[18] Several methods have been reported for the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles: (1) transformations from 5-$NH_2$-1,4-disubstituted-1,2,3-triazoles,[15b] (2) specific cycloaddition reaction between bromoalkynes and azides,[19] (3) substitution by trapping the carbon anion intermediate with $I_2$ or ICl as electrophilic reagents,[17] and (4) byproducts from Cu(I)-catalyzed Huisgen cycloaddition reactions.[20a] In our case, the synthesis of 5-halo-1,4-disubstituted-1,2,3-triazoles by trapping the carbon anion intermediate with electrophilic reagents is employed because of its benefits in efficiency and convenience, which come from the reactivity of negative carbon intermediates and the characteristics of multicomponent one-pot reactions.

**TABLE 2. Reactive Procedure under Different Catalyst Systems[a]**




| catalyst system | reaction time (h) | product | yield[b] (%) |
|---|---|---|---|
| CuI-NBS[c] | 1 | **3** | 50 |
| | 2 | **3** | 81 |
| | 3 | **3** | 90 |
| CuI[d] | 1 | **4** | 32 |
| | 2 | **4** | 85 |
| | 3 | **4** | 91 |
| CuI−$I_2$[e] | 1 | **4** + **3** | 0 |
| | 2 | **4** + **3** | 0 |
| | 10 | **4** + **3** | 0 |

[a] The reaction was performed under room temperature in dry THF, with 1 equiv of DIPEA added as the alkali. [b] Isolated yields. [c] The mole ratio of alkyne, azide, CuI, and NBS was 1:1.1:1.1:1.2, and 5-iodo-1,4-disubstituted-1,2,3-triazole was obtained. [d] The mole ratio of alkyne and azide was 1:1.1, and 1,4-disubstituted-1,2,3-triazole was obtained. [e] Tthe mole ratio of alkyne and azide was 1:1.1.

First, we selected $I_2$, NIS, and NBS as the source of $I^+$ or $Br^+$ for the halo substitution on the 5-position of 1,2,3-triazole by multicomponent one-pot click reaction of azidosugar **1a** with terminal alkyne **2a** using CuI as catalyst (Table 1). It was found that when $I_2$ was chosen as the source of $I^+$, no desired results were obtained. Under different temperatures in different solvents, no product was observed, and reactants remained intact, which suggested that the existence of excessive iodine could reduce the capability of $Cu^+$ to catalyze the click reaction. Then, NIS, as the active source of $I^+$, was chosen for the iodination. The desired product was obtained with low yield. As a control group, we applied NBS as the active source of $Br^+$ for bromination. The reaction proceeded smoothly under room temperature, and no obvious reactants were detected by TLC after 3 h. Very surprisingly, the ESI-MS revealed that the product from the reaction using NBS was identical and agreed with the 5-iodo-1,2,3-triazole. No bromide was found in ESI-MS and $^1H$ NMR. In addition, the reaction with CuI−NBS as catalyst provided 5-iodo-1,2,3-triazole in much higher yield than the reaction using the CuI−NIS system.

In order to explore the efficiency of this protocol for preparation of 5-iodo-1,2,3-triazoles, we compared the click reaction with three catalytic systems, NBS−CuI, CuI−$I_2$, and CuI, respectively (Table 2). It was found that the one-pot iodination click reaction with the CuI−NBS catalytic system had almost equivalent activity to the $Cu^+$-catalyzed click reaction in conversion rate of alkyne and azide. The reaction catalyzed with NBS−CuI proceeded for 3 h to give 5-iodo-

**SCHEME 1. Plausible Mechanism of Preparation of 5-Iodo-1,4-disubstituted-1,2,3-triazole with CuI and NBS**

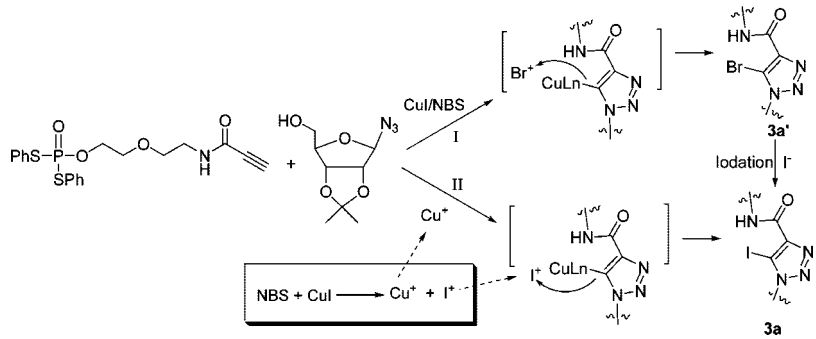
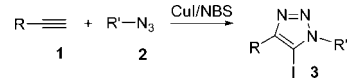
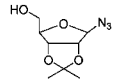
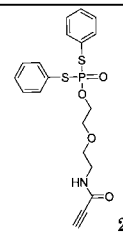
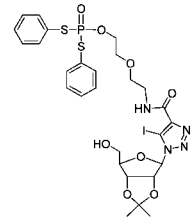
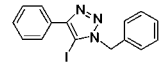
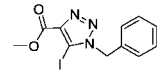
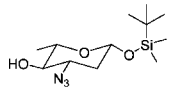
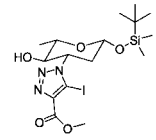
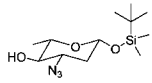
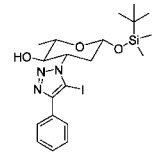
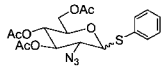
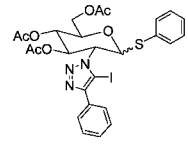
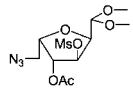
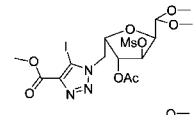
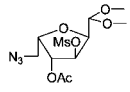
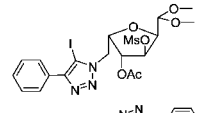
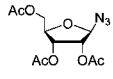
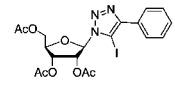


**TABLE 3. One-Pot Preparations of 5-Iodo-1,4-disubstituted-1,2,3-triazoles with CuI and NBS[a]**




| Entry | Azide | Alkyne | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 3 | 90 |
| 2 |  **1b** |  **2b** |  **3b** | 5 | 85 |
| 3 |  **1b** |  **2c** |  **3c** | 3 | 89 |
| 4 |  **1c** |  **2c** |  **3d** | 4 | 81 |
| 5 |  **1c** |  **2b** |  **3e** | 5 | 86 |
| 6 |  **1d** |  **2b** |  **3f** | 4 | 80 |
| 7 |  **1e** |  **2c** |  **3g** | 3 | 91 |
| 8 |  **1e** |  **2b** |  **3h** | 5 | 86 |
| 9 |  **1f** |  **2b** |  **3i** | 5 | 85 |

[a] The reaction was performed under room temperature in dry THF. The mole ratio of alkyne, azide, CuI, and NBS was 1:1.1:1.1:1.2, with 1 equiv of DIPEA added as the alkali. [b] Isolated yield.

1,4-disubstituted-1,2,3-triazole derivative in a yield of 90%, and no bromide was observed. In the absence of NBS, the reaction catalyzed with CuI gave 1,4-disubstituted-1,2,3-triazole derivative in a yield of 91% under the same conditions. The CuI−$I_2$ catalytic system did not show any reactivity under the same conditions; neither the 5-iodo-1,4-disubstituted-1,2,3-triazole derivative nor 1,4-disubstituted-1,2,3-triazole derivative was observed.

Different solvents were also applied for this one-pot iodination reaction. This reaction proceeded well in several common solvents, such as THF, $CH_3CN$, and $CH_3COCH_3$, with more than 89% yields, under room temperature within 3 h. But the reaction could not take place in methanol. Meanwhile, the reaction in dichloromethane was sluggish due to the poor solubility of CuI in it.

Based on the mechanisms of the click reaction in the literature,[2c,20b] two possible mechanisms (I and II) for the preparation of 5-iodo-1,4-disubstituted-1,2,3-triazole with CuI and NBS were proposed and are outlined in Scheme 1. In order to explore the rational mechanism of this multicomponent one-pot reaction, three reactions catalyzed by CuI/NBS were terminated after 1, 2, and 3 h, respectively. The yields of **3a** were 50%, 81%, and 90%, respectively (Table 2), and the intermediate **3a′** was not observed in all three cases. This result indicated that the reaction might not proceed via the mechanism I. This result also indicated the oxidation–reduction reaction must take place efficiently between NBS and CuI during this procedure. The in situ generated $I^+$ was then trapped by the carbon anion intermediate from the click reaction (mechanism II). During these processes, the $Cu^+$ did not suffer oxidation;

instead, it acted as catalyst for the click reaction. Consequently, CuI played double roles during this reaction procedure: (1) to provide $Cu^+$ as catalyst for Huisgen cycloaddition, in which catalytic amounts of CuI were enough, and (2) to provide iodo atom for the delivery of halogen in the reaction, in which stoichiometric amounts of CuI were needed. As to NBS, its possible role was to oxidize $I^-$ to $I^+$; thus, the stoichiometric amounts were needed.

The application of this new synthetic protocol was explored by using various alkynes and azides as building blocks to construct 5-iodo-1,4-disubstituted-1,2,3-triazole derivatives (Table 3).Different types of protective groups, such as acid-sensitive acetal and ketal, alkali-sensitive acetyl and *S*,*S*-diphenylphosphate, and TBDMS group could tolerate the reaction conditions. Some widely used active groups, like PhS- and MsO-, and functional groups like ester, ether, amide, and hydroxyl were also found to be intact under the CuI−NBS catalytic system. Moreover, benzyl azide or other aliphatic azides successfully reacted with corresponding alkynes to give 5-iodo-1,4-disubstituted-1,2,3-triazoles in good yields.

In conclusion, we have developed an efficient method for preparation of 5-iodo-1,4-disubstituted-1,2,3-triazole by a one-pot trapping carbon anion intermediate in click chemistry. The CuI−NBS system was found to be an effective source of $I^+$ and catalytic $Cu^+$ simultaneously. The further construction of diverse 1,4,5-trisubstituted-1,2,3-triazoles based on the 5-iodo-1,4-disubstituted-1,2,3-triazole and its application on synthesis of natural product mimetics are underway now.

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## Experimental Section

**Typical Procedure for the One-Pot Multicomponent Click Reaction. The Synthesis of *N*-[5″-(Phenylthio)phosphorylethoxy ethyl]-2′,3′-*O*-isopropylidene-5′-phosphoryl-5-I-1,2,3-triazole-4-amide-1-β-D-ribofuranoside 3a.** A mixture of **1a** (12 mg, 0.053 mmol), **2a** (20 mg, 0.048 mmol), CuI (10 mg, 0.053 mmol), DIPEA (7 mg, 0.053 mmol), and NBS (10 mg, 0.058 mmol) in 3 mL of THF was stirred at room temperature for 3 h. The mixture was evaporated, and the residue was partitioned between ethyl acetate and $H_2O$. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated. The residue was purified by silica gel column chromatography (1:50 $MeOH/CH_2Cl_2$) to give compound **3a** (33 mg, 90%): $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 7.50–7.34 (m, 10 H), 5. 94 (d, $J$ = 8.5 Hz, 1 H), 4.91–4.87 (m, 1 H), 4.79 (dd, $J$ = 7.5 Hz, 3.5 Hz, 1 H), 4.50–4.47 (m, 1 H), 4.35–4.31 (m, 2 H), 4.02 (dd, $J$ = 14 Hz, 3 Hz, 1 H), 3.80 (dd, $J$ = 14 Hz, 3 Hz, 1 H), 3.68–3.60 (m, 6 H), 2.82–2.80 (br, 1 H), 1.63, 1.44 (s, each 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$),$\delta$ 159.4, 142.7, 135.3, 129.5, 126.2, 110.7, 85.7, 82.8, 73.5, 73.1, 69.7, 66.9, 66.7, 64.7, 38.9, 29.7, 26.6, 25.1; HRMS $(M + H)^+$ (FT-ICRMS) calcd for $C_{27}H_{33}IN_4O_8PS_2^+$ 763.0517, found 763.0519.

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**Supporting Information Available:** Experimental procedures, characterization data, and copies of $^1H$ and $^{13}C$ NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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