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General method of synthesis of 1,4-disubstituted-5-halo-1,2,3-triazoles

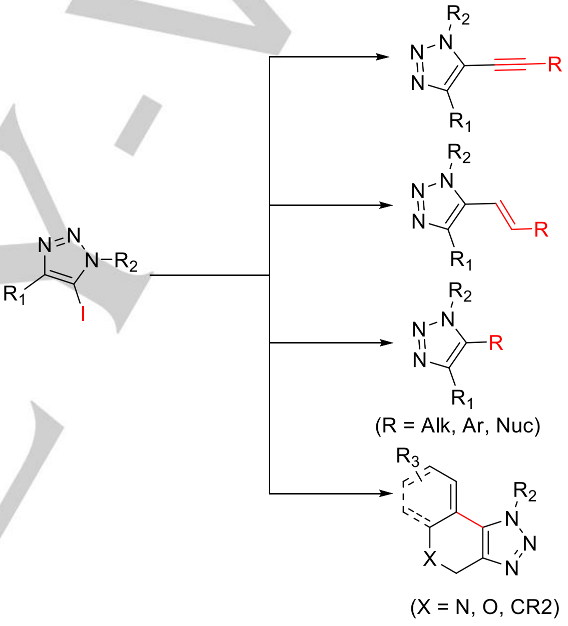
Pavel S. Gribanov,[a] Maxim A. Topchiy,[a] Iuliia V. Karsakova,[b] Gleb A. Chesnokov,[b] Alexander Yu. Smirnov[a], Lidiya I. Minaeva[c], Andrey F. Asachenko[a,c] and Mikhail S. Nechaev*[a,b]

Abstract: General method of synthesis of 1,4-disubstituted-5-halo-1,2,3-triazoles have been developed. The one-pot two-step process consists of CuAAC of copper(I) acetylide with organic azide catalyzed by (*a*NHC)CuCl, and following halogenation using NCS, NBS or I_2.

Introduction

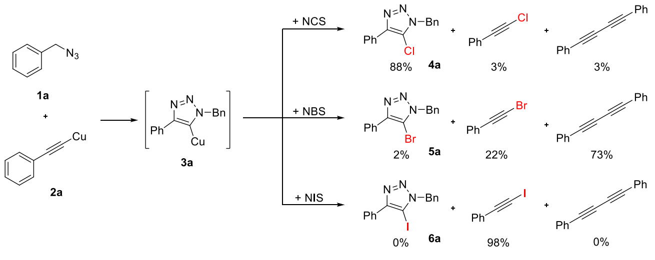
The discovery of copper catalyzed azide acetylene cycloaddition reaction (CuAAC) made 1,2,3-triazoles easily accessible compounds.[1] This have led to their broad utilization in various applications.[2] However this approach is not suitable, in most cases, for synthesis of 1,4,5-trisubstituted-1,2,3-triazoles. It have been recently shown that 1,4,5-trisubstituted-1,2,3-triazoles have high practical significance in organic synthesis, biomedical and material applications.[3] Convenient precursors for this class of compounds are 1,4-disubstituted-5-iodo-1,2,3-triazoles that can be functionalized via Sonogashira alkynylation,[3l, 3m, 3q, 4] alkylation,[5] arylation,[3g, 3p, 6] Heck reaction,[3k, 7] nucleophilic substitution,[3n, 8] and intramolecular cyclization (Scheme 1).[3f, 3h, 3i]

Recently, Yuefei Hu et al. reported on the development of the new original approach for synthesis of 1,4-disubstituted-5-chloro-1,2,3,-triazoles by mixing copper(I) aryl acetylides with benzyl azide in CH_2Cl_2 in presence of NCS (Scheme 2).[9] However, this approach is not applicable for synthesis of bromo- and iodo-derivatives using NBS and NIS, correspondingly.
The proposed method enabled to obtain 1-benzyl-4-phenyl-5-chloro-1,2,3-triazole (**4a**) in high yield (88%). However, upon substitution of NCS with NBS the target 5-bromo-1,2,3-triazole (**5a**) was obtained in only 2% yield. The main product of the reaction was 1,4-diphenylbutadiyne. The reaction in presence of NIS gave exclusively 1-iodophenylacetylene (98%). The obtained results were rationalized in terms of relative strengths of NXSs as electrophiles. Stronger electrophiles NBS and NIS quench copper(I) phenylacetylide, thus preventing its CuAAC reaction with organic azide. Contrary, NCS, as lower strength electrophile, reacts with copper(I) phenylacetylide at lower rate. Thus, copper(I) phenylacetylide predominantly reacts with benzyl azide to give copper(I) 1,2,3,-triazolide **3a**. Then, **3a** reacts with NCS to give **4a** in high yield. Arguably, this is due to lower lability of copper-carbon bond in **2a** than in **3a**, since **2a** is a polymeric complex.



Scheme 1. Functionalization of 5-iodo-1,2,3-triazoles.[10]

Using the developed protocol, Yuefei Hu performed synthesis of 20 examples of 5-chloro-1,2,3-triazoles in good to high yields. However, no examples derived from aryl azides, substrates, challenging for CuAAC reaction,[11] were reported. Moreover, the proposed method is not suitable for synthesis of 5-bromo and 5-iodo-1,2,3-triazoles which are valuable substrates for further transformations.



Scheme 2. Synthesis of 1,4-disubstituted 5-halo-1,2,3-triazoles.

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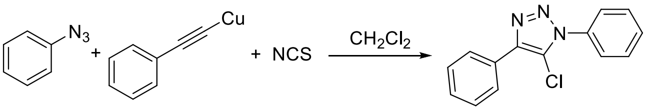
In this contribution, we report on the development of a general approach for synthesis of 1,4-disubstituted-5-halo-1,2,3-triazoles from copper(I) acetylides, organic azides, and halogenating agents.

Results and Discussion

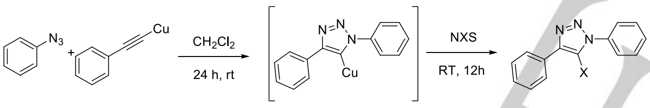
Initially, we tested the conditions, developed by Yuefei Hu[9] for synthesis of N-aryl-5-halo-1,2,3-triazoles by taking a phenyl azide as the azide component. The resulting N-phenyl-4-phenyl-5-chloro-1,2,3-triazole **4b** have been obtained in 41% yield (Scheme 3).



1b **2a** **4b** (41%)

Scheme 3. Preparation of N-phenyl-4-phenyl-5-chloro-1,2,3-triazole.

Then, we decided to sequence two reaction steps. First, phenyl azide was mixed with copper(I) phenylacetylide in CH_2Cl_2 (Scheme 4). Then, after 24 h, NCS was added. The resulting product **4b** was isolated in the same 41% yield. Analogously, the N-phenyl-4-phenyl-5-bromo-1,2,3-triazole **5b** was obtained by addition of NBS in 36% yield.



1b **2a** **3b**

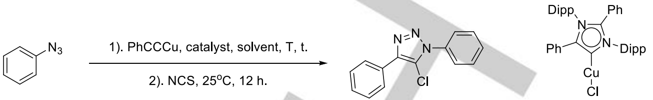
X = Cl, **4b** (41%)
X = Br, **5b** (36%)

Scheme 4. Sequential preparation of 5-chloro- and 5-brono N-phenyl-4-phenyl-1,2,3-triazoles.

Thus, contrary to previous results from Yuefei Hu's group (Scheme 2, 4),[9] upon sequential addition of copper phenylacetylide and NCS/NBS the obtained yields were similar. This have led us to the assumption that mixing of phenyl azide with copper(I) phenylacetylide in CH_2Cl_2 leads to the formation of copper(I) 1,2,3,-triazolide **3b** in 24 h in approximately 40% yield. Further, the obtained copper(I) 1,2,3,-triazolide reacts with NCS/NBS in virtually quantitative yield.

To increase the yield of copper(I) 1,2,3,-triazolide **3b**, and, subsequently, to increase the overall yield of the reaction, we performed optimization of reactions conditions.

It was previously shown that monomeric copper-acetylide complexes are not reactive towards organic azides. However, this reaction can be activated with corresponding copper catalysts.[10, 12] To enhance the rate of CuAAC reaction, we tested CuCl[12] and (*a*NHC)CuCl,[13] complex bearing the abnormal N-heterocyclic carbene ligand, as catalysts (Table 1). We also tested the 1,2-dichloroethane (1,2-DCE), a solvent with higher boiling temperature than for CH_2Cl_2, to increase the reaction temperature and decrease reaction time. As a result, the yield of N-phenyl-4-phenyl-5-chloro-1,2,3-triazole (**4b**) was raised to 87% (entry 6).



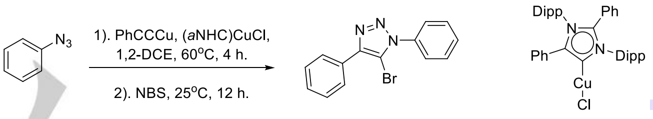
1b **4b** (*a*NHC)CuCl

Table 1. Optimization of reaction conditions of synthesis of N-phenyl-4-phenyl-5-chloro-1,2,3-triazole.

Entry	Catalyst	Solvent	T, °C	NCS (eq.)	Yield (%)
1	5 mol% CuCl	CH_2Cl_2	25	1.2	50[a]
2	1 mol% (*a*NHC)CuCl	CH_2Cl_2	25	1.2	58[a]
3	5 mol% CuCl	1,2-DCE	60	1.2	41[b]
4	1 mol% (*a*NHC)CuCl	1,2-DCE	60	1.2	55[b]
5	5 mol% CuCl	1,2-DCE	60	2.0	77[b]
6	1 mol% (*a*NHC)CuCl	1,2-DCE	60	2.0	87[b]

[a] CuAAC reaction time t = 24 h. [b] CuAAC reaction time t = 4 h.

Analogous optimization of synthesis of N-phenyl-4-phenyl-5-bromo-1,2,3-triazole (**5b**) using CuBr or (*a*NHC)CuCl) as catalysts (Table 2) enabled us to obtain the final product in nearly quantitative yield (99%, entry 4).

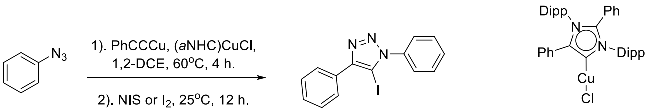


1b **5b** (*a*NHC)CuCl

Table 2. Optimization of reaction conditions of synthesis of N-phenyl-4-phenyl-5-bromo-1,2,3-triazole.

Entry	Catalyst	NBS (eq.)	Yield (%)
1	5 mol% CuBr	1.0	57
2	5 mol% CuBr	2.0	88
3	1 mol% (*a*NHC)CuCl	1.0	82
4	1 mol% (*a*NHC)CuCl	2.0	>99

The optimized conditions were used for the synthesis of N-phenyl-4-phenyl-5-iodo-1,2,3-triazole (**6b**) (Scheme 5). It was found that elemental iodine, as electrophile, performs better than NIS, corresponding yields are 63% and 38%.

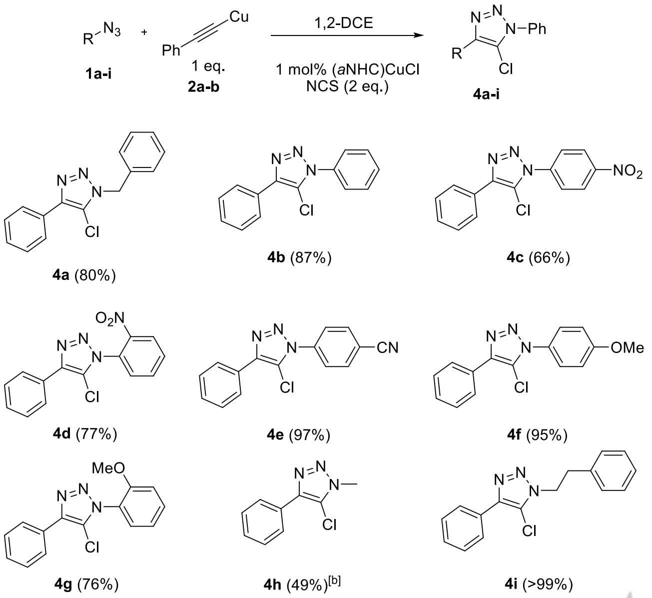


1b **6b** NIS: 38%
I_2: 63% (*a*NHC)CuCl

Scheme 5. Preparation of N-phenyl-4-phenyl-5-iodo-1,2,3-triazole.

To determine the scope and limitations of the new synthetic approach, we tested a series of reactions of different alkyl and aryl azides[14] with copper(I) and arylacetylides quenched by NCS (Scheme 6), and NBS or I_2 (Scheme 7).

Scheme 6: Preparation of 1,4-disubstituted-5-chloro-1,2,3-triazoles.[a]



[a] *Conditions*: alkynyl copper(I) (1 mmol.), 1,2-dichloroethane (2 ml.), azide (1 mmol.), (*a*NHC)CuCl (1 mol.%), 60°C, 4 h, NCS (2 mmol., 2 eq.), 4 h. [b] Room temperature.

The developed reaction protocol enabled us to obtain N-substituted-4-phenyl-5-chloro-1,2,3-triazoles from phenyl azide (**4b**), aryl azides bearing electron withdrawing (**4c**, **4d**, **4e**) as well as electron donating (**4f**, **4g**) substituents. The presence of ortho- substituents in aryl azide has no negative effect on the yields (**4d**, **4g**). Alkyl azides were also found to be suitable substrates for the developed protocol. Benzyl derivative **4a** was obtained in 80% yield, for the reaction of the (2-azidoethyl)benzene (**4i**) the yield was virtually quantitative. Due to high volatility of methyl azide, the first stage of the reaction was performed at room temperature for 12 h. The obtained yield of **4h** was 49%.

The new method of synthesis of N-substituted-4-phenyl-5-chloro-1,2,3-triazoles have several prominent advantages: (i) suitable substrates are not only reactive alkyl and benzyl azides,[9] but also less reactive aryl azides; (ii) mild reaction temperature. We avoid the use of (iii) expensive solvents (MeCN), special equipment (microwave);[3n] (iv) toxic organotin derivatives (Bu_3SnOMe);[15] and (v) flammable and functional groups intolerant reagents (dialkylalkynylaluminium).[16]

A series of 5-bromo triazoles were obtained from copper(I) aryl- (**5a** – **5e**, **5i** - **5l**), and propargyl ether acetylides (**5f** – **5h**, **5m**) upon reactions with phenyl azide (5b, 5f), aryl azides, bearing electron withdrawing (**5c** – **5e**, **5g**, **5h**), and electron donating (**5k**, **5l**) substituents, as well as alkyl azides (**5i**, **5j**, **5m**). The yield of N-methyl substituted 1,2,3,-triazole **5i** was moderate (51%) due to high volatility of starting methyl azide. Notably, 1,2,3,-triazoles **5f-5h** and **5m** were obtained using 1 eq. of NBS. Upon utilization of 2 eq. of NBS we observed the formation of side products, bromination of 4-tolyloxy substituent. We have also prepared two iodo-derivatives, **6a** and **6b** in good yields.

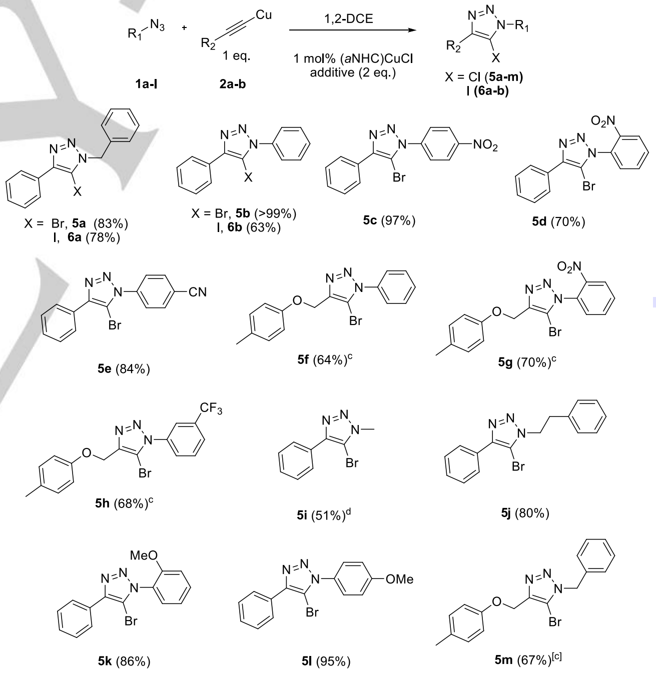
Main advantages of the new procedures of synthesis of 5-bromo- and 5-iodo-1,2,3-triazoles are: (i) the method is preparative; (ii) there is no need in high dilution of the reaction media with expensive THF (0.018 mol/L) [17] or highly hygroscopic CH_3CN (0.12 mol/L);[18] (iii) absence of side products, 5-H-1,2,3,-triazoles; (iv) high yields not only for alkyl-, and benzyl azides, but also for aryl azides.[18-19]

We performed a scale-up of synthesis of 1,2,3,-triazoles **4a**, **4c**, **5a**, **5b, 5g**. Compounds **4a** and **5a** were obtained on a 50 mmol scale, other examples were obtained on a 25 mmol scale.

Surprisingly, the yields in scale-up procedures reproduce small-scale experiments. The isolation of analytically pure products is simple. Notably, in certain cases solubility of products (**4c**) is low and special care should be taken to achieve complete dissolution of products upon isolation procedure.

A scale-up procedure is similar with the 1 mmol experiments, except reaction vessel was immersed into room temperature water bath due to moderate exothermicity upon addition of NXS.

Scheme 7: Preparation of 1,4-disubstituted 5-bromo- and 5-iodo-1,2,3-triazoles.[a,b]



[a] *Conditions*: alkynyl copper (I) (1 mmol), 1,2-dichloroethane (2 ml), azide (1 mmol), (*a*NHC)CuCl (1 mol.%), 60°C, 4h, NBS (2 mmol, 2 eq.), 4h. [b] *Conditions*: alkynyl copper (I) (1 mmol), 1,2-dichloroethane (2 ml), azide (1 mmol), (*a*NHC)CuCl (1 mol.%), 60°C, 4h, I_2 (2 mmol, 2 eq.), 4h. [c] NBS (1eq.).

All compounds were characterized with ^1H and ^{13}C NMR. Characteristic signals in ^1H NMR are low-filed doublets of 2H intensity corresponding to protons of aromatic ring attached to carbon atom. This is due to magnetic anisotropic effect of the 1,2,3,-triazole ring. This effect is not observed in 1,2,3,-triazoles obtained from propargyl ether derivative due to different molecular geometry.

Assignment of signals for **4f** was performed on the basis of 2D NMR: ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC (Supporting Information). For **4c-e**, **5c-e**, **5g**, and **5h** IR spectra were recorded. Signals corresponding to functional groups were detected. For **4c-e**, **5a**, **5m** and **6a** we also recorded UV-Vis spectra in $CHCl_3$. All compounds have absorption bands in the 250-300 nm region. There is no significant dependence of UV-Vis spectra from the nature of substituents or nature of halogen atom attached to 1,2,3,-triazole ring.

Conclusions

In conclusion, we developed a general approach for the synthesis of 1,4-disubstituted-5-halo-1,2,3-triazoles (Cl, Br, I). The one-pot two-step procedure consists of CuAAC reaction of copper(I) acetylides with organic azides (including challenging aryl azides) followed by quenching of copper(I) 1,2,3,-triazolide with the corresponding electrophile NCS, NBS or I_2 to obtain resulting 5-halo-1,2,3-triazoles in good to quantitative yields.

The developed method has several notable advantages: i) wide scope of azides, ii) high yields, iii) low amount of side products (5-H-1,2,3,-triazole), iv) simple and robust, v) easily scalable, vi) short reaction times and easy work-up. Thus, a new approach might find broad utilization in laboratory practice.

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Keywords: aryl azides • CuAAC • abnormal NHC • 1,2,3-triazoles • halogenation

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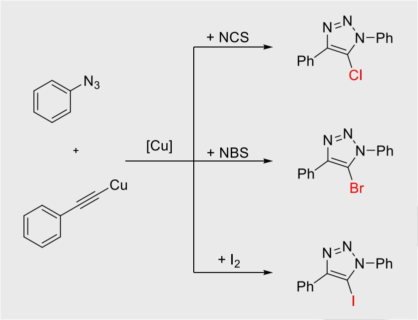

1,2,3-Triazole Synthesis

*Pavel S. Gribanov, Maxim A. Topchiy, Iuliia V. Karsakova, Gleb A. Chesnokov, Alexander Yu. Smirnov, Lidiya I. Minaeva, Andrey F. Asachenko, Mikhail S. Nechaev**

Page No. – Page No.

General method of synthesis of 1,4-disubstituted-5-halo-1,2,3-triazoles

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