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Three-component Assembly of 5-Halo-1,2,3-triazoles via Aerobic Oxidative Halogenation

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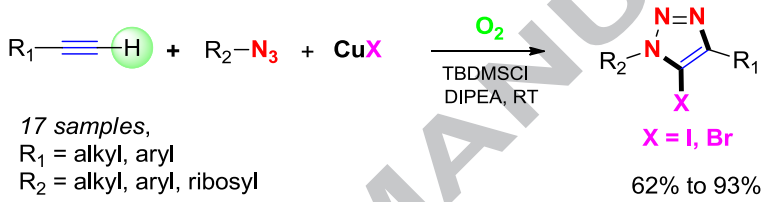
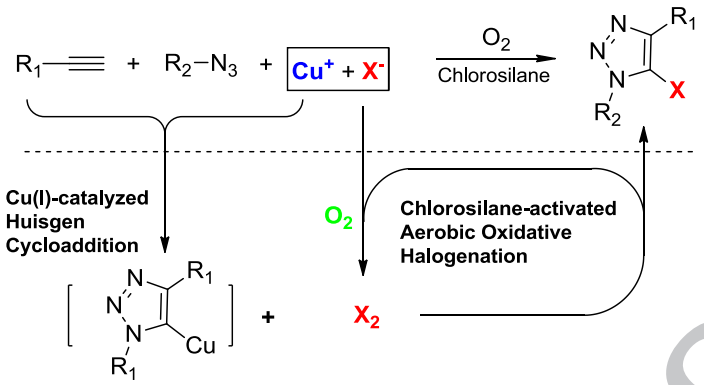


Abstract: An effective synthetic protocol for 5-halo-1,2,3-triazoles was developed by novel TBDMSCl (*tert*-Butyldimethylsilyl chloride)-activated aerobic oxidative halogenations in this paper. TBDMSCl, for the first time, was found to activate aerobic oxidation of CuX to produce X_2 with Cu^+ which then could effectively promote one-pot syntheses of 5-halo-1,2,3-triazole from alkyne, azide and CuX (X = I, Br) under O_2 atmosphere at room temperature. The advantages in this method include inexpensive and green O_2 as oxidant, use of mild and non-oxidative additive, and wide scope of substrates.

Keyword: aerobic oxidative halogenations, 5-halo-1,2,3-triazole, nucleoside

Recently, 1,2,3-triazole derivatives not only provide a desirable class of linkage,[1] but also represent useful functional moieties including peptide bond mimics,[2] nucleobase bioisosteres,[3] ligands in metal complex[4] and so on[5]. In this regard, 5-halo-1,2,3-triazoles are valuable structural derivatives of 1,2,3-triazole because they are established precursors to other functional groups,[6] as well as widely-used analogues for the SAR investigation.[7] Unfortunately, direct halogenation on 1,2,3-trizole ring is unsuccessful due to the electron deficiency of 1,2,3-triazoles. Diazotization of 5-NH_2-1,2,3-triazole was initially used to incorporation of iodine into 1,2,3-triazole.[8] Then the cycloaddition reactions of alkynyl-iodine and alkynyl-bromide with azide were developed to preparation of 5-halo-1,2,3-trizoles by Sharpless groups [9a], García-Álvarez[9b] and Rutjes groups[10]. Meanwhile, an alternative tandem oxidative halogenation and Husigen cycloadditon protocol has stepwise developed for the preparation of 5-iodo-1,2,3-triazole directly from the multi-component reaction of iodide, alkyne and azide [11a, 12, 13]. This protocol allows the reactions proceed under mild conditions without the pre-prepared active alkynyl-halogen and complex ligands, which has been used in the preparation of the sugar drugs [14] and I^{125}-labled peptides [15]. However, the metal or organic oxidants are still involved in this protocol. O_2 as an oxidant has attracted interest in both of academic research and industry due to its natural, inexpensive, and environmentally friendly characters [16]. Herein, we reported the first effective tandem *aerobic oxidative halogenation* and Husigen cycoladditon reaction for the preparation of 5-iodo-1,2,3-triazole and 5-bromo-1,2,3-triazole via an *in situ* activated procedure

(Scheme 1).

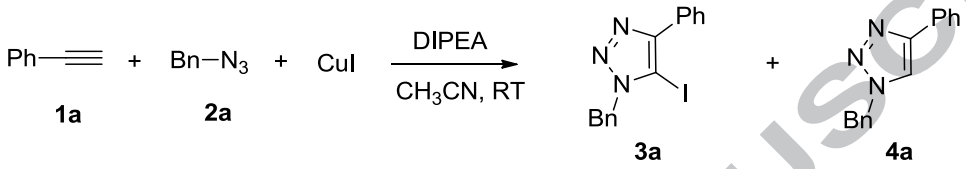


Scheme 1 Tandem halogenation and Husigen cycloaddition reaction via *in situ* chlorosilane-activated aerobic oxidative procedure

5-Halo-1,2,3-triazoles are firstly found as trace by-products in CuAAC reaction[17]. These compounds are considered to be produced from trapping of Cu-triazolyl intermediate with electrophilic halogen. But this aerobic oxidative halogenation in CuAAC reaction is very sluggish. For example, van Maarseveen et al. found 5-iodo-1,2,3-triazole analogues in cyclic tetrapeptide could be obtained under CuI (2.0 equvi)/2,4-ludtidine/DIPEA systems with 14% yield after 3 days.[18] In fact, it is still a challenge to improve the efficiency of the aerobic oxidative halogenation for a long time, because direct activation of O_2 at mild conditions is very difficult.[19] Several methods have been developed in this field. For example, MX/TFA/$NOBF_4$/O_2 [20], MX/$RuCl_3$/O_2[21] HX/[bmim][NO_3][22] and HX/[BMIM(SO_3H)][NO_3][23] have been reported to effectively promote aerobic oxidative halogenation. The systems, however, often require strong acidic condition, co-oxidant or high reaction temperature, which is hard to be compatible to the copper(I) catalyst and copper-triazolyl complex in CuAAC reaction. Therefore, the goal of this work was to

find a mild and facile method for activation of the aerobic oxidative halogenation during CuAAC procedure, then to develop an aerobic oxidative one-pot assembly of terminal alkyne, azide and CuX to 5-halo-1,2,3-triazole.

Table 1. The effect of additives on one-pot synthesis of 5-iodo-1,2,3-triazole.



Entry[a]	Additive (equiv.)	Oxidant	Base	Solvent	Isolated yield	
					3a (%)	4a (%)
1	TMSCl (1.1)	Air	DIPEA	CH_3CN	65	22
2	TBDMSCl (1.1)	Air	DIPEA	CH_3CN	81	4
3	TBDMSCl (0.5)	Air	DIPEA	CH_3CN	78	11
4	TBDMSCl (0.1)	Air	DIPEA	CH_3CN	49	20
5	--	Air	DIPEA	CH_3CN	9	83
6	**TBDMSCl (0.5)**	**O_2**	**DIPEA**	**CH_3CN**	**93**	**5**
7	$NaNO_2$ (0.5)	O_2	DIPEA	CH_3CN	--[b]	--[b]
8	TBDMSCl (0.5)	N_2	DIPEA	CH_3CN	--[b]	89
9	TBDMSCl (0.5)	O_2	DIPEA	THF	66	6
10	TBDMSCl (0.5)	O_2	TEA	CH_3CN	78	20
11	TBDMSCl (0.5)	O_2	K_2CO_3	CH_3CN	50	46

[a] Reaction conditions: A mixture of **1a** (17 mg, 0.17mmol), **2a** (23 mg, 0.17mmol), CuI (32 mg, 0.17mmol), and DIPEA (30 μL, 0.17 mmol) with different additives and oxidants was stirred in 3 mL solvent at room temperature for 18 h.[b] No product were detected.

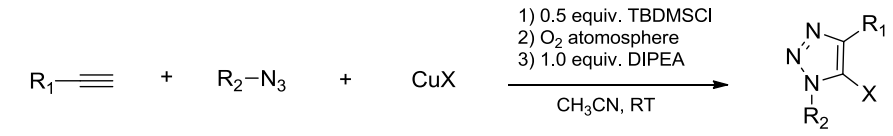
The investigation for activation of the aerobic oxidative halogenation in CuAAC was

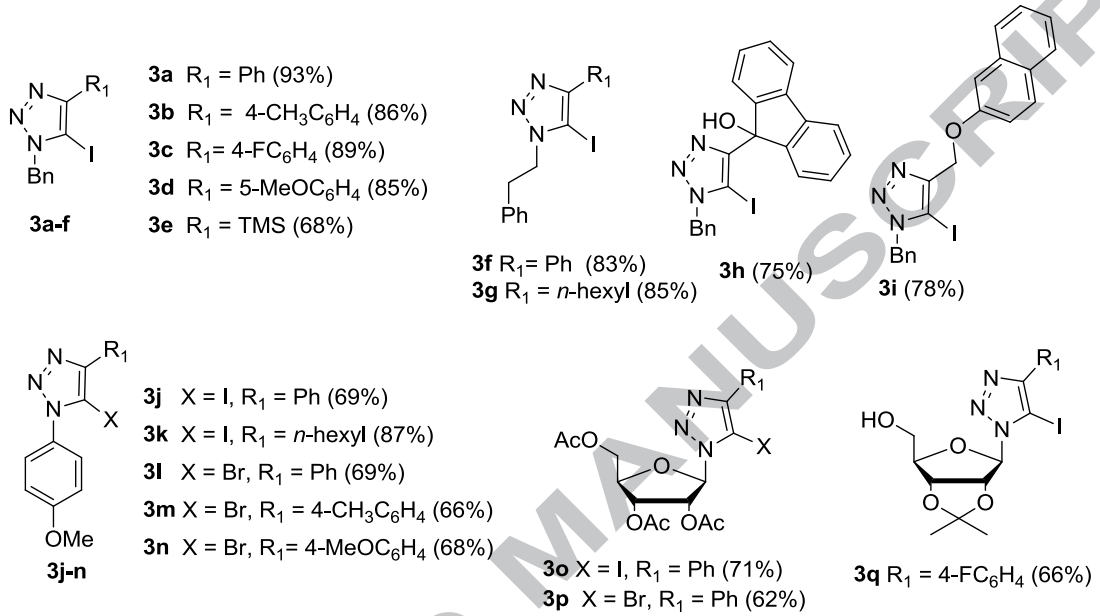
carried out in Table 1. Firstly, we found increase of the amount of CuI could not improve the yield of 5-iodo-1,2,3-triazole. In presence of 1.1 equiv. CuI, the yield of **3a** was still 9% after 18 hours, with 83% 1,2,3-triazole **4a**. Then 0.5 equiv. $NaNO_2$ as co-oxidant was tried, but neither of 1,2,3-triazole and 5-iodo-1,2,3-triazole could be obtained under these conditions with total recovery of starting materials. To our delight, the activation effects of chlorosilan on the aerobic oxidative iodination was found by accidently when addition of TMSCl into the reaction of CuI, **1a** and **2a** in presence of DIPEA. Unexpectedly, no 5-TMS-1,2,3-triazole was found, instead, 5-iodo-1,2,3-triazole **3a** was obtained in 65%. With this result in hand, we continued to optimize silica reagents, solvents and reaction temperature. With 0.5 equiv. TBDMSCl, 1.1 equiv. DIPEA under O_2 atmosphere, product **3a** was obtained in 93% yield after 18 hours at room temperature in CH_3CN as solvent (Entry 6 in Table 1).

Having optimized reaction conditions, we next investigated the substrate scope of this one-pot preparation of 5-iodo-1,2,3-triazole in Table 2. It was found that substituted aromatic alkynes carrying electron-withdrawing or electron-donating groups reacted smoothly with benzyl azide to produce 5-iodo-1,2,3-triazoles with excellent yields (85%-93%). Aliphatic terminal alkynes also reacted well with benzyl azide to give target compounds with 68%-78% yields. Even the bulky 9-ethynyl-9H-fluoren-9-ol could condense smoothly to give a yield of 75% of desired product. Various azides were used. Phenyl azide and phenethyl azide reacted with terminal alkyne to produce 5-iodo-1,2,3-triazoles with 69%-87% yields. Various acidic and basic sensitive groups like ketal, methoxyl, ribosyl, trimethyl and ether were tolerated under the reaction

conditions. For example, ribosyl azides, alkyne and CuX were condensed to give 5-iodo-1,2,3-triazoles with 71% and 66% yields, which provided very useful intermediates for the preparations of unnatural base nucleosides.[24] Trimethylsilyacetylene reacted smoothly with azide to give 4-TMS-5-iodo-1,2,3-triazole, which could be conveniently converted into 1,5-disubstituted-1,2,3-triazole after deprotection of trimethylsilyl protective group [25]. Furthermore, preparations of 5-bromo-1,2,3-triazole were also investigated with CuBr-TBDMSCl systems. It was expected to be more difficult to activate the areobic oxidative bromination due to the higher standard electrode potential of Br_2 compared to that of I_2. To our delight, however, under the current conditions, 5-bromo-1,2,3-triazoles could also be obtained effectively from TBDMSCl/CuBr/Alkyne/Azide reaction system with 62%-69% yields (**3l-3n**, **3p** in Table 2).

Table 2 Substrate scope of TBDMSCl-promoted one-pot alkyne/azide/CuX reaction





Reaction conditions: A mixture of azide **1** (0.17mmol), alkyne **2** (0.17mmol), CuI (32mg, 0.17mmol), DIPEA (30 μL, 0.17 mmol) and TBDMSCl (12mg, 0.08 mmol) was stirred in 3 mL CH_3CN under O_2 atmosphere at room temperature for 18 h.

To gain some insight of the reaction mechanism, the possible roles of TBDMSCl in the aerobic oxidative one-pot synthesis of 5-halo-1,2,3-triazole were investigated. Firstly, an evident dissolution process of CuI was observed after addition of TBDMSCl under the present conditions. A possible mechanism involved in this procedure was that TBDMSCl and CuI reacted to produce CuCl and soluble TBDMSI[26], by which the effective concentration of iodide was expected to dramatically increase in organic phase. Secondly, additional two reactions (Eq-1 and Eq-2 in Figure 1) were designed. Reaction mixture of Eq-1 turned into a light purple

after being stirred under air atmosphere for 18 hours at room temperature. This light purple solution can make 0.5% soluble starch solution into deep blue (solution C). Comparedly, the reaction mixture of Eq-2 after being stirred under same conditions in absence of TBDMSCl for 18 hours could not make soluble starch solution blue. Thirdly, UV spectrums of the Eq-1 reaction mixture and control groups were also investigated as shown in Figure 2. The solution of I_2 in CH_3CN showed two absorption bands at 294 nm, 367 nm (purple trace in Figure 2) which were consistent to the reported data in literature.[27] Absorption spectrum of reaction mixture of Eq-1 contained two bands at 294 nm and 367 nm (green trace in Figure 2), which perfectly agreed with the two absorption bonds of iodine in CH_3CN solution. But in the absorption spectrum of TBDMSCl and CuI, the corresponding bonds at 294 nm and 367 nm were not observed. These experiments indicated that I_2 could be effectively produced from reaction of CuI and oxygen in air in presence of TBDMSCl (Eq-1), while in absence of TBDMSCl, I_2 could hardly be detected from the reaction of CuI and oxygen in the reaction of Eq-2. Thus, a key promotion of TBDMSCl on the aerobic oxidative iodination could be concluded from the results. To our best knowledge, this is the first report about the activation of chlorosilane on aerobic oxidative iodination reaction. Moreover, no appearance of a copper (II) d-d transition bond in the 700 nm range also suggested that this TBDMSCl-activated aerobic oxidative iodination didn’t cause the oxidation of Cu(I) to Cu(II). The presence of sufficient Cu (I) could provide effective catalyst for the following Husigen cycloaddition.

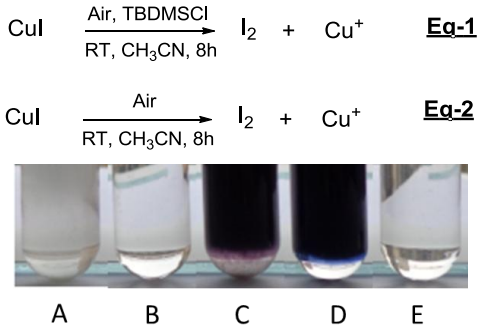


Figure 1. (A) Adding reaction mixture of Eq-2 solution (0.06 mol/L) into 0.5% soluble starch solution; (B) Adding 0.06 mol/L TBDMSCl (CH_3CN) into 0.5% soluble starch solution; (C) Adding resulting reaction mixture of Eq-1 solution (0.06 mol/L) into 0.5% soluble starch solution; (D) Adding 0.03 mol/L I_2 (CH_3CN) into 0.5% soluble starch solution; (E) Blank control: 0.5% soluble starch solution.

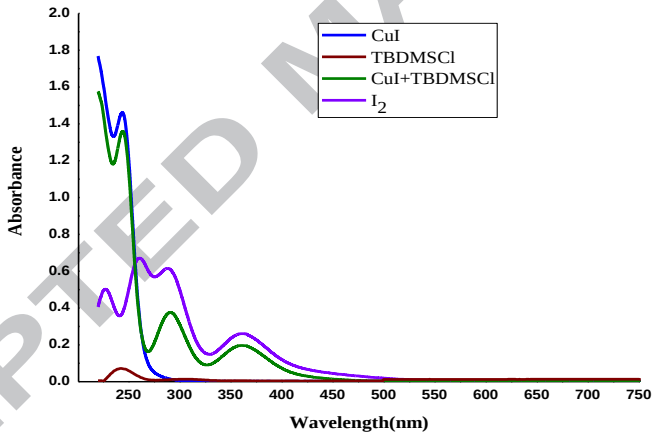
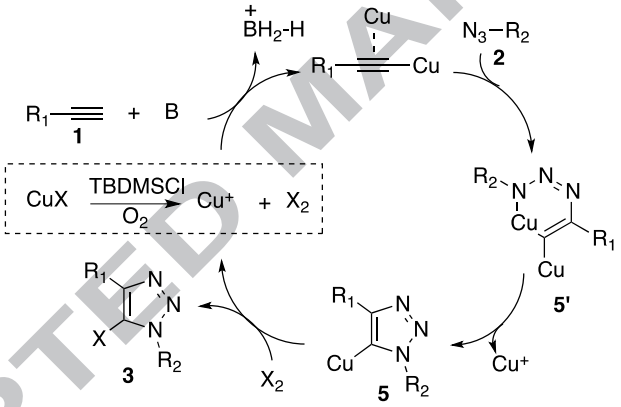


Figure 2. Absorption spectra of solution of CuI (0.2 mM, blue), TBDMSCl (2 mM, red), Resulting reaction mixture of Eq-1 (0.2 mM green), and iodine (0.2 mM) in CH_3CN.

On the basis of the above preliminary results and the known nucleophilic trapping mechanism models of 5-iodotriazoles[28], a possible reaction mechanism of the TBDMSCl-CuX promoted one-pot reaction of terminal alkyne and azide was proposed in Scheme 2. The X_2 produced in situ from the TBDMSCl-activated aerobic

oxidative halogenation attacked the copper-triazolyl complex **5** to form the sp2 C-X bond on the 5-carbon of 1,2,3-triaozle. During the reaction procedure, two main roles of TBDMSCl could be suggested, (1) enhancing the effective concentration of halogen in organic solvent through conversion of halide anion to TBDMSX, (2) promoting the aerobic oxidation of halide to produce reactive X_2 *in situ*. However, the detailed mechanism of TBDMSCl-activated aerobic oxidative halogenation reaction such as the TBDMSCl-O_2-X^- intermediate was still not clear at present.



Scheme 2. The possible reaction mechanism of the tandem aerobic oxidative halogenation and Huisgen cycloaddition reaction

In brief, an effective synthetic protocol for 5-halo-1,2,3-triazoles was developed by a novel TBDMSCl-activated aerobic oxidative halogenation in this paper. 5-iodo-1,4-disubstituted-1,2,3-triazole and 5-bromo-1,4-disubstituted-1,2,3-triazole can be effectively prepared from terminal alkyne, organic azide and CuI or CuBr in the presence of 0.5 equiv. TBDMSCl. The advantages in the current work include inexpensive and green O_2 as oxidant, use of mild and non-oxidative additive, and

wider scope of substrate compared to the existing methods. The high tolerance of sensitive groups and successful application on nucleoside analogues make potential of this method for design and synthesis of biomolecules and their mimics. The further mechanism studies on chlorosilane-activated aerobic oxidative halogenation and application of this new pathway for the preparation of natural product analogues are underway in our lab.

Experimental Section

Typical Procedure for the One-pot Tricomponent Reaction for the Synthesis of 5-Halo-1,2,3-triazole. A mixture of **1** (0.17 mmol), **2** (0.17mmol), CuX (0.17mmol), DIPEA (0.17 mmol), and TBDMSCl (0.08 mmol) in 3 mL of anhydrous CH_3CN was stirred at room temperature under dry air atmosphere for 18 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 to give compound **3**.

Acknowledgments

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Supporting Information Available: Characterization of compounds **3a-3q** and full

spectroscopic data for all new compounds.

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