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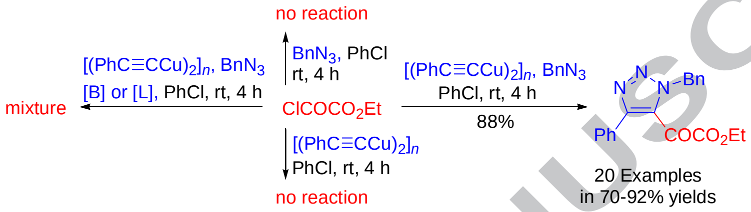

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ABSTRACT

We found that alkoxalyl chloride ($ClCOCO_2R$) did not carry out an acylation on 1-copper(I) alkyne in solvent without additives, but chemoselectively on 5-copper(I) 1,2,3-triazole (an intermediate in cycloaddition of 1-copper(I) alkyne and azide). Thus, a one-pot preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazole was achieved by simply stirring the mixture of 1-copper(I) alkyne, azide and alkoxalyl chloride at room temperature for 4 h.

Since CuAAC reaction was discovered in 2002,[1] the applications of 1,2,3-triazole have been increased continuously in organic synthesis, biology and material science.[2] As shown in Figure 1, all types of substituted 1,2,3-triazoles (**1-4**) have been prepared by metal-catalyzed cycloaddition of alkynes and organoazides to data. Recently, many 1,4,5-trisubstituted 1,2,3-triazoles (**4**) have shown novel properties[3] and more of them are expected because they possess the most substituents and structural diversity. But, their preparation remains a challenging task comparing with other types of 1,2,3-triazoles (**1-3**).

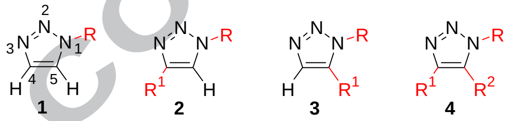

Figure 1. 1,2,3-Triazoles from metal-catalyzed cycloaddition of alkynes and organoazides.

Among all types of 1,2,3-triazoles, 1,4-disubstituted 1,2,3-triazole (**2**) could be prepared most easily by CuAAC reaction.[2a,2h,2i,4] As shown in Figure 2, realizing 5-Cu(I)-1,2,3-triazole (**8**) was the intermediate of CuAAC reaction,[1a,5] many attempts have been made to trap **8** by an exogenous electrophile (E^+) to prepare 1,4,5-trisubstituted 1,2,3-triazoles (**4**) in the early studies.[6] But, the desired product **4** usually was obtained as a mixture accompanied by **2** as a byproduct. This drawback is inevitably caused by the fact that two electrophilic substitutions on the Cu-C bond of **8** occurred competitively between the exogenous electrophile E^+ and the endogenous electrophile H^+ (from the terminal alkyne **5**).

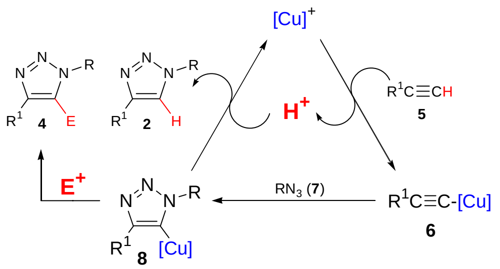

Figure 2. Competitive electrophilic substitution between E^+ and H^+.

Thus, the cycloadditions of some structurally novel 1-substituted alkynes have been developed to overcome the

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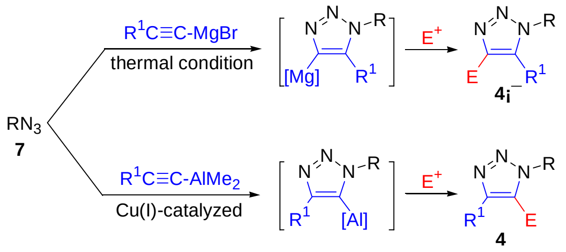
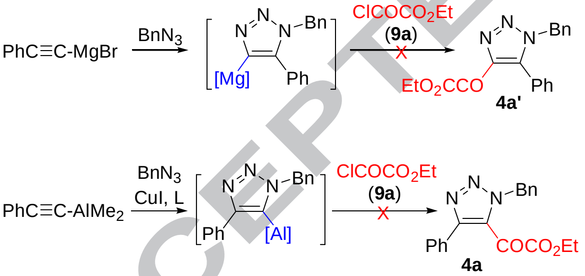
Corresponding author. Tel.: +86-10-62795380; fax: +86-10-62771149; e-mail: yfh@mail.tsinghua.edu.cn drawbacks caused by the terminal alkynes. For example, 5-bromo,[7] 5-iodide[8] and 5-Au-1,4,5-trisubstituted 1,2,3-triazoles[9] were prepared smoothly from the corresponding 1-bromo, 1-iodide and 1-Au-alkynes. Both 1-Mg[10] and 1-Al-alkynes[11] have become considerably important because they could be used to prepare a range of 1,4,5-trisubstituted 1,2,3-triazoles. As shown in Scheme 1, each of them initially carried out a cycloaddition to give 4-Mg or 5-Al-1,2,3-triazole as an intermediate, respectively. Then, the intermediates were trapped by a variety of electrophiles, such as D_2O, I_2, CO_2, $ClCO_2Me$, PhCHO, PhCNO, $(CCl_3)CO_3$ or $ClCONR_2$, to give the corresponding products **4’** or **4**.

Scheme 1



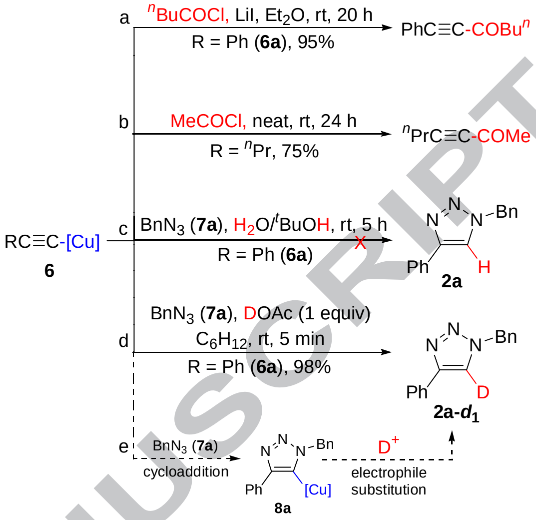
Recently, our research projects need a number of 1,4,5-trisubstituted 1,2,3-triazoles. Among three substitutents, at least one is electron-withdrawing-group and 2-alkoxy-1,2-dioxoethyl group ($-COCO_2R$) is one of them. Unfortunately, the complicated mixtures were obtained by using ethoxalyl chloride ($ClCOCO_2Et$, **9a**) as an electrophile under the standard conditions of 1-Mg-alkyne or 1-Al-alkyne. As shown in Scheme 2, the problems may be caused by the incontrollable reactivity of the M-C bonds in the intermediates. In fact, no acylation product was reported to be prepared from 1-Mg-alkyne or 1-Al-alkyne in their original articles.[10,11]

Scheme 2



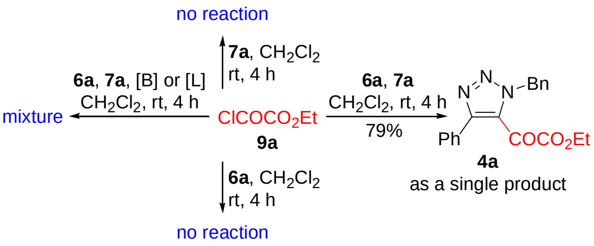
Thus, there is a necessary to find other 1-metal alkynes for our synthetic purpose. We were surprised to find that 1-Cu(I)-alkyne (**6**) has been recognized as an intermediates in CuAAC reaction, but it never used for the preparation of 1,4,5-trisubsituted triazoles. However, the investigation of literature gave us two opposite suggestions. As shown in Scheme 3, one indicated that **6** could not be used for our purpose because it directly reacted with acyl chlorides to give -ynones in moderate to high yields in the presence of an additive (base or ligand) (entry a)[12a-c] or under solvent-free conditions (entry b).[12d] Furthermore, 1-Cu(I)-phenyethyne (**6a**) has proven to be ineffective in its cycloaddition with benzyl azide (**7a**) under Sharpless conditions (entry c).[5,13] On the contrary, the other one implied that **6** may work well for our purpose because it reacted with acyl chlorides extremely slow in solvents without additives.[12] Additionally, 5-D-1-benzyl-4-phenyl-1,2,3-trazole (**2a-*d*$_1$**) was produced in 98% yield from the cycloaddition of **6a** and **7a** when DOAc was used as an electrophile (entry d).[13] This result indicated that the cycloaddition of **6a** and **7a** proceeded indeed and 5-Cu(I)-1,2,3-triazole (**8a**) must be an intermediate (entry e).

Scheme 3



Thus, a group of conditional experiments were tested. As shown in Scheme 4, the experiments proved that **9a** reacted neither with **6a** nor with **7a** in CH_2Cl_2 without additives. In the presence of a base or a ligand, such as NEt_3, DIPEA, 1,10-phenanthroline or pyridine, the suspension of **6a**, **7a** and **9a** in CH_2Cl_2 gave a complicated mixture as a result. To our delight, the same suspension gave the desired product **4a** in 79% yield as a single product under the base-free or ligand-free conditions. Furthermore, the structure of 1-(3-methylbutyl)-4-phenyl-5-(2-ethoxy-1,2-dioxoethyl)-1,2,3-triazole (**4h**) was confirmed by single crystal X-ray diffraction analysis (Figure 3).

Scheme 4



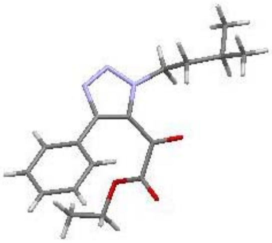
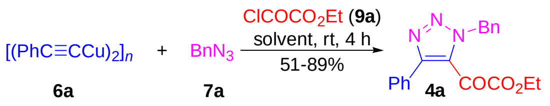


Figure 3. The structure of **4h**.

The regioselective formation of **4a** (but not **4a’**) confirmed that the cycloaddition of **6a** and **7a** have occurred to give **8a** as an intermediate. It also revealed a rare chemoselectivity that **9a** preferred to carry out an acylation on the intermediate **8a** (with an *in situ* formed Cu-C bond) rather than on the substrate **6a** (with a pre-made Cu-C bond). This may result in the fact that **6a** structurally is a metal cluster (also a polymeric dinuclear complex)[14] with extremely chemical stability. Since copper-catalyzed cycloaddition between **6a** and **7a** is a "click reaction" having a high thermodynamic driving force, therefore the cycloaddition occurred preferentially. As shown in Table 1, this method is so easy that it could be operated in most common solvents (entries 1-7). As shown in entries 8 and 9, the aromatic solvents gave the best yields. Finally, the entry 9 was assigned as our standard conditions because chlorobenzene also was a good solvent for other substrates.

Table 1. The effect of solvent on the reaction[a]



Entry	Solvent	Yield of **4a** (%)[b]
1	1,4-dioxane	51
2	MeCN	53
3	THF	62
4	$CHCl_3$	65
5	$BrCH_2CH_2Br$	78
6	CH_2Cl_2	79
7	$ClCH_2CH_2Cl$	84
8	C_6H_5Me	87
9	C_6H_5Cl	89

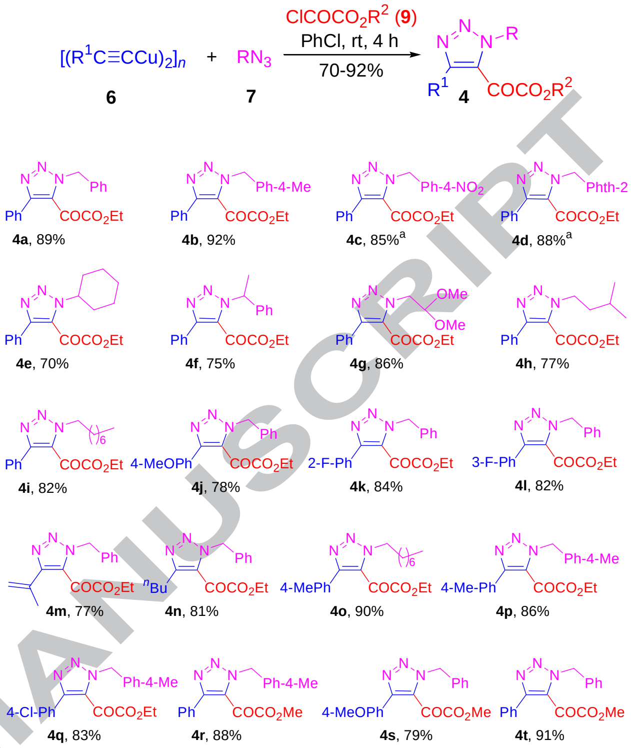
[a] To the suspension of **6a** (82 mg, 0.5 mmol) and **7a** (80 mg, 0.6 mmol) in solvent (1 mL) was added **9a** (68 mg, 0.5 mmol) dropwise. The resultant mixture was then stirred at room temperature for 4 h in air.

[b] The isolated yields were obtained.

As shown in Scheme 5, this method was quite general for wide range of substrates. By fixing 1-Cu(I)-phenyethyne (**6a**), different azides were tested to give the desirable products **4a-4i**. The product **4e** was obtained in the lowest yield possibly because the cyclohexyl azide has bulky size. By fixing benzyl azide (**7a**), the tested 1-Cu(I)-alkynes (prepared from alkyl or aryl substituted alkynes) all gave the desirable products **4j-4n** in comparable yields. It is worthy to note that no matter the products were obtained in good or excellent yields, they were the only products in the reaction with very easy work-up procedures. Under the standard conditions, products **4a** and **4h** have been synthesized in five grams scales to give the similar yields.

In conclusion, we found that 1-Cu(I)-alkyne does not react with alkoxalyl chloride in solvent under base-free and ligand-free conditions since it is a metal cluster and has extremely chemical stability. But it can be converted into 5-Cu(I)-1,4,5-trisubstituted 1,2,3-triazole intermediate by cycloaddition with azides. Thus, a rare chemoselectivity was discovered, by which the Cu-C bond in 5-Cu(I)-1,2,3-triazole intermediate (*in situ* formed) was trapped selectively by alkoxalyl chloride in the presence of 1-Cu-alkyne (pre-made). Finally, a novel one-pot three-component method for efficient preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazoles was established. This novel chemoselectivity also be observed by using other electrophiles, further works for preparation of a series of 1,4,5-trisubstituted 1,2,3-triazoles will be reported in due course.

Scheme 5



a. Products **4c** and **4d** were obtained by using CH_2Cl_2 as reaction solvent.

Acknowledgments

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Supplementary Material

Supplementary data (Experiments, characterization, ^{1}H NMR and ^{13}C NMR spectra for products **4a-4t**, as well as and CIF file for the single crystal X-ray diffraction analysis of **4h**.) associated with this article can be found, in the online version, at http://dx.doi.org/

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