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Copper(I)-Catalyzed Three-Component Click/Persulfuration Cascade: Regioselective Synthesis of Triazole Disulfides

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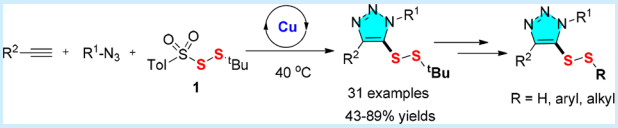
Supporting Information

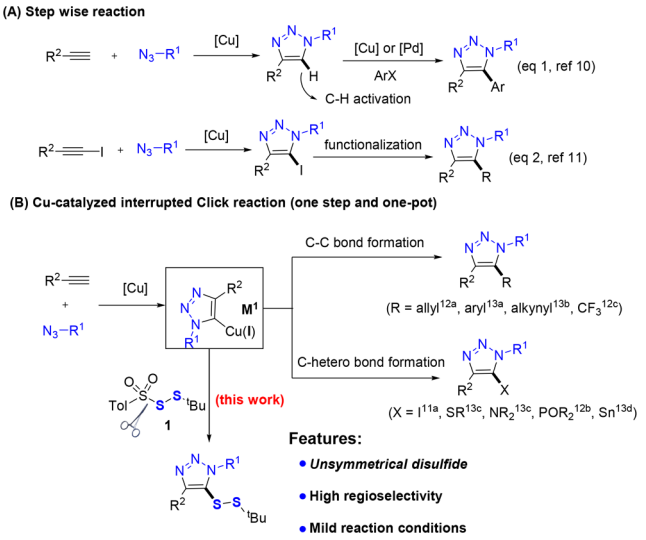
ABSTRACT: A copper(I)-catalyzed three-component CuAAC/persulfuration reaction providing rapid access to asymmetric triazole disulfides has been developed. The interrupted click reaction shows broad substrate scope, complete regioselectivity, and excellent functional group tolerability.



In 2002, the Sharpless[1] and Meldal[2] groups independently reported a copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction, and this has been established as a prime example of "click chemistry" for assembling complex molecules widely used in organic chemistry,[3] polymer chemistry and materials science,[4] and biological conjugation.[5] A CuAAC reaction regioselectively delivers 1,4-disubstituted 1,2,3-triazoles from terminal alkynes under extremely mild conditions; however, such reaction of internal alkyne affording trisubstituted triazoles is much more difficult under the classic CuAAC conditions, because internal alkynes could not form the key copper acetylide intermediate with a copper(I) catalyst. The recently developed RuAAC[6a] and IrAAC[6b] reactions have partially addressed this challenge; however, the regioselectivities are highly substrate-dependent and noble metal catalysts are required. Thus, the development of an unified strategy to access diverse fully substituted triazoles beyond click chemistry has been an important yet challenging priority,[7] especially given that such nitrogen heterocyclic compounds are indispensable motifs in medicinal chemistry[8] and important ligands,[9a] directing groups,[9b] and carbene precursors[9c] in organic synthesis.

Recently, a CuAAC reaction and subsequent copper- or palladium-catalyzed direct arylation reaction have been developed[10] (eq 1 in Scheme 1A); however, quite harsh conditions are required to cleave the inert C−H bond. Direct cycloaddition of iodoalkynes with azides could afford 5-iodo-1,2,3-triazoles, which could be transformed to fully substituted triazoels via Pd-catalyzed coupling reactions (eq 2, Scheme 1A).[11] Multiple reaction steps are required in all of these reactions. The recently developed interrupted click reaction is the most straightforward approach to build fully substituted triazoles from easily available terminal alkynes with a multicomponent reaction in one step and in one pot (Scheme 1B).[12,13] The cuprate-triazole **M**[1] is the key intermediate in a CuAAC reaction. By using active electrophilic reagents such as ICl[11a] and allyl iodide,[12a] or proper nucleophilic reagents such as H-phosphate[12b] and $TMSCF_3$[12c] under oxidative conditions to intercept this in-situ-formed intermediate **M**[1], densely functionalized trisubstituted triazoles were constructed via a cascade C−C or C−heteroatom bond formation sequence. For instance, we recently applied a Cu/Pd transmetalation step to intercept **M**[1], diverse 5-arylated trisubstituted triazoles were regioselectively synthesized in excellent yields in one step.[13a] Very recently, we noticed that a proper electrophilic reagent, which is active enough, but does not affect the cycloaddition reaction of copper acetylide with azide, could be applied in an interrupted click reaction to construct fully substituted triazoles. For instance, bromoalkynes can be used in the three-

Scheme 1. Synthesis of the Fully Substituted 1,2,3-Triazoles by CuAAC Reaction



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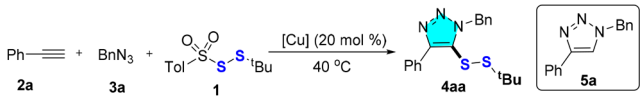
component reaction to intercept the intermediate $\mathbf{M^1}$ to construct 5-alkynyl-1,2,3-triazoles.[13b] Benzenesulfonothioate, which is an active electrophilic sulfenylating reagent as a result of the good leaving properties of benzenesulfinate, has also been utilized in this interrupted click reaction to generate 5-thio triazoles.[13c] Following this concept, we were intrigued by the question of whether an electrophilic persulfur reagent SS-*t*-butyl *p*-toluenesulfono(dithioperoxoate) (**1**) could intercept the intermediate $\mathbf{M^1}$ to construct triazole disulfide (Scheme 1B). Disulfides, which exist extensively in natural products[14] and commercial peptide drugs, present wide application in food chemistry,[15a] pharmaceutical industry,[15b] and chemical biology.[15c,d] Symmetrical disulfides can be easily formed by oxidative coupling of thiols, but the synthesis of asymmetric disulfides is still a challenge in organic synthesis, and it has drawn tremendous attention for decades.[16] In this communication, we report our preliminary results.

SS-*t*-butyl *p*-toluenesulfono(dithioperoxoate) (**1**) was synthesized in one step by the reaction of potassium *p*-toluenesulfonothioate with *t*-butyl thiochloride formed in situ (see the Supporting Information (SI) for details).[17] The reaction was scaled up to 4.3 g and **1** was isolated in 78% yield as a bench-stable oil. There are two weak S−S bonds in this compound, and the good leaving tendency of the arylsulfone moiety may help cleave the thioester bond, rather than the persulfur bond, realizing the desired electrophilic persulfur transfer reaction. To test this hypothesis, phenlyacetylene **2a**, benzyl azide **3a**, and **1** were selected as model substrates to optimize the reaction conditions (see the SI for details). We first investigated the influence of solvents (toluene, aceonitrile (MeCN), hexane, dioxane, dimethylsulfoxide (DMSO), 1,2-dichloroethane (DCE), and tetrahydrofuran (THF)) (see Table 1, entries 1−7) in the presence of 20 mol % CuI and LiO^{t}Bu as the base. The normal click product 1,4-disubstituted 1,2,3-triazole **5a** is the major side product, and, to our delight,

Table 1. Optimization of Reaction Conditions[a]



2a 3a 1 4aa 5a

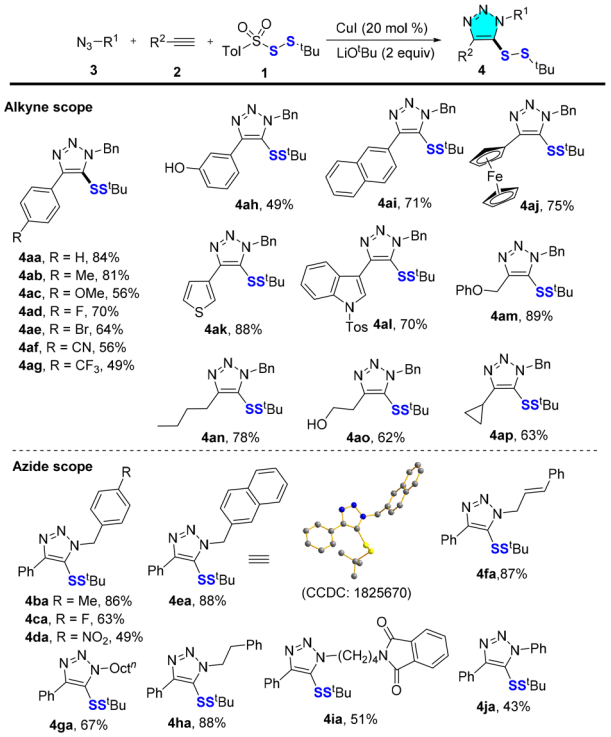
entry	cat.	base	solvent	Yield[b] (%) 4aa	5a
1	CuI	LiO^{t}Bu	toluene	69	11
2	CuI	LiO^{t}Bu	CH_3CN	66	trace
3	CuI	LiO^{t}Bu	hexane	32	54
4	CuI	LiO^{t}Bu	dioxane	75	12
5	CuI	LiO^{t}Bu	DMSO	23	58
6	CuI	LiO^{t}Bu	DCE	73	trace
7	**CuI**	**LiO^{t}Bu**	**THF**	**90 (84%)**	**trace**
8	CuI	Et_3N	THF	12	76
9	CuI	KO^{t}Bu	THF	30	57
10	CuI	Cs_2CO_3	THF	40	47
11	$CuSO_4$	LiO^{t}Bu	THF	trace	trace
12	CuSCN	LiO^{t}Bu	THF	83	13
13	TcCu	LiO^{t}Bu	THF	63	21
14[c]	CuI	LiO^{t}Bu	THF	81	trace

[a]Reaction conditions: **2a** (0.2 mmol), **3a** (0.3 mmol), **1** (0.4 mmol), [Cu] (20 mol %), base (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), solvent (1 mL) was stirred at 40 °C under N_2 atmosphere for 12 h. [b]Determined by ^{1}H NMR using trimethoxybenzene as the internal standard. The isolated yield is shown in parentheses. [c]At 25 °C.

the undesired alkyne persulfuration reaction and possible desulfuration reaction were not observed in the reaction system. THF was the best solvent affording the desired product **4aa** in 84% isolated yield and almost no side products were observed under this condition, which is the optimal reaction condition (Table 1, entry 7). Further optimization of different bases and different copper catalyst finds that LiO^{t}Bu and CuI are still the optimal choices (Table 1, entries 8−13). With the addition of phosphine or nitrogen ligands into the reaction system, the side product **5a** increased (for details, see the SI). The reaction proceeds efficiently at room temperature, giving slightly lower 81% NMR yield (Table 1, entry 14).

After establishing the optimal reaction conditions, the three-component click/electrophilic persulfuration reaction was investigated comprehensively (see Scheme 2). A wide range

Scheme 2. Scope for Three-Component Electrophilic Persulfuration[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), **3** (0.3 mmol), CuI (20 mol %), LiO^{t}Bu (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), THF (1 mL) was stirred at 40 °C under N_2 atmosphere for 12 h. Isolated yields were reported.

of various terminal alkynes, including aromatic and aliphatic alkynes, was evaluated and a large variety of 5-persulfur functionalized triazoles were obtained in moderate to excellent yields and as single regioisomers. Aromatic alkynes bearing an electron-rich or electron-poor phenyl ring, or naphthalene, ferrocene, and heterocycles such as indole and thiophene were all applicable in this transformation and gave good yields of the corresponding products (**4aa**−**4al**). Notably, electron-rich aromatic rings and free phenol groups remain intact under these electrophilic reaction conditions. A series of functional groups such as methoxyl, fluoro, bromo, cyano, trifluoromethyl are well-tolerated in this reaction, thus allowing further functionalization as necessary. Aliphatic alkynes (**4am**−**4ap**) are also suitable for this transformation.

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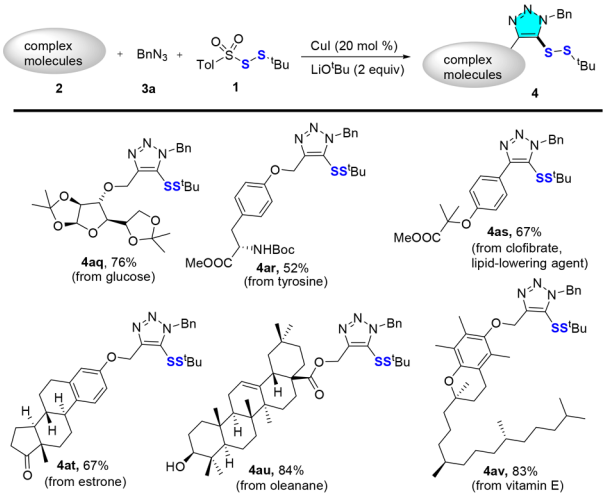
Alkynes substituted with a cyclopropyl ring (**4ap**) also react efficiently under the standard conditions, furnishing the desired triazoles in 63% yield.

The scope of the transformation, with respect to various azides, was explored (Scheme 2). All the aliphatic azides tested reacted smoothly under standard conditions, giving the corresponding disulfides (**4ba**–**4ia**) in good to excellent yields. The structure of **4ea** was unambiguously characterized by single-crystal X-ray crystallography. An aromatic azide such as 2-azidobenzene also produces the target product (**4ja**) in 43% yield.

Next, we explored the possibility of applying this transformation in the late-stage functionalization of bioactive natural products and pharmaceuticals. The results are shown in Scheme 3. Functionalized alkynes derived from glucose,

Scheme 3. Late-Stage Click/Electrophilic Persulfuration of Complex Molecules[a]

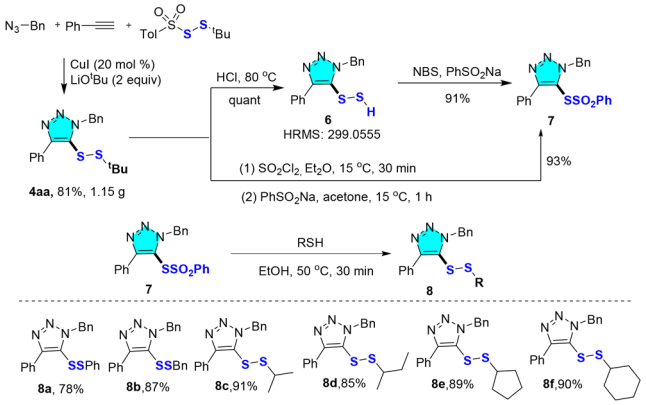


[a]Standard conditions were employed and isolated yields were reported.

tyrosine, clofibrate (which is a cardiovascular drug), estrone, oleanane triterpenes, and vitamin E can easily be transformed to the corresponding triazole disulfides in good yields under the standard conditions. These reactions suggest that this transformation has good potential for the discovery of interesting new biologically active molecules.

Scaling up of this reaction to the gram scale under the standard conditions was accomplished and 1.15 g of the disulfide (**4aa**) was isolated in 81% yield (see Scheme 4). Further synthetic transformations of the synthetic disulfide were also explored. The protecting *t*-butyl group can be removed under acidic conditions, giving the hydropersulfide (**6**) in quantitive yield. Hydropersulfides (RSSH) play a very important role in redox cell signaling[18] and are key intermediates in the function of anticancer natural products.[19] This reaction offers an efficient approach to this unstable and short-lived intermediate. The hydropersulfide (**6**) can be transformed under oxidative conditions in 91% yield into the triazolebenzenesulfonothioate (**7**), which can also be synthesized from the disulfide (**4aa**) in 93% yield by the sequential reaction with SO_2Cl_2 and $PhSO_2Na$. By the reaction of various thiols with this electrophilic triazolebenzenesulfonothioate (**7**), various aromatic- or aliphatic-substituted unsymmetrical

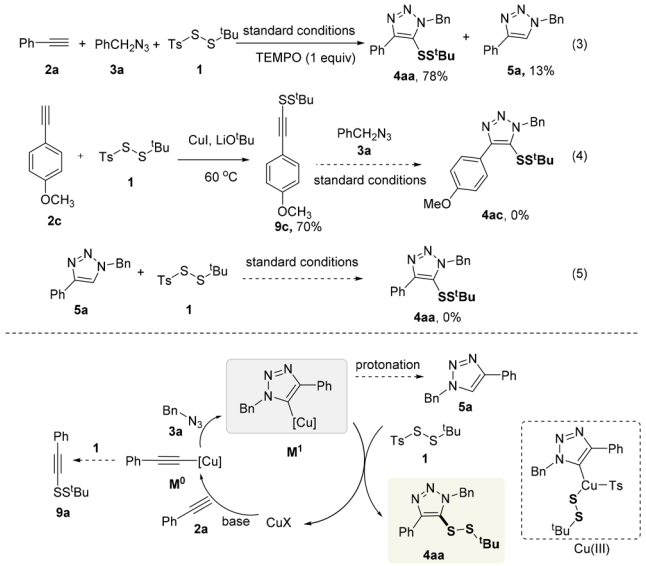
Scheme 4. Further Synthetic Applications of Triazole Disulfide



triazole disulfides (**8a**–**8f**) were synthesized in good to excellent yields.

To gain an improved understanding of the reaction mechanism, several controlled experiments were conducted (see Scheme 5). The reaction proceeded well when 1 equiv of

Scheme 5. Control Experiments and Proposed Mechanism



tetramethylpiperidine-1-oxyl (TEMPO) was added into the standard reaction, which indicated that a radical reaction may not be involved (eq 3 in Scheme 5). Disulfide **9c** could be obtained in 70% yield by the reaction of terminal alkyne **2c** with **1** at relative higher temperature (60 °C) in the presence of a copper catalyst, and such reactions failed at lower temperature. The reaction of **9c** with benzyl azide (**3a**), under standard conditions, failed to afford triazole **4ac**, indicating that **9c** is not the reaction intermediate (eq 4 in Scheme 5). Disubstituted triazoles (**5a**) failed to react with **1** to form **4aa** (eq 5 in Scheme 5), indicating click reaction and subsequent C–H functionalization pathway is not possible.

Based on these experiments, a possible mechanism was proposed (Scheme 5). First, the reaction of CuI and terminal alkyne in the presence of base generating copper(I) acetylide $\mathbf{M}^0$. The relatively low reactivity of copper(I) acetylide toward electrophiles results in its fast cycloaddition with an azide to

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form the key cuprate-triazole intermediate ($\mathbf{M^1}$). This aryl copper(I) intermediate is more nucleophilic than copper(I) acetylide and it could react with the persulfur electrophile (**1**) to form the triazole disulfide (**4aa**). This step might occur through an oxidative addition and reductive elimination sequence to regenerate the Cu(I) catalyst.

In summary, we have developed an efficient click/electrophilic persulfuration reaction to construct triazole disulfides. Such compounds, containing the important triazole and disulfide moieties, are very useful in medicinal chemistry. Notable features of this method include very simple and mild reaction conditions, inexpensive copper catalysts, a very broad substrate scope, and applicability in late-stage functionalization of complex bioactive compounds. Further application of this interrupted click reaction is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01002.

Experimental details and spectral data for new compounds (PDF)

Accession Codes

CCDC 1825670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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