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Copper-Catalyzed Tandem Reaction of Terminal Alkynes and Sulfonyl Azides for the Assembly of Substituted Aminotriazoles

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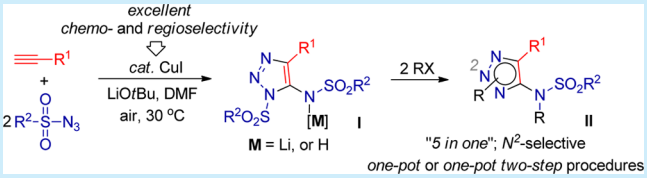
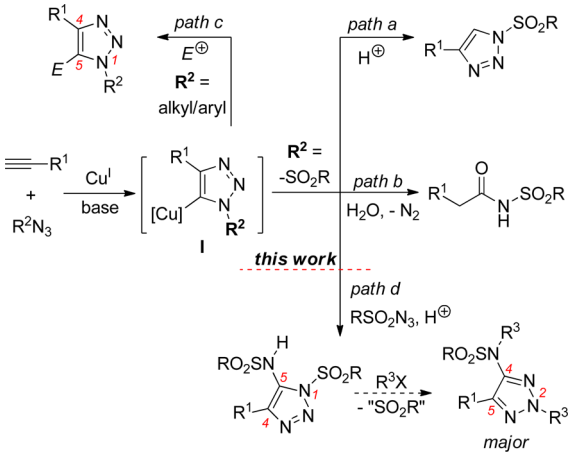
Supporting Information

ABSTRACT: A simple combination of CuI/LiO*t*Bu/DMF enables the tandem Huisgen [3 + 2] cycloaddition/amidation reaction of terminal alkynes and sulfonyl azides to 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles **I**, which can undergo an alkylation/desulfonation sequence to deliver highly substituted aminotriazoles **II** by one-pot or one-pot, two-step procedures.



The copper-catalyzed azide−alkyne cycloaddition (CuAAC) is among the most important click reactions because of its efficiency and biocompatibility.[1,2] This stepwise Huisgen [3 + 2] cycloaddition process provides a reliable method for the regioselective construction of 1,4-disubstituted-1,2,3-triazoles with 5-cuprated triazole **I** as the key intermediate (Scheme 1).[3] In this regard, it is well-known that the transformations of sulfonyl azide substrates appear somewhat different from those of alkyl or aryl azides because the corresponding *N*-sulfonyltriazole intermediates (**I**, R^2 = $-SO_2R$) are less stable than the *N*-alkyl/aryltriazole species (**I**, R^2 = alkyl or aryl).[4] The pioneering investigations[5] by Chang, Fokin, and Sharpless have elegantly demonstrated that judicious choice of reaction conditions could enable the Cu-catalyzed conversion of sulfonyl azides and terminal alkynes to either conventional triazoles (Scheme 1, path a) or denitrogenation/hydration products (Scheme 1, path b) with excellent selectivity, which cannot be attained by Huisgen thermal approaches.[6] On the other hand, probably due to the obstacle arising from their inherent ring-opening/denitrogenation tendency, very limited attention has been devoted to capturing these *N*-sulfonyltriazole species with an electrophile to produce 1,4,5-trisubstituted triazoles,[5c,7] although significant progress has recently been achieved in the similar transformations of their *N*-alkyl/aryl counterparts with a wide scope of electrophiles (Scheme 1, path c).[8] In the latter case, notably, terminal alkynes have been successfully employed to assemble alkynyl-substituted triazoles via C−C bond formation.[9]

Scheme 1. Copper-Catalyzed Reactions of Organic Azides and Terminal Alkynes



Herein, we present a chemo- and regioselective Cu-catalyzed tandem reaction of two sulfonyl azides and a terminal alkynes upon treatment with stochimetric amounts of LiO*t*Bu in DMF, leading to the formation of 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles (Scheme 1, path d). Intriguingly, the combination of this transformation with a subsequent alkylation/desulfonation sequence provides an expedient access to highly substituted aminotriazoles. To the best of our knowledge, the use of organic azides to capture the cuprated triazole intermediates deriving from a CuAAC reaction remains unsuccessful in the published literature, although these reagents have recently emerged as versatile amino sources in organic synthesis for transition-metal-catalyzed C−H amination reactions.[10]

This study was initiated by a serendipitous finding that the mixture of ethynylbenzene (**1a**) and 4-methylbenzenesulfonyl azide (**2a**) in THF could give 5-sulfamide-1,2,3-triazole **3a** in 35% yield upon treatment with CuI (10 mol %) and LiO*t*Bu (120 mol %);[11] however, compound **3a** was unstable in the case of being free of any solvents (Scheme 2).[12] Given the increasing significance of substitued 1,2,3-triazole units as ubiquitous structural motifs in bioactive molecules[13] and functional materials[14] as well as readily accessible scaffolds in organic synthesis,[15] preliminary investigation on the formation of triazole **3a** was carried out. While switching the solvent THF to CH_2Cl_2 could not afford any desired product, the use of DMF instead furnished **3a** in excellent yield. Remarkably, in DMF, both the ratio of substrates (**1a**/**2a** = 1:1, 0.6:1, and 0.3:1) and the addition of H_2O showed slightly influence on the

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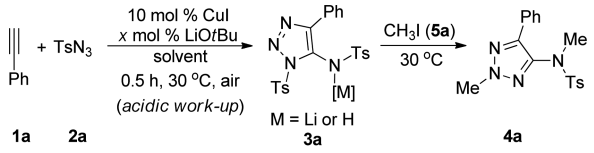
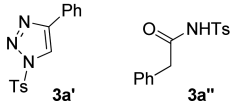
Scheme 2. Copper-Catalyzed Reaction of Two Azides and an Alkyne[a]



1a / 2a (mol/mol)	solvent	x (mol %)	3a yield
1:1	THF	120	35%
1:1	CH_2Cl_2	120	—
1:1	DMF	120	95%
0.6:1	DMF	120	95% (90%)
0.3:1	DMF	120	90%
0.6:1	DMF	60	90%

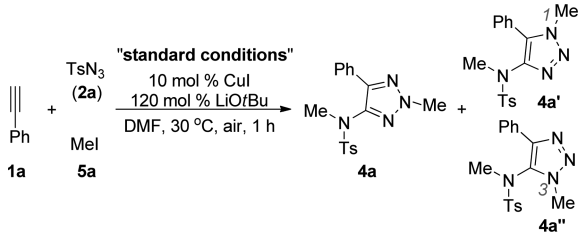


[a]Reaction conditions: **2a** (0.4 mmol), **1a**, LiO*t*Bu (*x* mol %), CuI (0.04 mmol, 10 mol %), solvent (2 mL), 30 °C, 0.5 h. Yields were determined by ^{1}H NMR analysis. Yield in parentheses for an entry in the presence of H_2O (4 mmol).

product yield and cleanly furnished **3a** without detectable 1,4-disubstituted triazole **3a′** or imide **3a″**. As expected, reducing the amount of LiO*t*Bu from 120 to 60 mol % also prompted this reaction with comparable results. However, when triethylamine (120 mol %) was used as the base in DMF, imide **3a″** was isolated as the product (35%) instead. To our delight, it was found that 2,4,5-trisubstituted triazole **4a** could be readily afforded by in situ methylation using excess amounts of iodomethane (**5a**) with concurrent elimination of a tosyl group. This result demonstrated the feasibility of *N*-tosyltriazole **3a** as an easily available substrate for the synthesis of N^2-substituted triazole compounds.[16]

Encouraged by these results, we chose alkyne **1a** and azide **2a** as the model substrates with iodide **5a** as the alkylating reagent to prepare highly substituted triazole compounds (Table 1). Intriguingly, the Cu-catalyzed reaction of **1a** and **2a** could be accomplished in the presence of **5a** and directly gave the desired N^2-alkylated product **4a** in 73% isolated yield with 10 mol % of CuI and 120 mol % of LiO*t*Bu in DMF at 30 °C for 1 h under air atmosphere (Table 1, entry 1), along with 23% of an unseparated mixture of N^1- and N^3-methyl isomers **4a′** and **4a″**. Control experiments showed that no obvious variation in the yield was observed when this reaction was manipulated by a one-pot, two-step procedure (Table 1, entry 2). While decreasing the amount of CuI from 10 to 5 mol % also worked well despite requiring an extended reaction time (6 h), other copper salts such as CuCl, $Cu(OAc)_2$, and CuTC reduced the yield significantly (Table 1, entries 3−6). It appeared that solvents dramatically influenced the reaction outcomes; for example, the yield was reduced to 29% with THF as the solvent instead, and the targeted product was not detected in CH_2Cl_2 (Table 1, entries 7 and 8). Several inorganic bases including LiO*t*Bu, KO*t*Bu, LiOH, and Cs_2CO_3 performed this reaction in varying yields, while Et_3N could not give the desired product (Table 1, entries 9−13). Finally, in the presence of H_2O or under nitrogen atmosphere, the reaction proceeded smoothly to produce the targeted compound **4a** in similar yields (Table 1, entries 14 and 15).

Table 1. Optimization of Reaction Conditions[a]



entry	variation of standard conditions	4a[b] (%)
1	none	73
2	**5a** was added after the reaction of **1a** and **2a**	72
3	5 mol % of CuI and 6 h	70
4	CuCl and 4 h instead of CuI and 1 h	40
5	$Cu(OAc)_2$ and 4 h	25
6	CuTC and 4 h	54
7	THF and 4 h instead of DMF and 1 h	29
8	CH_2Cl_2 and 4 h	
9	60 mol % LiO*t*Bu	45
10	KO*t*Bu and 2 h instead of LiO*t*Bu and 1 h	32
11	LiOH and 4 h	58
12	Cs_2CO_3 and 4 h	61
13	Et_3N and 4 h	
14	4 mmol of H_2O was added	67
15	N_2 instead of air	70

[a]Standard conditions: **2a** (0.4 mmol), **1a** (0.24 mmol), MeI (0.6 mmol), CuI (0.04 mmol, 10 mol %), LiO*t*Bu (0.48 mmol, 120 mol %) in DMF (2.0 mL), 30 °C, under air for 1 h. [b]Isolated yield. CuTC = copper(I) thiophene-2-carboxylate.

With the optimized reaction conditions in hand, we next evaluated the scope of substrates (Scheme 3). Thus, a set of benzenesulfonylazides containing different substituents readily underwent the reaction with alkyne **1a** and MeI (**5a**) to afford products **4a**, **4c**, and **4d** along with their regioisomers in 87−96% combined yields, respectively. On the other hand, the scope of monosubstituted acetylenes **1** was also tested with **2a** and **5a** as the reaction partners. Variation of substituent R^1 showed that different ethynylbenzenes bearing an electron-donating group (−OMe, −Me) or an electron-withdrawing group ($-NO_2$), as well as a chlorine at the *para*-position of benzene rings, partook in the reaction efficiently, giving triazoles **4e−h** and their isomers. 2-Ethynylbenzaldehyde was also a suitable partner, albeit with reduced yield (**4i**). Other aryl alkynes including 4-ethynylbenzo[*d*][1,3]dioxole, 1-ethynylnaphthalene, and 2-ethynylthiophene readily underwent this conversion to furnish **4j−l**. Aliphatic substituents such as phenylethynyl, 1-cyclohexenyl, cyclopropyl, and 3-chloropropyl could also be introduced to this reaction, delivering the targeted compounds **4m−p** in reasonably good yields, considering the functional group tolerance. Meanwhile, it was observed that alkylating agents **5** could control the regioselectivity of *N*-alkylation reactions presumably due to a steric hindrance effect; for example, the use of benzyl bromide **5b** gave N^2-alkylation compounds **4q** (65%), **4r** (81%), and **4s** (72%), respectively, accompanied by trace amounts of N^1- and N^3-isomers.

While a mixture of **1a**, **2a**, and allylic bromides **6** under the standard conditions led to complicated products, an alternative one-pot, two-step procedure worked well and cleanly gave the desired products **4t** and **4u** in 79% and 71% yield, respectively (eq 1).

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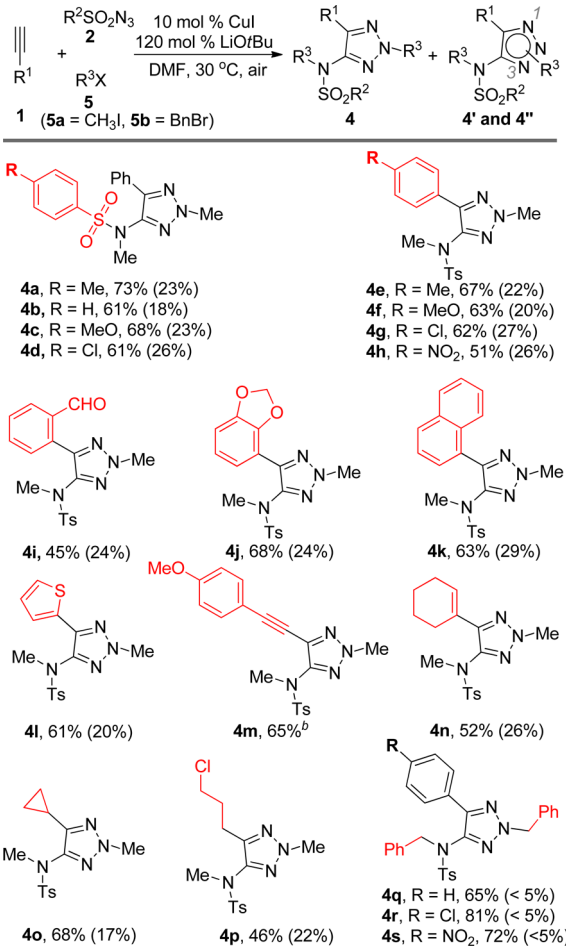
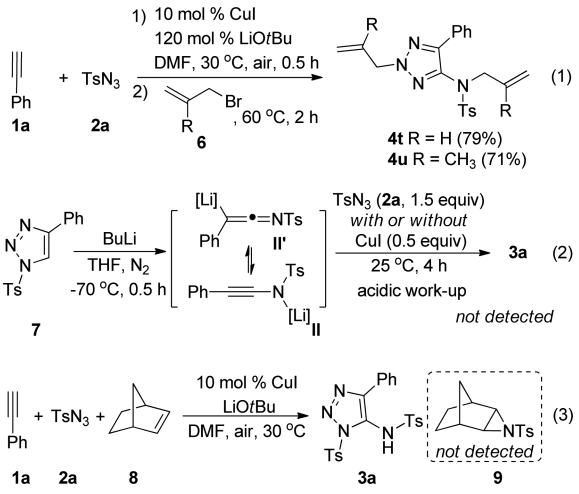
Scheme 3. Substrate Scopes for One-Pot Synthesis of 4[a]



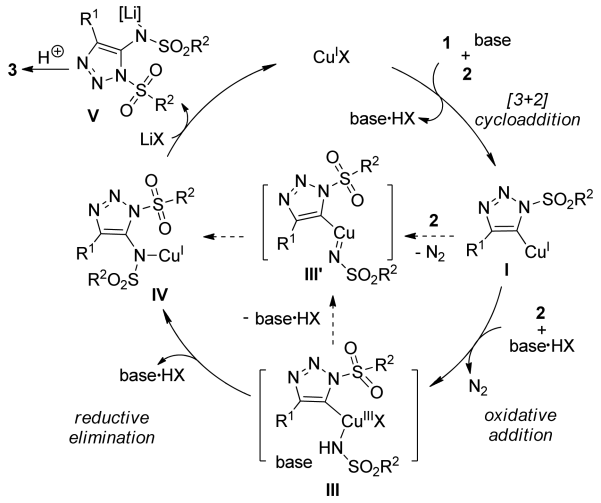
[a]**2** (0.4 mmol), **1** (0.24 mmol), **5** (0.6 mmol), CuI (0.04 mmol, 10 mol %), LiO*t*Bu (0.48 mmol, 120 mol %), DMF (2.0 mL), 30 °C, air, 1−4 h. Yields are of the isolated products. Yields in parentheses are of the mixtures of **4′** and **4′′**. [b]Mixtures of **4m** and one isomer in 2.3:1 ratio according to ^{1}H NMR spectra.



To gain insight into this copper-catalyzed transformation to **3**, control experiments using 1-sulfonyltriazole **7** and azide **2a** were conducted (eq 2). After complete decomposition[5c,17] of **7**, as detected by TLC, subsequent addition of azide **2a** could not generate triazole **3a** at all in the presence or absence of CuI, indicating that neither ynamidate **II** nor its tautomer metalated ketenimine **II′** was a key intermediate leading to product **3a** through a possible [3 + 2] cycloaddition.[18] On the other hand, addition of norbornylene (**8**) to a reaction of **1a** and **2a** did not result in azacyclopropane analogue **9**[19] according to ^{1}H NMR analysis (eq 3, see the Supporting Information). The absence of **9** cannot give a direct evidence to support the intermediacy of a copper−nitrenoid species herein.[20]

A tentative pathway for this copper-catalyzed conversion of two sulfonyl azides and an alkyne is proposed in Scheme 4.

Scheme 4. Proposed Reaction Pathway



Initial Cu^I-mediated stepwise [3 + 2] cycloaddition of alkyne **1** and azide **2** generates 5-cuprated triazole **I**,[3] which can be converted into cuprated amide **IV** upon treatment with another molecular azide **2**. This process presumably proceeds via a high valent Cu^{III} species **III** by oxidative addition and subsequent reductive elimination.[21] Formal metal exchange of **IV** delivers lithium salt **V** and the Cu^I catalyst, and final acidic workup gives triazole **3**. However, we cannot rule out a reasonable copper−nitrenoid intermediate **III′** in this process despite the unsuccessful trapping experiment (eq 3). Although the detailed action is currently not very clear, it is proposed that both DMF and lithium salts facilitate the transformation of **I** into **IV** to overcome competing protodecupration or ring-opening denitrogenization sequences.

In conclusion, we have presented an unprecedented copper-catalyzed conversion of sulfonyl azides and terminal alkynes upon treatment with stoichiometric amounts of LiO*t*Bu in DMF at 30 °C under air atmosphere, providing a direct access to 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles in high chemo- and regioselectivity. The resulting triazole products constitute accessible precursors for the preparation of highly substituted aminotriazoles through one-pot alkylation/desulfonation procedures. Further investigations are underway to elucidate the mechanistic details and to exploit the synthetic application of readily available 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data of new compounds (PDF)
X-ray crystallographic data of compounds **A** and **4a** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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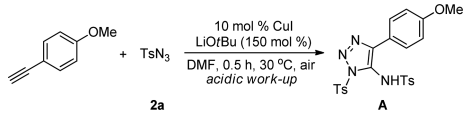
(12) The structure of **3a** was unambiguously confirmed upon single-crystal X-ray diffraction analysis of its analogue **A**, which was obtained from 1-ethynyl-4-methoxybenzene and **2a**.



2a A

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