Synthetic Methods

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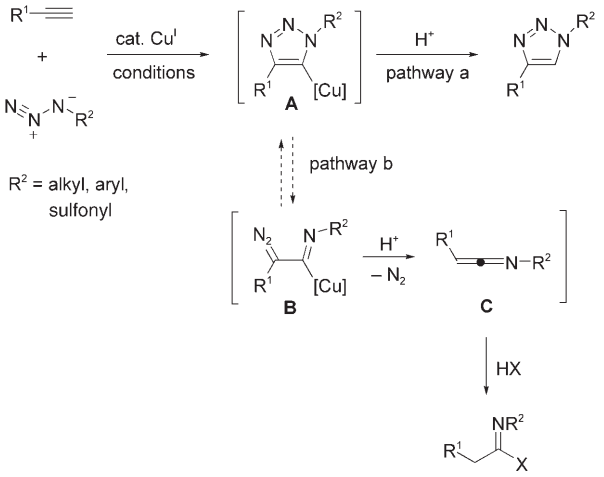
Copper-Catalyzed Synthesis of *N*-Sulfonyl-1,2,3-triazoles: Controlling Selectivity**

Eun Jeong Yoo, Mårten Ahlquist, Seok Hwan Kim, Imhyuck Bae, Valery V. Fokin, K. Barry Sharpless, and Sukbok Chang**

The recent advent of the Cu-catalyzed azide–alkyne cycloaddition (CuAAC),[1] one of the most reliable click reactions,[2] has enabled practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles from an unprecedented range of substrates with excellent selectivity, which cannot be attained with the traditional Huisgen thermal approaches.[3] In the thermal azide–alkyne cycloaddition, the type of reacting azide is especially important for the control of product distribution. For example, whereas aryl and alkyl azides react with activated alkynes to produce the corresponding 1,2,3-triazoles, *N*-sulfonyltriazoles arising from the reaction of sulfonyl azides with those acetylene compounds can undergo a rearrangement process leading to a mixture of triazoles and their ring-opened tautomers, α-diazoimino species.[4] The reversibility of the ring–chain tautomerism, known as the Dimroth rearrangement,[5] is governed by various factors, which include temperature and reaction medium, in addition to the nature of the ring substituents.[6] The stability of 5-metalated *N*-sulfonyltriazoles is even further reduced[7e] so that CuAAC with sulfonyl azides does not usually produce *N*-sulfonyltriazoles (Scheme 1). Indeed, the facile conversion of 5-cuprated triazole intermediate **A** into the presumed ketenimine species (**C**, R^2 = sulfonyl) results, upon reaction with amines, alcohols, or water, in the formation of amidines, imidates, or amides, respectively (Scheme 1, pathway b).[7] As implied in Scheme 1, the outcome of the reaction is determined by the fate of intermediate **A**. Herein, we describe the development of a copper(I)-catalyzed preparative procedure of *N*-sulfonyl-1,2,3-triazoles[8] on the basis of mechanistic insights and computational studies (pathway a).



Scheme 1. Copper-catalyzed azide–alkyne cycloaddition (pathway a) and triazole opening process (pathway b)

To investigate the loss of nitrogen gas from the *N*-sulfonyltriazolyl copper intermediate and to compare it with that from the analogous *N*-alkyltriazolyl species, we undertook a computational study (B3LYP/LACV3P*+) of the key reaction steps.[9] Complexes **D** and **G** (Figure 1), which differ only in the substitution of N^1 (**D** has a methylsulfonyl substituent (-SO_2Me) whereas **G** has a methyl group in its place), were chosen as a starting point. A transition state ($\mathbf{E}_{TS}$) for the conversion of **D** into ring-opened tautomer **F**, in which the N^1–N^2 bond is broken, was located. The activation barrier for this transformation was calculated to be 64 kJ mol^{-1} with a N^1–N^2 bond length of 2.11 Å. The formation of diazoimine complex **F** was calculated to be endothermic by 27 kJ mol^{-1}.

Although the loss of nitrogen gas has not been observed when alkyl or aryl azides are used in the reaction, the corresponding step was also investigated for *N*-methyltriazolyl copper complex **G**. The barrier was found to be much higher (148 kJ mol^{-1}; $\mathbf{H}_{TS}$), which could explain why intermediate **I** has not been observed to date. Additionally, resulting diazoimine intermediate **I** was much less stable relative to triazolyl precursor **G**, with a calculated endothermicity for the transformation of 131 kJ mol^{-1}. The N^1–N^2 distance in $\mathbf{H}_{TS}$ was calculated to be 2.42 Å, which indicates a later transition state than that for the sulfonyl-substituted **D**.

According to our hypothesis, the opening of the triazole ring is followed by the loss of nitrogen gas on the path toward

[*] E. J. Yoo, S. H. Kim, Dr. I. Bae, Prof. Dr. S. Chang
Center for Molecular Design and Synthesis (CMDS)
Department of Chemistry and
School of Molecular Science (BK21)
Korea Advanced Institute of Science and Technology (KAIST)
Daejon 305-701 (Korea)
Fax: (+82) 42-869-2810
E-mail: sbchang@kaist.ac.kr
M. Ahlquist
Department of Chemistry
Building 201, Kemitorvet
Technical University of Denmark
2888 Lyngby (Denmark)
Prof. Dr. V. V. Fokin, Prof. Dr. K. B. Sharpless
Department of Chemistry and
The Skaggs Institute of Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7562
E-mail: fokin@scripps.edu

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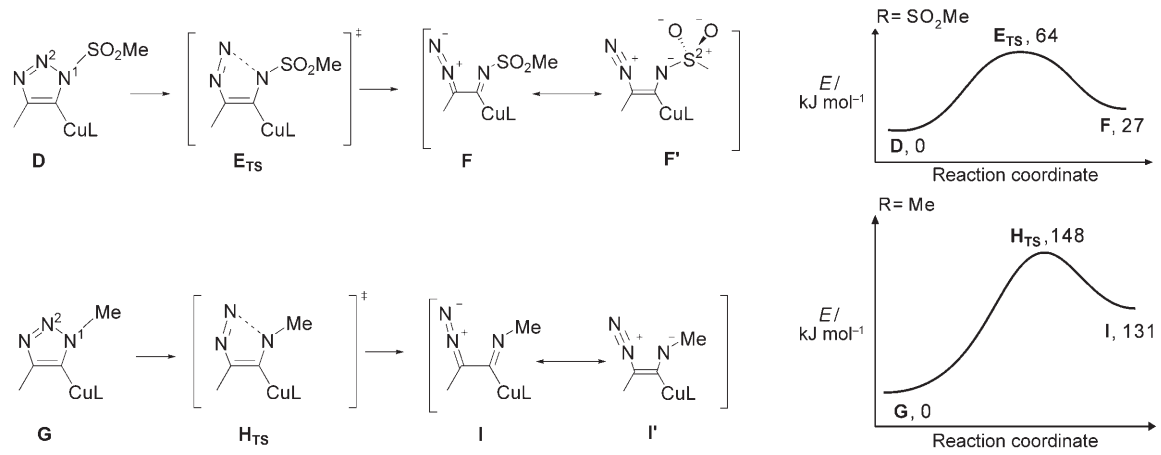
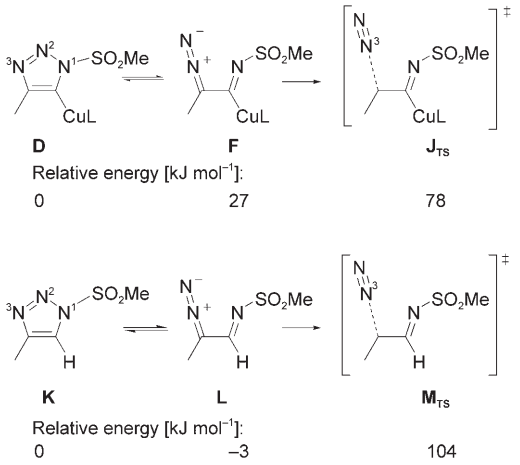


Figure 1. DFT investigation of the cleavage of the N^1–N^2 bond in triazolyl intermediates **D** and **G** (L indicates a spectator ligand, which was water in this case).

the ketenimine. As shown in Scheme 2, a copper-bound transition state in which the C–N^3 bond is broken ($\mathbf{J}_{TS}$) was located. The barrier from corresponding diazoimine intermediate **F** was calculated to be 51 kJ mol^{-1}, which makes the overall barrier for the breakdown of triazolyl **D** to be 78 kJ mol^{-1}. The breaking C–N^3 bond in the transition state is stretched to 1.7 Å. To explore whether this transformation is facilitated in the presence of copper, an analogous process was modeled with a protonated *N*-sulfonyl triazole (**K**). The ring opening of **K** to give diazoimine **L** was calculated to be exothermic by 3 kJ mol^{-1} with a barrier of 69 kJ mol^{-1}, which is only slightly higher than that of Cu triazole species **D** (64 kJ mol^{-1}, Figure 1).



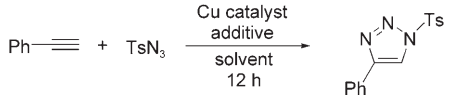
Scheme 2. Relative energy difference between Cu triazole and its protonated analogue in the ring-opening processes.

However, the following step, in which a molecule of N_2 is lost via $\mathbf{M}_{TS}$, showed a barrier that is 56 kJ mol^{-1} higher than that of the corresponding cuprated species. Transition state $\mathbf{M}_{TS}$ appears later than $\mathbf{J}_{TS}$ because the breaking C–N bond was found to be 2.1 Å long compared with 1.7 Å for $\mathbf{J}_{TS}$. In short, the loss of N_2 from the triazolyl copper species (**D**) proceeds with a 26 kJ mol^{-1} lower barrier than that from the protonated species (**K**), which corresponds to a rate difference of 5 orders of magnitude.

The computational insights described above and the previously reported mechanistic studies of the CuACC process[10] revealed to us that by changing the reaction conditions, the triazolyl intermediate could be trapped. By facilitating the protonation of the intermediate and by lowering the temperature to suppress entropically favored processes such as the formation of the dissociative $\mathbf{J}_{TS}$, we believed that triazole formation could be preferred. Consequently, we tested a wide range of reaction parameters, including temperatures and additives, as well as copper catalysts and solvents, in a test reaction of phenylacetylene with *p*-toluenesulfonyl azide (Table 1).

Whereas only a low yield of desired product 1-(*N*-tosyl)-4-phenyl-1,2,3-triazole was obtained under the standard aque-

Table 1: Cu-catalyzed *N*-sulfonyltriazole formation under the various conditions.[a]



Entry	Catalyst	Additive	Solvent	*T* [°C]	Yield [%][b]
1	$CuSO_4 \cdot 5H_2O$	Na ascorbate[c]	H_2O/ *t*BuOH[d]	25	12
2	CuI	2,6-lutidine	H_2O/ *t*BuOH[d]	25	15
3	CuI	2,6-lutidine	$CHCl_3$	25	37
4	CuI	2,6-lutidine	$CHCl_3$	0	80
5	CuI	2,6-lutidine	$CHCl_3$	70	4
6	CuI	–	$CHCl_3$	0	3
7	CuI	2,6-lutidine[e]	$CHCl_3$	0	73
8	CuI	DIPEA	$CHCl_3$	0	<1

[a] Phenylacetylene (0.60 mmol), TsN_3 (0.50 mmol), additive (0.60 mmol except entries 1, 6, and 7), and [Cu] (0.05 mmol) in solvent (1.0 mL) were used. Ts = *p*-toluenesulfonyl; DIPEA = *N*,*N*-diisopropylethylamine. [b] NMR yield based on an internal standard (1,3-benzodioxole). [c] 0.1 equiv was employed. [d] H_2O/*t*BuOH = 1:2. [e] 0.2 equiv was used.

ous ascorbate conditions (Table 1, entry 1),[1a] variation of the key reaction parameters resulted in significantly improved yields.[11] For example, among several copper salts tested, CuI showed the highest catalytic activity in anhydrous conditions (chloroform). Unsurprisingly, temperature had a dramatic impact on the efficiency of the triazole-forming process (pathway a); the highest yield was obtained at 0 °C and dropped rapidly as the temperature was increased (compare Table 1, entries 3, 4, and 5). Although 2,6-lutidine is required, it can be used in substoichiometric amounts (Table 1, entry 7). Interestingly, 2,6-lutidine was uniquely superior to other organic and inorganic bases we examined.[11]

Under the optimized conditions, a range of terminal alkynes reacted smoothly with several sulfonyl azides to produce 1-(*N*-sulfonyl)-4-substituted 1,2,3-triazoles in good to excellent yields (Table 2). Electronic variation in the phenylacetylene derivatives did not alter the efficiency of the reaction (Table 2, entries 1–4). A heteroaromatic substituent was also readily introduced into the triazole skeleton at the 4-position (Table 2, entry 5). Reaction of a conjugated enyne with a sulfonyl azide took place without difficulty (Table 2, entry 6). Additionally, a range of aliphatic terminal alkynes bearing functional groups readily react with sulfonyl azides under the established conditions (Table 2, entries 7–8). Cycloaddition of terminal propargylic amides and alcohols was also facile and afforded the corresponding functionalized *N*-sulfonyl-1,2,3-triazoles in acceptable yields (Table 2, entries 9 and 10, respectively).

The scope of the reaction with respect to the azide component was also investigated by including a variety of sulfonyl azides (Table 2, entries 11–13). Synthesis of *N*-sulfonyltriazoles was performed on a gram scale without encountering problems.

It has been reported that the introduction of a sulfonyl group into a wide range of heterocyclic compounds results in significant changes in the bioactivity of the compounds.[12] Therefore, the present work of synthesizing sulfonyl triazoles may initiate a new search for bioactive triazole molecules, especially in medicinal chemistry. In addition, because the CuAAC reaction has emerged as a highly efficient means of bioconjugation, especially in recent years,[2] the developed protocol can be utilized to expand the scope of the tool greatly . Moreover, the sulfonyl group could be readily removed under mild conditions by using magnesium in methanol[13] to provide 4-substituted *N*-H-triazoles in excellent yields.[14]

In summary, mechanistic insights and computational studies of the CuAAC reaction enabled the development of a new practical procedure for the preparation of 4-substituted 1-(*N*-sulfonyl)-1,2,3-triazoles. The important heterocycles were obtained regioselectively in good to excellent yield by performing the reactions at low temperature in chloroform in the presence of 2,6-lutidine and a catalytic amount of CuI.

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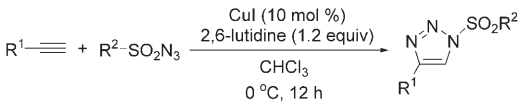
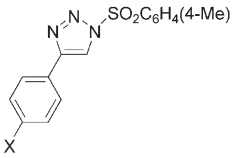
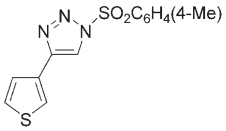
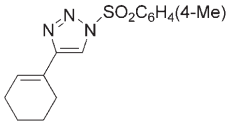
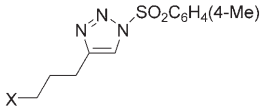
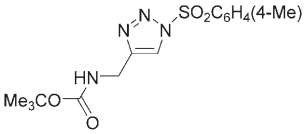
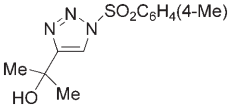
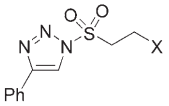
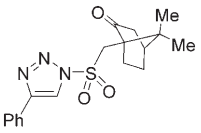
Table 2: Cu-catalyzed cycloaddition of terminal alkynes and sulfonyl azides.[a]



Entry	Product		Yield [%][b]
1		X = H	83
2		Me	78
3		CF_3	84
4		Br	95
5			90
6			61
7		X = Cl	68
8		OC(O)Me	57
9			60
10			75
11		X = Et	80
12		$SiMe_3$	84
13			56

[a] A solution of alkyne (0.60 mmol), sulfonyl azide (0.50 mmol), 2,6-lutidine (0.60 mmol), and CuI (0.05 mmol) in $CHCl_3$ (1.0 mL) was stirred for 12 h at 0 °C. [b] Yield of isolated product after column chromatography.

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