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Copper-Catalyzed Sulfonyl Azide−Alkyne Cycloaddition Reactions: Simultaneous Generation and Trapping of Copper−Triazoles and −Ketenimines for the Synthesis of Triazolopyrimidines

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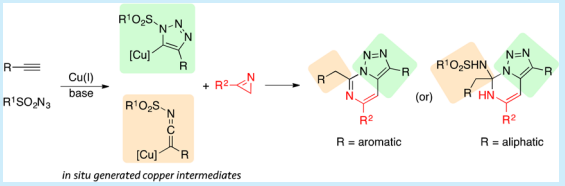
Supporting Information

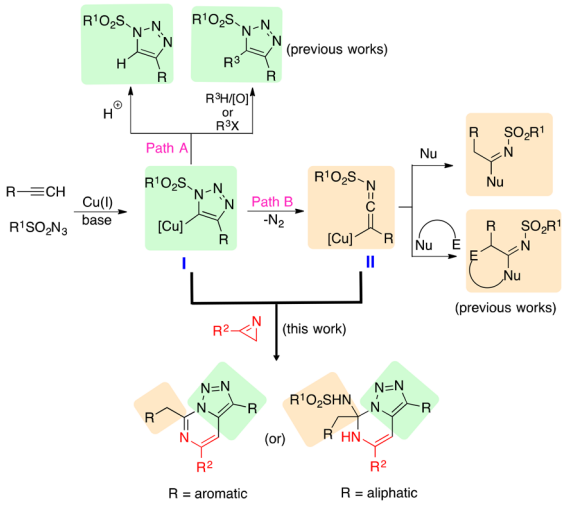
ABSTRACT: First simultaneous generation and utilization of both copper−triazole and −ketenimine intermediates in copper-catalyzed sulfonyl azide−alkyne cycloaddition reactions is achieved for the one-pot synthesis of triazolopyrimidines via a novel copper-catalyzed multicomponent cascade of sulfonyl azides, alkynes, and azirines. Significantly, the reaction proceeds under very mild conditions in good yields.



Developing new synthetic methods that enable rapid and straightforward access to useful molecules is the key focus of organic synthesis.[1] In this context, cascade/domino reactions have proven to be a powerful approach for the construction of complex molecules in a single step and have wide applications ranging from discovery of new bioactive molecules to advanced material synthesis.[2] A key challenge in the development of cascade reactions lies in achieving control over the reactivity of the *in situ* generated intermediates. This is especially critical in multicomponent cascade reactions[3] since it has several intermediates and reactants in the system. A significant advancement made in the last decades is the development of catalytic versions that ensure high selectivity and efficiency. Accordingly, many elegant metal[4]/organic[5] catalysts have been reported for multicomponent cascade reactions.

Copper-catalyzed sulfonyl azide−alkyne cycloaddition reactions involving the reactive intermediates, copper−triazoles and −ketenimines have recently attracted huge attention from various research groups, after the seminal contributions made by the groups of Chang[6b,c,7c,8g,h,l−n] and Fokin.[6c,7c,8j,k] These *in situ* generated intermediates have been trapped independently with various coupling partners, enabling the development of a diverse range of synthetically useful reactions (Scheme 1).[6−8] These reactions proceed via the copper-catalyzed [3 + 2] cycloaddition of sulfonyl azides and terminal alkynes to form a copper−triazole intermediate **I**. This intermediate **I** can be trapped as a triazole adduct (Scheme 1, path A)[7] or, alternatively, undergoes a ring opening rearrangement to a copper−ketenimine species **II**, which would be used for subsequent reactions (Scheme 1, path B).[8] Notably, by altering the reaction conditions, the reactivity of the copper−triazole[9] intermediate **I** can be controlled either toward path A or path B (Scheme 1). For instance, in the presence of strong nucleophiles and highly basic conditions, path B predominates. In contrast, under low temperatures and relatively acidic conditions, intermediate **I** can be trapped as triazole adducts (Scheme 1, path A). Thus, the relative population of these two intermediates at a given point of time is very sensitive to the reaction conditions and, also, on the nature of the third component.[6c] So far, most reports deal with only the independent trapping of these intermediates for further reactions. To the best of our knowledge, there are no reported conditions in the literature that simultaneously utilize both the copper−triazole **I** and −ketenimine **II** intermediates in copper-catalyzed sulfonyl azide−alkyne cycloaddition reactions. Herein, we report the first successful simultaneous generation and utilization of both copper−triazole and −ketenimine intermediates via a novel copper-catalyzed multicomponent cascade reaction of sulfonyl azides, alkynes, and azirines for the one-pot synthesis of triazolopyrimidines, a highly privileged structure in

Scheme 1. Generation and Reactivity of Copper−Triazole I and −Ketenimine II Intermediates from Sulfonyl Azides and Alkynes



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drug discovery and development.[10] Interestingly, the present isomer [1,2,3]triazolo[1,5-*c*]pyrimidine is very rare in literature, and to the best of our knowledge, there are only two reports available for the synthesis of these core structures.[11] Both the reports have employed strong oxidants like $Pb(OAc)_4$ or MnO_2 to access these structures from the corresponding pyrimidine hydrazones. Certainly, the present report for the synthesis of [1,2,3]triazolo[1,5-*c*]pyrimidines is advantageous as it does not require strong oxidizing agents and preformed pyrimidine derivatives.

We have also shown keen interest in this area of research[12] and have recently demonstrated that copper-ketenimines **II** can be activated by *N*-heterocyclic carbenes (NHCs) toward the synthesis of functionalized oxindoles via a cooperative relay catalysis strategy using NHCs as organocatalysts and copper as a transition metal catalyst.[12b] In continuation of our studies on developing new reactions involving sulfonyl azides and alkynes, we envisioned the potential of 2*H*-azirines in these reactions. Azirines have been widely used in the generation of interesting aza-heterocyclic scaffolds with broad applications in the field of drug discovery.[13] In an initial attempt, we tried to react 2*H*-azirine **3a** with tosyl azide **2a** and phenylacetylene **1a** in the presence of CuI as the catalyst, and triethylamine (TEA) as the base in toluene at room temperature (Table 1, entry 1). To our surprise, besides the copper−ketenimine species **II**, the copper−triazole intermediate **I** also simultaneously participated in the azirine ring opening and produced triazolopyrimidine **4a** in a decent 59% isolated yield. This is in strict contrast to the anticipated pyrrole structure, which would result if only the copper−ketenimine **II** had participated in the azirine ring opening (Supporting Information (SI), Scheme S1). The structure of **4a** was determined by spectroscopic analyses and X-ray crystallography of its derivative **4b** (Figure 1 and SI Figure S1), which confirmed that both the triazole and ketenimine species were incorporated into the product.[14]

Encouraged by these results, we undertook a detailed optimization study on the ideal reaction conditions, and the results are summarized in Table 1. Initially the conditions that strictly favor the path A (with weak bases and at low

Table 1. Optimization Conditions[a]

entry	catalyst	base	additive	solvent	yield, %[b]
1	CuI	TEA	none	toluene	59
2	CuI	TEA	none	toluene	11[c]
3	CuI	TEA	none	toluene	18[d]
4	CuI	DIPEA	none	toluene	14
5	CuI	K_2CO_3	none	toluene	9
6	CuI	DBU	none	toluene	12
7	CuI	KO^{t}Bu	none	toluene	trace
8	CuI	TEA	PhCOOH	toluene	91
9	CuI	TEA	4-Cl phenol	toluene	94
10	***CuI***	***TEA***	***H_2O***	***toluene***	***95***[e]
11	CuI	TEA	H_2O	toluene	37[f]
12	CuI	TEA	CH_3COOH	toluene	25
13	CuI	TEA	CF_3COOH	toluene	trace
14	CuI	TEA	H_2O	DCM	95
15	CuI	TEA	H_2O	$CHCl_3$	63
16	CuI	TEA	H_2O	DCE	92
17	CuI	TEA	H_2O	ACN	trace
18	CuI	TEA	H_2O	THF	90
19	CuCl	TEA	H_2O	toluene	86
20	CuBr	TEA	H_2O	toluene	72

[a]Conditions: **1a** (0.84 mmol), **2a** (0.84 mmol), **3a** (0.4 mmol), base (0.44 mmol), additive (0.4 mmol), CuI (0.04 mmol), and toluene (2 mL), at 25 °C, 30 min. [b]Isolated yield. [c]At 0 °C. [d]At 45 °C. [e]2.5 equiv of H_2O was used. [f]**1a** (0.4 mmol), **2a** (0.4 mmol), and **3a** (0.4 mmol) were used.

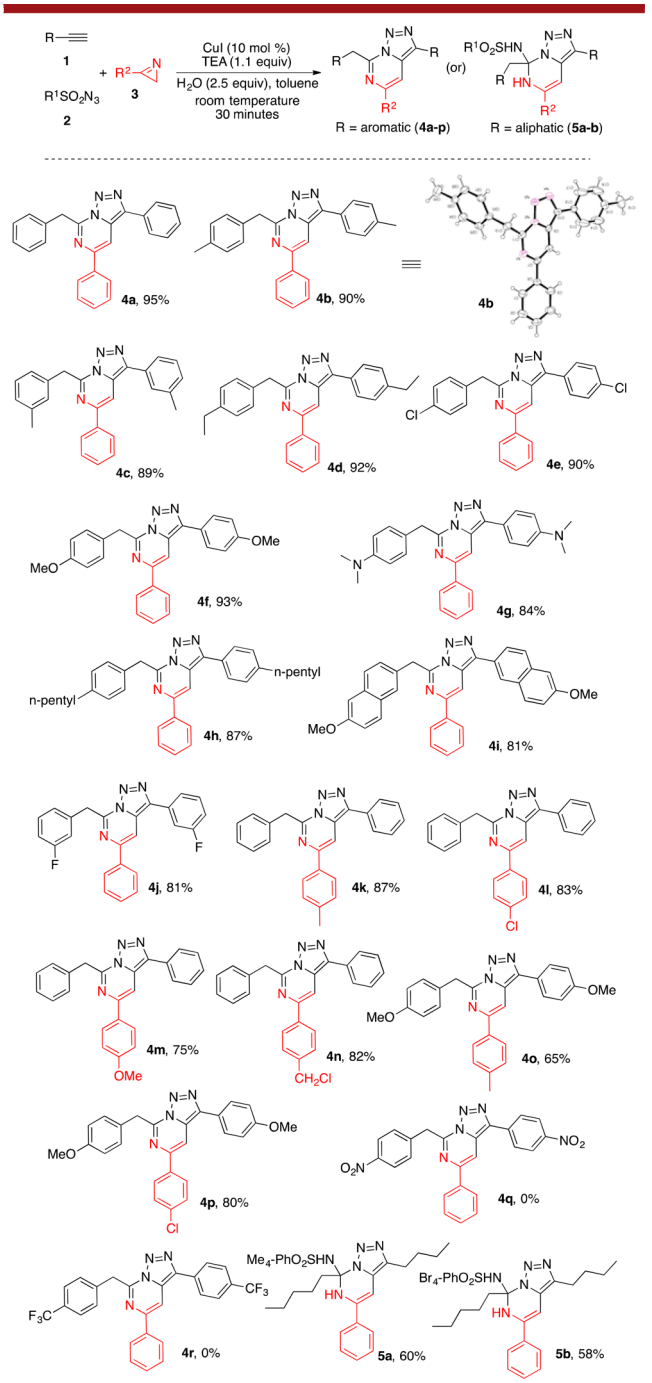

Figure 1. Scope of the reaction. Conditions: **1** (0.84 mmol), **2** (0.84 mmol), **3** (0.4 mmol), TEA (0.44 mmol), H_2O (1 mmol), CuI (0.04 mmol), and toluene (2 mL), at 25 °C, 30 min. Yields are those of isolated products. X-ray structure of **4b** is shown.

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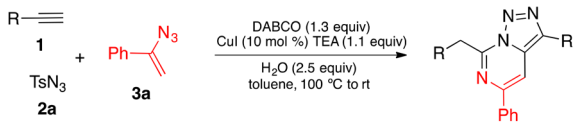
temperatures) and path B (with strong bases and at high temperatures) were tested. Consistent with our mechanistic hypothesis, both the conditions did not work well and gave only very poor yields (Table 1, entries 2−7). Interestingly, when the successful initial condition was modified with the use of mild acid additives in combination with TEA, the yields increased significantly (Table 1, entries 8−10). A maximum yield of 95% was obtained with water as the additive (entry 10). When identical equivalents of azides, alkynes, and azirines were tested, as expected, reactions yield less products (entry 11). However, when slightly stronger acids like acetic and trifluoroacetic acids were employed, lesser yields of products were obtained (Table 1, entries 12 and 13). Next, we attempted the reaction with various solvents such as dichloromethane (DCM), dichloroethane (DCE), chloroform ($CHCl_3$), acetonitrile (ACN), and tetrahydofuran (THF), but no significant differences were observed (Table 1, entries 14−18). Other copper sources like CuBr and CuCl were also examined and found to be less effective in catalyzing this reaction (Table 1, entries 19 and 20).

With the optimized reaction conditions in hand, substrate scope was explored with the catalyst CuI, the base TEA, and the additive water in toluene at room temperature (25 °C) , and the results are summarized in Figure 1. A series of aromatic alkynes with various substituents including electron withdrawing and electron donating functional groups on the aromatic ring, formed the corresponding triazolopyrimidines in good to excellent yields (**4a−j**). Notably, the substrates with *N*,*N*-dimethyl substituent or bulky naphthyl also worked well, and the corresponding products **4g** and **4i** were isolated in high yields (84% and 81%, respectively). The scope of the reaction with respect to various azirines was next surveyed. Aromatic azirines bearing both electron withdrawing and electron donating substituents were also found to give the products in moderate to high yields (**4k−p**). However, when alkynes with strongly electron-withdrawing groups such as *p*-NO_2 and *p*-CF_3 were employed, though all the starting materials were consumed, multiple spots were observed by thin layer chromatography, and we could not isolate any products (**4q** and **4r**). Interestingly, when aliphatic alkynes were used, sulfonamide incorporated more functionalized triazole structures and **5a** and **5b** were obtained. This may be attributed to the absence of phenonium ion intermediate, which is most likely involved when aromatic alkynes are used. Furthermore, we found that this methodology is scalable as exemplified by a gram scale (2 g) synthesis of **4a** with 97% yield (see SI).

The scope of this method can also be extended to a one-pot sequential synthesis of triazolopyrimidines starting from vinyl azides. Initially, vinyl azide was heated in the presence of DABCO in toluene for 60 min. After the consumption of all the vinyl azide (from TLC), the reaction was allowed to cool down to room temperature when CuI, tosyl azide, TEA, and different alkynes were added. The overall process proceeded smoothly to afford the corresponding triazolopyrimidines in slightly lesser yields (Scheme 2). This new one-pot sequence allows the rapid synthesis of the triazolopyrimidines from vinyl azides without isolating the azirines.

To understand the mechanism, control experiments starting from *N*-sulfonyl triazoles and *N*-H triazoles were performed, and the results are summarized in Scheme S2, SI. For both the cases, when the preformed triazoles were treated with azirine under the optimized reaction conditions, no reaction was observed and starting materials were fully recovered. Based on these control experiments and literature proceedings, a plausible mechanism for the copper-catalyzed multicomponent cascade reaction of

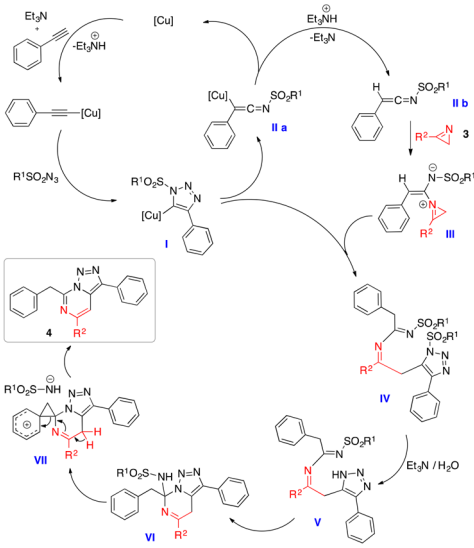
Scheme 2. Copper-Catalyzed One-Pot Sequential Synthesis of Triazolopyrimidine from Vinyl Azide, Alkyne, and Tosyl Azide



4a: R = Ph, 94%
4b: R = 4-MePh, 83%
4c: R = 4-EtPh, 85%
4d: R = 4-OMePh, 83%

sulfonyl azides, alkynes, and azirines is shown in Scheme 3.[15] Initially, the reaction of a terminal alkyne with the copper catalyst

Scheme 3. Plausible Mechanistic Pathway for the One-Pot Synthesis of Triazolopyrimidines



in the presence of stoichiometric base gives a copper−acetylide. This will then undergo [3 + 2] cycloaddition with sulfonyl azide to form a copper−triazole intermediate **I**, which can either give rise to a copper−ketenimine intermediate **IIa** or open the zwitterionic intermediate **III**, formed in situ from the ketenimine intermediate **IIb** and azirine. This intermediate **III** can trap the copper−triazole **I** to form ring-opened product **IV**. Finally, the intermediate **IV** undergoes base-mediated *N*-detosylation using H_2O as the proton source to form intermediate **V**, which spontaneously undergoes cyclization and elimination of sulfonamide to yield product **4** via a phenonium ion intermediate.

In summary, an unprecedented copper-catalyzed multicomponent cascade reaction of sulfonyl azides, alkynes, and azirines for the direct synthesis of triazolopyrimidines has been developed. A variety of medicinally important triazolopyrimidines were synthesized in good to excellent yields under very mild reaction conditions. In addition, the reaction is certainly scalable, and the products thus obtained can be easily derivatized further into more functional triazolopyrimidines. Notably, the cascade functionalization of triazoles achieved through simultaneous trapping of copper−triazole and −ketenimine intermediates with 2*H*-azirines complements and expands our current knowledge of copper−ketenimine chemistry. Our results presented here are expected to have an impact on novel reaction

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design and the development of multicomponent cascade reaction involving sulfonyl azides and alkynes. Further method development studies utilizing these unique reaction pathways are currently under investigation 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.7b01500.

Experimental procedures and characterization of all new compounds including ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1532151 contains supplementary crystallographic data for the compound **4b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(15) An alternate plausible mechanism is also proposed in the SI, Figure S2.

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