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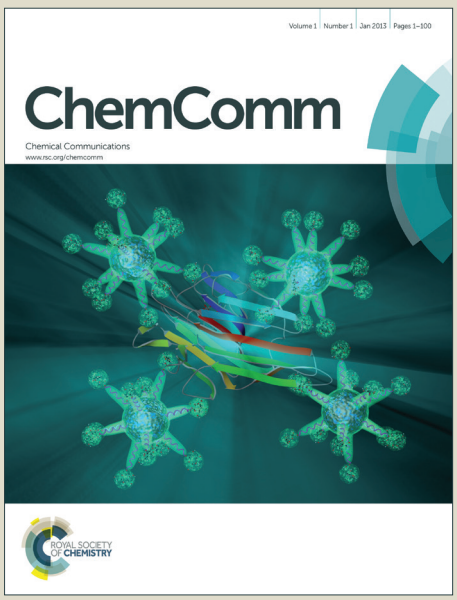

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Copper-Catalyzed Cascade Cyclization of 1,7-Enynes with Aromatic Sulfonyl Chlorides toward Benzo[*j*]phenanthridin-6(5*H*)-ones

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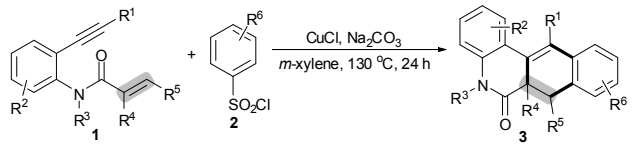
A step-economic method for the cascade cyclization of 1,7-enynes with aromatic sulfonyl chlorides by using a low-cost and more abundant Cu catalyst is presented. This method allows access to benzo[*j*]phenanthridin-6(5*H*)-ones and represents a new Cu-catalyzed cascade cyclization of 1,*n*-enynes.

The cyclization of 1,*n*-enynes is among the most important synthetic tools for the construction of complex cyclic compounds in an atom- and step-economical manner.[1-3] The catalytic cyclization of 1,*n*-enynes has been the focus of extensive investigation, and the vast majority of which involve the use of various transition-metal complexes (often noble Pd, Rh, Ru, Pt and Au complexes) as catalysts.[1] The use of complexes of low-cost and more abundant metals, especially copper, in the cyclization of 1,*n*-enynes has attracted recent attention,[2,3] because it contributes to the understanding of the reactions and discovery of new reactions, and makes the cyclization of 1,*n*-enynes more conducive to industrial processes. However, approaches of 1,*n*-enyne cyclization using Cu catalysts are quite rare.[2] The Cu-catalyzed cyclization of 1,*n*-enynes reported to date only involve a) skeletal rearrangement of tertiary 5-en-1-yn-3-ols,[2a-b] b) asymmetric borylative cyclization of 1,6-enynes with nucleophilic B_2pin_2[2c] and c) oxidative cyclization of 1,6-enynes with the additional reagents that started from the first addition to the alkene moiety leading to alkyl-Cu intermediate followed by cyclization of alkyl-Cu intermediate with the alkyne moiety.[2d-e] It has been reported that the Cu catalysts had a strong affinity for alkynes and led to the formation of the alkenyl-Cu intermediates;[4] however, it is very difficult to add the alkenyl-Cu intermediates to alkenes due to the relatively weaker affinity of the alkenyl-Cu intermediates to alkenes. Remarkably, only one paper has been reported by the group of Tian and Lin on the *5-exo*-trig borylative cyclization of 1,6-enynes with nucleophilic B_2pin_2 via the addition of alkenyl-Cu intermediates to enones, and methods for the cyclization of 1,7-enynes with the electrophilic additional reagents using the same strategy are lacking. Thus, the development of some new routes to realize the addition of alkenyl-Cu intermediates to alkenes is highly desirable and essential.

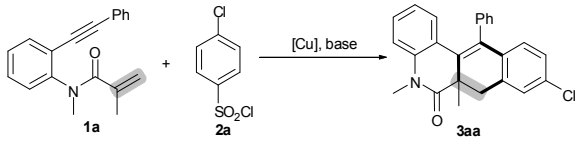
Herein, we report a new Cu-catalyzed cascade cyclization of 1,7-enynes with aromatic sulfonyl chlorides[5] for selective assembly of benzo[*j*]phenanthridin-6(5*H*)-ones, important heterocyclic compounds that have been recognized as potential lead compounds for the development of anticancer, antiinflammatory and cardiovascular agents (Scheme 1).[6] This method achieves the addition of alkenyl-Cu intermediate, generated in-situ from an alkyne and an inexpensive and commercial-available CuCl salt, to alkenes, and involves the cascade cyclization with *ortho*-C(sp^2)-H bonds of aromatic sulfonyl chlorides to construct two new six-membered rings in one reaction. To best of our knowledge, this work represents a new example of using Cu catalysts for the cascade cyclization of 1,*n*-enynes with electrophilic reagents via an alkenyl-Cu intermediate strategy.



Scheme 1 Cu-Catalyzed Cascade Cyclization of 1,7-Enynes.

We began our investigation by exploring cyclization of *N*-methyl-*N*-(2-(phenylethynyl)phenyl)methacrylamide (**1a**) with 4-chlorobenzene-1-sulfonyl chloride (**2a**) in the presence of several Cu catalysts, bases and solvents for reaction condition optimization (Table 1). Evaluation of a number of common Cu catalysts, including CuCl, CuBr, CuI and $CuCl_2$, revealed that the reaction catalyzed by CuCl gave the best results (entries 1-4). In the presence of CuCl and Na_2CO_3, 78% yield of the desired product **3aa** was isolated from acrylamide **1a** with chloride **2a** in *p*-xylene at 130 °C (entry 1). The results disclosed that the amount of CuCl affected the reaction (entries 1, 5 and 6), and the optimum amount of CuCl is 20 mol% in terms of yield and reaction time (entry 1). Notably, the reaction did not take place in the absence of either Cu catalysts or bases (entries 7 and 8). Thus, the effect of bases was subsequently examined (entries 9-11). Screening revealed that other bases, such as K_2CO_3, Cs_2CO_3 and NaOAc, were less effective than Na_2CO_3 (entries 9-11 versus entry 1). Control reactions confirmed that solvent had strong effect on the reaction. The use of toluene as the solvent could deliver the expected product **3aa**, albeit with a lower yield (entry 12). However, the use of DMF or DMSO as the solvent completely suppressed the reaction (entries 13 and 14). It is noteworthy that the reaction temperature plays a critical role in the reaction: the reaction at 120 °C gave lower conversion to **3aa** (entry 15), and at 140 °C resulted in decomposition of acrylamide **1a** (entry 16).

Table 1 Screening of Optimal Conditions[a]



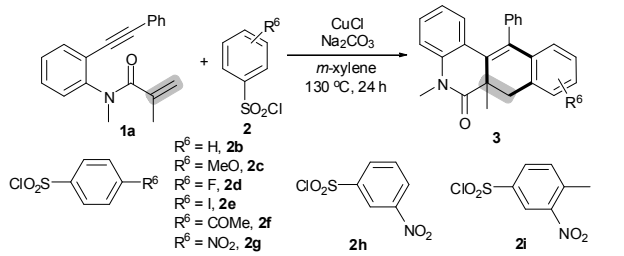
Entry	[Cu] (mol%)	Base	Solvent	T [°C]	Yield (%)[b]
1	CuCl (20)	Na_2CO_3	*m*-xylene	130	84
2	CuBr (20)	Na_2CO_3	*m*-xylene	130	18
3	CuI (20)	Na_2CO_3	*m*-xylene	130	22
4	$CuCl_2$ (20)	Na_2CO_3	*m*-xylene	130	81
5[c]	CuCl (10)	Na_2CO_3	*m*-xylene	130	80
6	CuCl (30)	Na_2CO_3	*m*-xylene	130	78
7	—	Na_2CO_3	*m*-xylene	130	0
8	CuCl (20)	—	*m*-xylene	130	0
9	CuCl (20)	K_2CO_3	*m*-xylene	130	70
10	CuCl (20)	Cs_2CO_3	*m*-xylene	130	34
11	CuCl (20)	NaOAC	*m*-xylene	130	73
12	CuCl (20)	Na_2CO_3	*m*-xylene	130	18
13	CuCl (20)	Na_2CO_3	DMF	130	trace
14	CuCl (20)	Na_2CO_3	DMSO	130	trace
15	CuCl (20)	Na_2CO_3	*m*-xylene	120	20
16[d]	CuCl (20)	Na_2CO_3	*m*-xylene	140	25

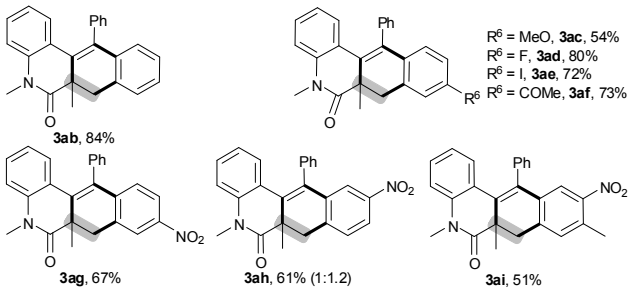
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2.0 equiv), [Cu], base (2.0 equiv) and solvent (2 mL) for 24 h in argon. [b] Isolated yield. [c] For 36h. [d] Some substrate **1a** was decomposed.

After determining the optimal reaction conditions, we decided to explore the scope of this cascade cyclization reaction (Tables 2 and 3). As shown in Table 2, a series of aromatic sulfonyl chlorides **2b-2i** were first investigated in the presence of acrylamide **1a**, CuCl and Na_2CO_3 (Products **3ab-ai**). Gratifyingly, this protocol could be applicable to aromatic sulfonyl chlorides **2b-i**, among which several substituents, including MeO, F, I, MeCO and NO_2, on the aromatic ring were well-tolerated. For example, benzenesulfonyl chloride (**2b**) gave the desired product **3ab** in 84% yield. The use of MeO-substituted chloride **2c** led to the formation of **3ac** in moderate yield. Importantly, chlorides **2a**, **2d** and **2e** with a halo group, such as F, Cl or I, on the aromatic ring were compatible with the optimal conditions, thereby providing a chance for additional modifications at the halogenated position (**3aa**, **3ad** and **3ae**). Chlorides **2g** and **2h** having a *para*- or *meta*-NO_2 group could be applied in generating **3ag** and **3ah** in 67% and 61% yields, respectively. Chloride **2i** with two substituents, a Me group and a NO_2 group, was also a suitable substrate, providing **3ai** in moderate yield.

The applicability of this protocol to the cascade cyclization of various *N*-(2-ethynylaryl)acrylamides **1** with chloride **2b** was next examined (Table 3). Upon exposure to the optimal conditions, *N*-Bn or *N*-allyl-containing acrylamides **1b** and **1c** successfully underwent this reaction, with the corresponding products **3bb** and **3cb** in good yields. However, acrylamide **1d** with a free N-H bond has no reactivity (**3db**). A series of aryl substituents, including 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4 and 4-BrC_6H_4, at the terminal alkynes were found to be well-tolerated, giving **3eb-ib** in moderate to good yields. Additionally, heteroaryl substituents, including pyridin-2-yl, thiophen-2-yl and thiophen-3-yl groups, at the terminal

Table 2 Screening the Viable Aromatic Sulfonyl Chlorides (**2**) [a]

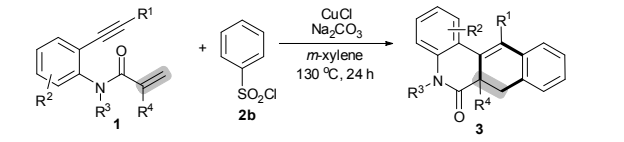


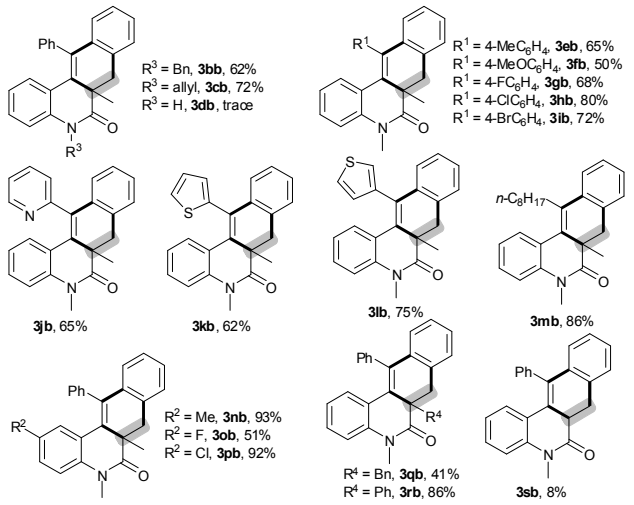


[a] Reaction conditions: **1a** (0.3 mmol), **2** (2.0 equiv), CuCl (20 mol%), Na_2CO_3 (2.0 equiv) and *m*-xylene (2 mL) at 130 °C in argon for 24 h.

alkynes were compatible with the optimal conditions, as demonstrated by the formation of **3jb-lb** in good yields. Using aliphatic alkyne **1m**, good yield was still achieved (**3mb**). Acrylamides **1n-1p** with a substituent, such as Me, F or Cl, on the aryl ring of the N-aryl moiety were competent to this protocol, leading to **3nb-pb** in 93%, 51% and 92% yields, respectively. We found that a benzyl group or a phenyl group at the 2 position of the acrylamide moiety was also tolerated,

Table 3 Scope of 1,7-Enynes (**1**)[a]

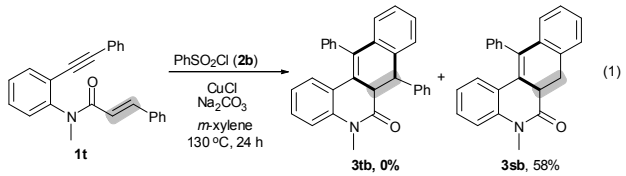




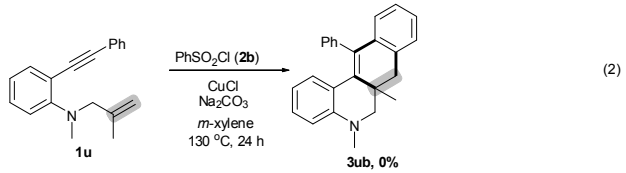
[a] Reaction conditions: **1** (0.3 mmol), **2b** (2.0 equiv), CuCl (20 mol%), Na_2CO_3 (2.0 mmol) and *m*-xylene (2 mL) at 130 °C in argon for 24 h.

and the corresponding desired products **3qb** and **3rb** were obtained in moderate to good yields. However, alkene **1s** without substituents at the 2 position has a relatively lower reactivity (**3sb**).

To our surprise, benzenesulfonyl chloride (**2b**) did not participate in the cascade cyclization of *N*-methyl-*N*-(2-(phenylethynyl)phenyl)cinnamamide (**1t**), an internal alkene (Eq 1). Alkene **1t** underwent an intramolecular cyclization reaction, not the current cascade cyclization with chloride **2b**, to afford **3sb** in 58% yield. However, substrate **1u** contained a non-activated alkene has no reactivity (Eq 2).



(1)



(2)

In summary, we have developed a new alkenyl-Cu strategy for the cascade cyclization of 1,7-enynes with aromatic sulfonyl chlorides. This reaction is operationally simple and represents a step-economical way to build molecular complexity with high functional group compatibility. Moreover, this method allows access to important benzo[*j*]phenanthridin-6(5*H*)-ones, thereby making this methodology more useful with wide potential applications in organic synthesis and medicinal chemistry.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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