Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Silver(I)- and Base-Mediated [3 + 3]-Cycloaddition of *C,N*-Cyclic Azomethine Imines with Aza-oxyallyl Cations

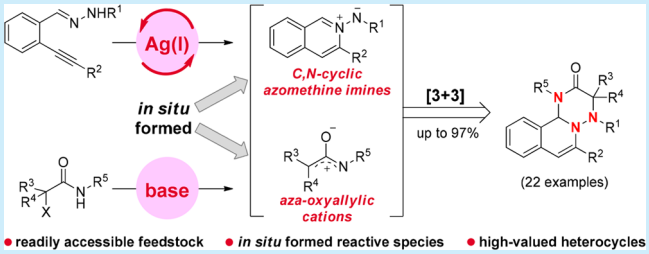
Xiao Cheng,[†] Xia Cao,[†] Jun Xuan,*[,†] and Wen-Jing Xiao[‡]

[†]Department of Chemistry, Anhui University, Hefei, Anhui 230601, People's Republic of China

[‡]Hubei International Scientific and Technological Cooperation Base of Pesticide and Green Synthesis, Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, People's Republic of China

Supporting Information

ABSTRACT: A silver(I) and base-mediated [3 + 3]-cycloaddition reaction of in situ generated *C,N*-cyclic azomethine imines with in situ formed aza-oxyallyl cations is reported. This one-pot cycloaddition process shows broad substrate scope an excellent functional group tolerance and provides the corresponding biologically important isoquinoline-fused triazines in good to excellent yields.



Nitrogen-containing heterocyclic compounds are widely found in many natural isolates, biologically active compounds, medicinally relevant structures, and some fine chemicals.[1] Among them, the 1,2,4-triazines and isoquinolines represent two of the most important heterocycles due to their rich biological activities (Figure 1). For instance, lamictal and azaribine, which contain the 1,2,4-triazine scaffold, are well-known anticonvulsant drugs and antiviral drugs.[2] The BMS 690514 is an EGFR tyrosine kinase inhibitor.[3] Representive examples of isoquinoline-containing heterocycles, such as PD 102807, are efficient selective M_4 muscarinic receptor antagonists,[4] while the natural alkaloid lamellarin I exhibits potential antitumor activities.[5] Driven by their rich biological activities, the development of novel and efficient methods for the synthesis of these two heterocycles is of widespread interest

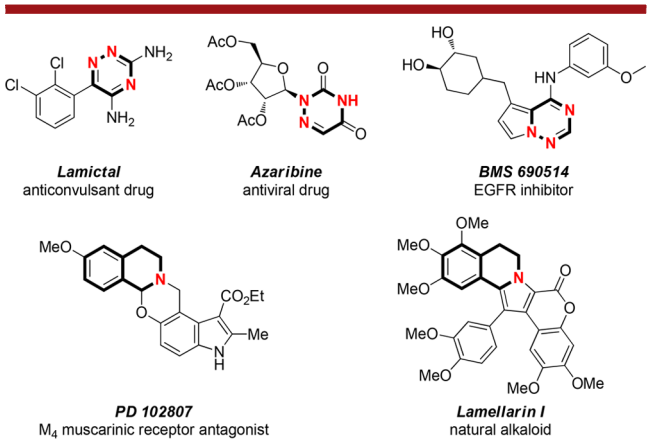
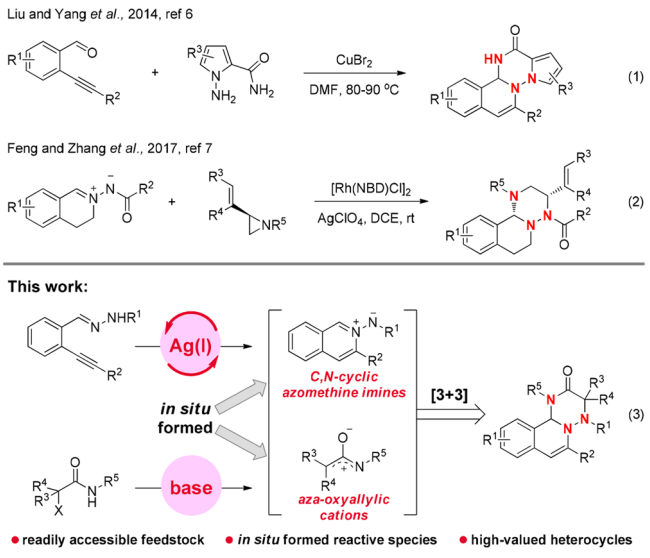


Figure 1. Examples of biologically important molecules containing 1,2,4-triazine or isoquinoline motifs.

Scheme 1. Methods toward the Construction of Isoquinoline-Fused Triazines



in synthetic organic chemistry. However, to the best of our knowledge, methods toward the construction of isoquinoline-fused triazines which contain both 1,2,4-triazine or isoquinoline motifs are still challenging and rare.

In 2014, Liu, Yang, and co-workers developed a one-pot Cu(II)-catalyzed coupling−cyclization process which provided an efficient route to pyrrolo[2,1-*f*][1,2,4]triazine-fused isoquinolines in average good yields (Scheme 1, eq 1).[6] Recently,

Received: October 26, 2017

DOI: 10.1021/acs.orglett.7b03344
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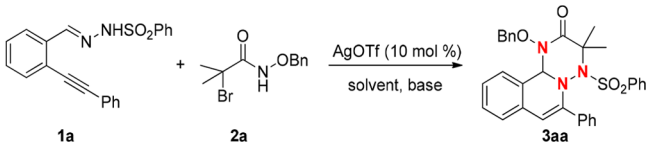
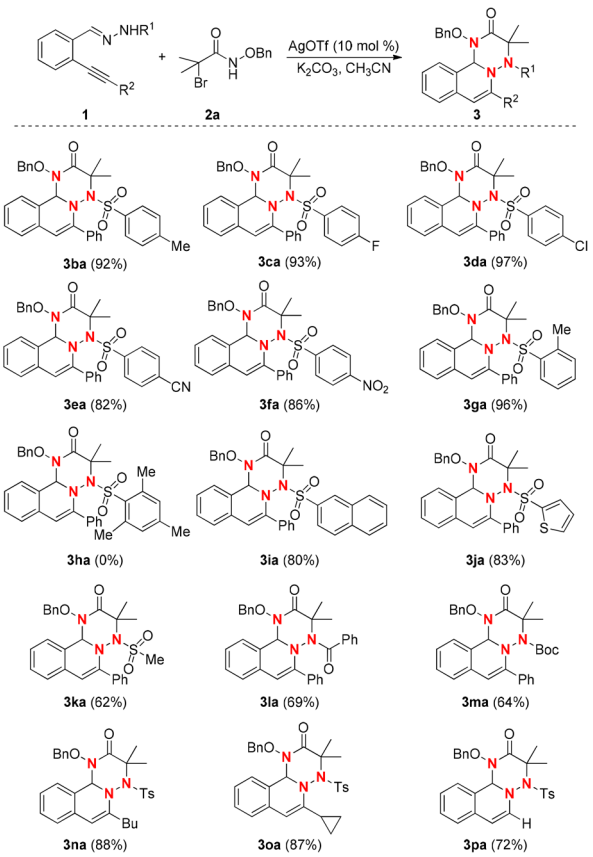
Table 1. Reaction Optimization between 1a and 2a[a]



entry	solvent	base	yield[b] (%)
1	CH_3CN	K_2CO_3	66
2	HFIP	K_2CO_3	NR
3	DCM	K_2CO_3	47
4	DCE	K_2CO_3	36
5	THF	K_2CO_3	11
6	EtOAc	K_2CO_3	trace
7	DMF	K_2CO_3	NR
8	CH_3CN	Na_2CO_3	47
9	CH_3CN	Cs_2CO_3	52
10	CH_3CN	DABCO	trace
11	CH_3CN	Et_3N	13
12	CH_3CN	DBU	16
13[c]	**CH_3CN**	**K_2CO_3**	**88**
14[d]	CH_3CN	K_2CO_3	84

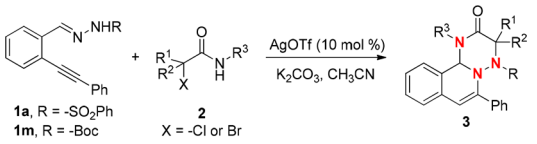
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), AgOTf (0.01 mmol), and base (2.0 equiv) in solvent (1.5 mL). [b]Isolated yield. [c]The ratio of **1a**/**2a** = 1:2. [d]The ratio of **1a**/**2a** = 2:1. HFIP = hexafluoroisopropanol, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

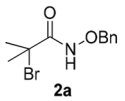
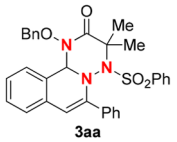
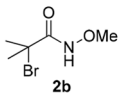
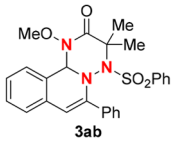
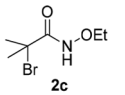
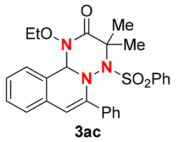
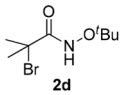
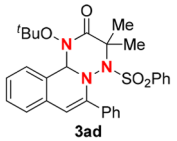
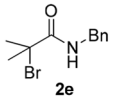
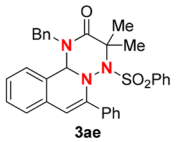
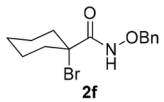
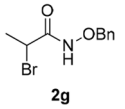
Scheme 2. Substrate Scope of Hydrazide 1[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), AgOTf (0.01 mmol), and K_2CO_3 (2.0 equiv) in CH_3CN (1.5 mL). [b]Isolated yield.

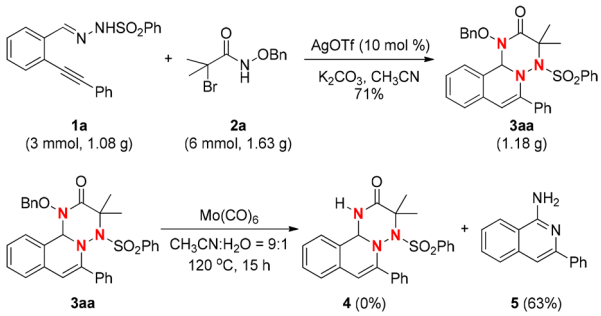
Table 2. Substrate Scope of α-Halohydroxamates 2[a]



entry	2	3	yield (%)[b]
1	 **2a**	 **3aa**	88
2	 **2b**	 **3ab**	79
3	 **2c**	 **3ac**	86
4	 **2d**	 **3ad**	89
5	 **2e**	 **3ae**	0
6	 **2f**	 **3mf**	76
7	 **2g**	 **3ag**	ND[c]

[a]Reaction conditions: **1a** or **1m** (0.1 mmol), **2** (0.2 mmol), AgOTf (0.01 mmol), and K_2CO_3 (2.0 equiv) in CH_3CN (1.5 mL). [b]Isolated yield. [c]ND = not detected.

Scheme 3. Follow-up Chemistry



DOI: 10.1021/acs.orglett.7b03344
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Feng and Zhang et al. reported a rhodium-catalyzed intermolecular [3 + 3]-cycloaddition of vinylaziridines with *C,N*-cyclic azomethine imines for the synthesis of isoquinoline-fused triazines with excellent diastereoselectivities (Scheme 1, eq 2).[7] Despite those elegant contributions, further development of efficient methodologies for the synthesis of biologically important isoquinoline-fused triazines from readily available precursors is still appealing and highly desirable.

The utilization of in situ generated aza-oxyallyl cations as ideal synthons in [3+*m*]-cycloaddition reactions has attracted considerable attention in the past several years.[8,9] Different types of m-units including sulfur ylides,[10] indole derivatives,[11] carbonyl compounds,[12] 1,3-dipoles,[13] and others[14] were sequentially investigated to conduct such valuable cycloaddition processes. Nevertheless, the cycloaddition of the in situ formed aza-oxyallyl cations with another in situ generated reactive species has not been investigated yet. Considering this shortage and the lack of sufficient methods toward the construction of biologically important isoquinoline-fused triazine scaffolds, we developed a Ag(I)- and base-mediated [3 + 3]-cycloaddition of in situ formed *C,N*-cyclic azomethine imines[15] with aza-oxyallyl cations (Scheme 1, eq 3). The significance of this method is not only due to its great potential for accessing a wide range of isoquinoline-fused triazine derivatives but also because it realizes the first example of the in situ generated aza-oxyallyl cations react with another in situ formed reactive species.

Our investigations commenced using hydrazide **1a** as the *C,N*-cyclic azomethine imine precursor and α-halohydroxamate **2a** as the aza-oxyallyl cation precursor (Table 1). It was reported that hydrazide **1a** can be easily transferred to *C,N*-cyclic azomethine imine with the assistance of AgOTf.[15c−e,i] To our delight, 66% yield of the corresponding isoquinoline-fused triazine **3aa** was obtained by using 10 mol % AgOTf with K_2CO_3 as the base in CH_3CN (Table 1, entry 1). Encouraged by this preliminary result, other reaction media were then systematically varied. As shown in Table 1, the commonly used HIFP in the cycloaddition reaction of aza-oxyallyl cations did not suitable for the process (Table 1, entry 2). Other solvents such as DCM, DCE, THF, and EtOAc turned out to be less efficient for this [3 + 3]-cycloaddition reaction (Table 1, entries 3−6), and no reaction occurred when the reaction was applied in DMF (Table 1, entry 7).[16] To further improve the reaction yields, the influence of base was next examined (Table 1, entries 8−12). Replacement of K_2CO_3 to Na_2CO_3 and Cs_2CO_3 decreased the yield of **3aa** to 47% and 52%, respectively. Notably, worse results were achieved when organic bases, such as DABCO, Et_3N, and DUB were involved (Table 1, entries 10−12). A further enhancement in the yield of **3aa** was observed upon varying the ratio of **1a** and **2a** (Table 1, entries 13 and 14), and the highest yield was achieved when 2.0 equiv of **2a** was used (88%) (Table 1, entry 13).

We then investigated the scope of this [3 + 3]-cycloaddition process by reacting various of hydrazide **1** with *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a**. As shown in Scheme 2, both electron-donating (−Me) and electron-withdrawing groups (−F, −Cl, −CN, $-NO_2$) can be successfully introduced to the *ortho*- or *para*-positions of the phenyl ring of the benzenesulfonyl moiety, affording the corresponding cycloaddition products **3ba−ga** in excellent yields (82−97%). The result clearly revealed that the electronic properties or substitution patterns variation has no obvious effect on the reaction efficiency. However, the 2,4,6-trimethylbenzenesulfonyl-substituted hydrazide **1h** did not work at all, which might because of the steric effect (**3ha**). Note that other nitrogen sulfonyl protected substrates **1i−k** also reacted well with **2a**, giving the desired heterocycles **3ia−ka** in good to excellent yields (62−83%). Remarkably, benzoyl-protected substrate **3l** and *tert*-butyloxycarbonyl-protected substrate **3m** could also be well tolerated in this reaction with the desired products **3la** and **3ma** being formed in in 69% and 64% yield, respectively. It is worth noting that the R^2-phenyl substituent could be replaced by an alkyl substituent as documented for the butyl and cyclopropyl congener. The corresponding isoquinoline-fused triazines **3na** and **3oa** were isolated in good yields. More significantly, the terminal alkyne moiety in hydrazide **1** was also proved to be suitable for this [3 + 3]-cycloaddition process, providing isoquinoline-fused triazine derivative **3pa** in 72% isolated yield.

We next turned our attention to explore the substrate scope with respect to the α-halohydroxamate component (Table 2). Good yields were also obtained when the activating benzyloxy group in α-halohydroxamates was replaced by its structural analogues, such as methyloxy, ethyloxy, and *tert*-butyloxy group (**3ab−ad**). As expected, *N*-benzyl-2-bromo-2-methylpropanamide **2e** did not react at all (**3ae**, 0%), showing that the alkoxyl group on the N atom was necessary for this [3 + 3]-cycloaddition process.[9−13] Importantly, the cyclohexyl-substituted hydroxamate **2f** worked well under the optimized reaction conditions afforded isoquinoline-fused triazine product **3mf** in 76% yield. It should be pointed out that the mono-α-substituted halohydroxamate **2g** was not suitable for this process. The reaction system was very complex, and the desired product **3ag** was not detected in this case.

The preparative utility of this method can be further demonstrated by investigating the follow-up chemistry as shown in Scheme 3. First, a gram-scale reaction of **1a** (3.0 mmol, 1.08 g) and **2a** (6.0 mmol, 1.63 g) was performed. To our delight, the reaction proceeded smoothly to give the corresponding heterocyle **3aa** in 71% yield. In order to remove the phenyl methoxyl group in the final product, we treated **3aa** with $Mo(CO)_6$ in the mixture solvent at refluxing conditions as the literature report.[13] However, the desired N−O bond cleavage product **4** was not observed. Instead, the 1-aminoisoquinoline derivative **5**, an important class of heterocycles with potentially bioactivities,[17] was isolated in 63% yield.

In conclusion, we have developed a Ag(I)-mediated [3 + 3]-cycloaddition reaction of *C,N*-cyclic azomethine imines with aza-oxyallyl cations. The method utilizes two in situ generated reactive species as the key intermediate which provides an efficient method to access a series of biologically important isoquinoline-fused triazine derivatives in good to excellent yields. More importantly, the gram-scale reaction and the transformation of the final product to biologically important 1-aminoisoquinoline derivative further renders this approach attractive and valuable. The further discovery of new cycloaddition reactions by using the in situ generated azaoxyallyl cations with other in situ formed reactive species is currently underway 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.7b03344.

DOI: 10.1021/acs.orglett.7b03344
Org. Lett. XXXX, XXX, XXX−XXX

Experimental procedures, characterization data, and ^{1}H, and ^{13}C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: xuanjun@ahu.edu.cn.

ORCID

Jun Xuan: 0000-0003-0578-9330

Wen-Jing Xiao: 0000-0002-9318-6021

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (No. 21702001) and the Start-up Grant from Anhui University for financial support of this work.

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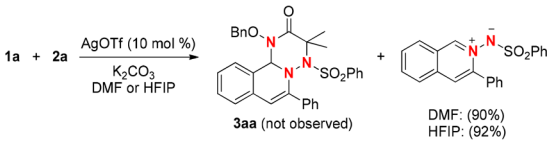

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DOI: 10.1021/acs.orglett.7b03344
Org. Lett. XXXX, XXX, XXX−XXX