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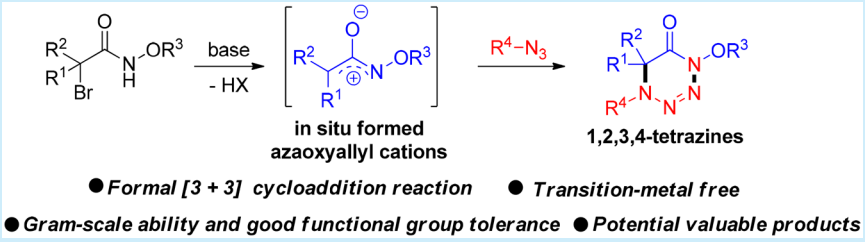
[3 + 3] Cycloaddition of Azides with in Situ Formed Azaoxyallyl Cations To Synthesize 1,2,3,4-Tetrazines

Xiaoying Xu,[†] Kaifan Zhang,[†] Panpan Li, Hequan Yao,* and Aijun Lin*

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China

Supporting Information



ABSTRACT: A formal [3 + 3] cycloaddition reaction between azides and in situ formed azaoxyallyl cations has been realized. This reaction provided an efficient and practical pathway to synthesize 1,2,3,4-tetrazines in good yields under mild conditions. Biologically active molecules could also be well compatible, highlighting the potential value of this reaction.

Heterocycles containing contiguous multinitrogen atoms are crucial motifs featured in a variety of natural products, drugs, and biologically active molecules.[1] Moreover, they could serve as pivotal intermediates or building blocks in biochemistry and materials chemistry.[2] Thus, development of efficient methods to achieve such heterocycles has attracted considerable attention over the past decades. Azides, as a class of significant nitrogen source, have been utilized to construct these frameworks.[3] Since the seminal discovery of the Huisgen reaction,[4] the transition-metal-catalyzed azide−alkyne click reaction (CuAAC,[5] RuAAC,[6] AgAAC,[7] IrAAC,[8] NiAAC,[9] RhAAC[10]) and organocatalytic [3 + 2] cycloaddition[11] of azides with in situ generated enamines, enolates, zwitterions, and acyl azoliums were applied to produce triazoles (Scheme 1, A). Moreover, triazines could be prepared through [3 + 3] cycloaddition reactions of azides with enynones/enynals and cyclopropanes (Scheme 1, B).[12] Cycloaddition of azides with nitriles, alkynes, aldehyde hydrazones, and amides was developed to gain tetrazoles (Scheme 1, C).[13] 1,2,3,4-Tetrazines with NNNN linkages were demonstrated to possess a wide spectrum of biological activities such as anticancer and antimicrobial properties.[14] However, methods to synthesize such skeletons from azides have been rarely reported and generally suffer from operational inconvenience, harsh reaction conditions, and narrow substrate scope (Scheme 1, D).[15] Therefore, developing novel and practical methods to construct 1,2,3,4-tetrazines and analogues from simple starting materials under mild conditions is highly desirable.

Cycloaddition reactions with in situ formed azaoxyallyl cations, pioneered by Jeffrey,[16] allowed the straightforward assembly of nitrogen heterocycles.[17] In this regard, we previously realized [3 + 2][18] and [3 + 3][19] cycloaddition reactions to synthesize oxazolidin-4-ones and tetrahydro-β-carbolinones with high efficiency. With our continuing interest in exploring the reaction property of in situ formed azaoxyallyl cations and constructing functional *N*-containing heterocycles, herein we present our latest work on the [3 + 3] cycloaddition reaction between azides

Scheme 1. Synthesis of Heterocycles Bearing Contiguous Multi-Nitrogen Atoms from Azides

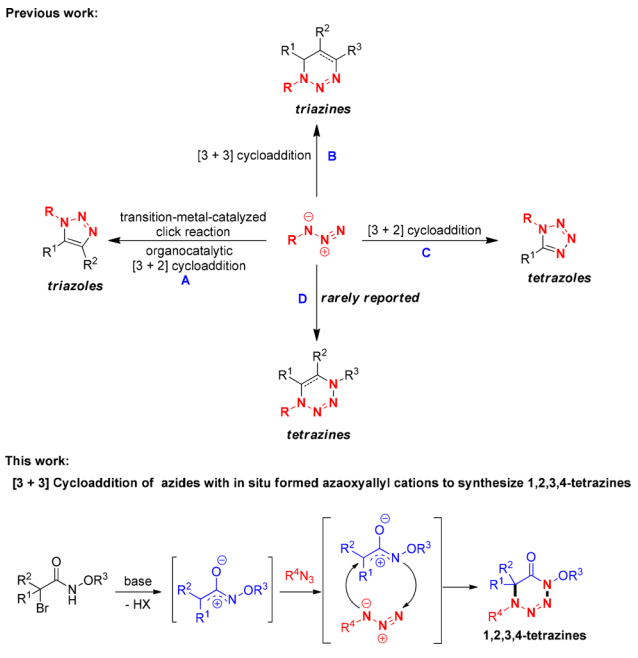


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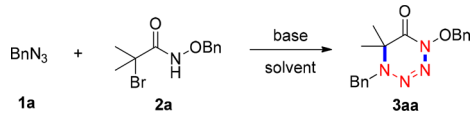
Table 1. Optimization of Reaction Conditions[a]

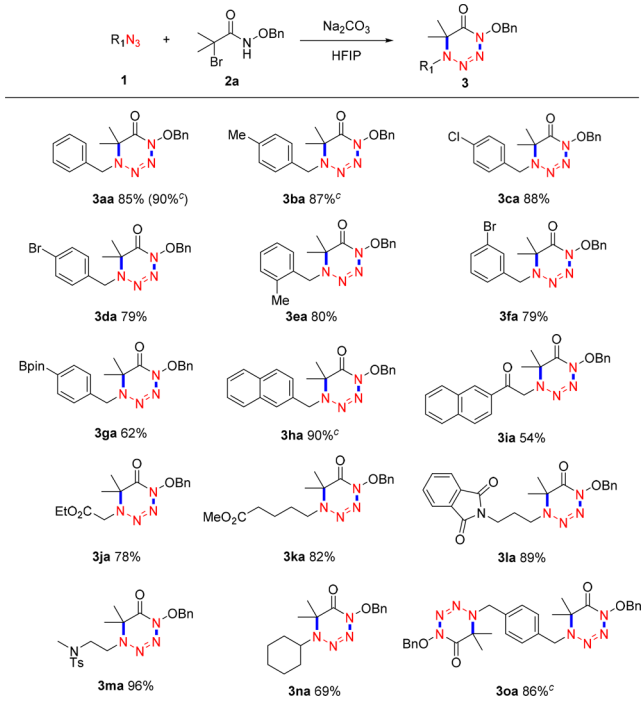


1a 2a 3aa

entry	base	solvent	time (h)	yield[b,c] (%)
1	Na_2CO_3	CH_3CN	12	nr
2	Na_2CO_3	DCM	12	nr
3	Na_2CO_3	DMF	12	nr
4	Na_2CO_3	TFE	12	22
5	Na_2CO_3	TFP	12	20
6	Na_2CO_3	HFIP	2	81
7	K_2CO_3	HFIP	2	67
8	$KHCO_3$	HFIP	2	79
9	NaOH	HFIP	2	35
10	Et_3N	HFIP	2	10
11	DIPEA	HFIP	2	43
12	DMAP	HFIP	2	73
13[d]	**Na_2CO_3**	**HFIP**	**2**	**85**

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), base (2.0 equiv) in solvent (1.0 mL) for 2 h at room temperature. [b]Isolated yields. [c]nr = no reaction. [d]1.2 equiv of **2a** was used.

Scheme 2. Substrate Scope of Azides[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.3 mmol), Na_2CO_3 (0.5 mmol) in HFIP (1.0 mL) for 2 h at room temperature. [b]Isolated yields. [c]0 °C for 10 h.

and in situ formed azaoxyallyl cations to synthesize 1,2,3,4-tetrazines (Scheme 1).

At the outset of our study, we chose (azidomethyl)benzene **1a** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** as model substrates to optimize the reaction conditions. During initial screening, the choice of CH_3CN, DCM, or DMF as the solvent gave no product in the presence of Na_2CO_3 (Table 1, entries 1−3). Considering that fluorinated solvents could stabilize the azaoxyallyl cation,[17a] we employed 2,2,2-trifluoroethanol (TFE)

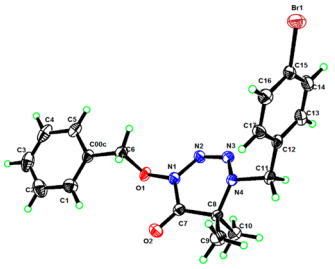
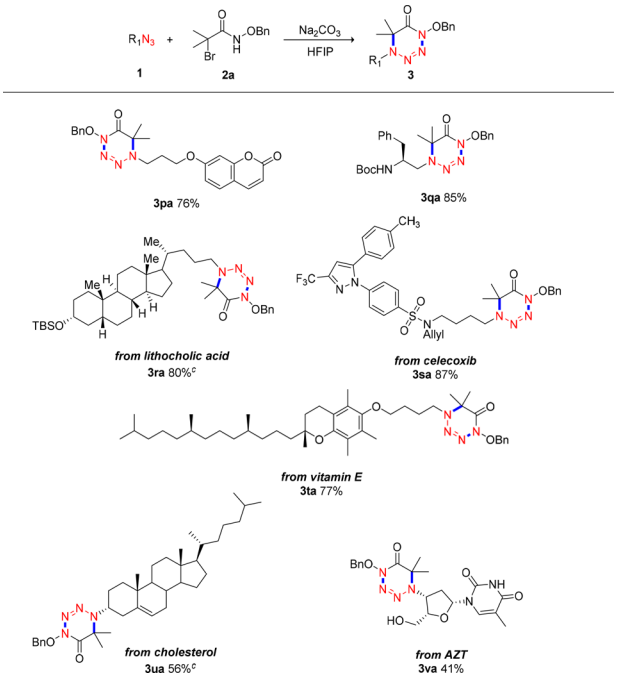


Figure 1. X-ray structure of product **3da**.

Scheme 3. Substrate Scope of Azides with Biologically Active Molecules[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.3 mmol), Na_2CO_3 (0.5 mmol) in HFIP (1.0 mL) for 2 h at room temperature. [b]Isolated yields. [c]0 °C for 10 h.

and 2,2,3,3-tetrafluoro-1-propanol (TFP) as the solvents, and the desired product **3aa** was obtained in 22% and 20% yields (Table 1, entries 4 and 5). The yield of **3aa** could be increased to 81% when hexafluoroisopropanol (HFIP) was employed (Table 1, entry 6). Na_2CO_3 gave the best results during the base test experiments (Table 1, entries 6−12). As shown in entry 13, the yield could be further improved to 85% by slightly increasing the loading amount of **2a** to 1.2 equiv.

With the optimized reaction conditions in hand, we then tested the substrate scope of azides **1**. As shown in Scheme 2, products **3ba**−**da** with methyl and halogen groups at the *para*-position of benzene ring were obtained in 79−88% yields. X-ray crystallography of **3da** unambiguously determined its configuration as shown in Figure 1. Steric hindrance did not affect the reactivity (**3ea** and **3fa**). A functional group such as Bpin was highly compatible and gave **3ga** in 62% yield. 1-Naphthyl azide functioned well and provided **3ha** in 90% yield. Satisfactorily, products **3ia** with an acyl group, **3ja** and **3ka** with ester groups, **3la** with a maleimide group, and **3ma** with a 4-methylbenzenesulfonamide group were all prepared in good yields. When secondary azide **1n** was tested, **3na** was obtained in 69% yield.

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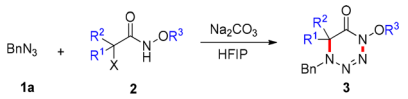
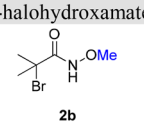
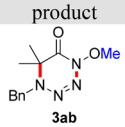
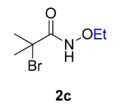
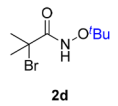
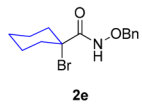
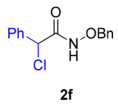
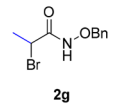
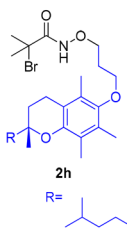
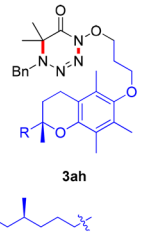
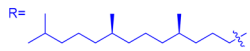
Table 2. Substrate Scope of α-Halohydroxamates[a,b]



entry	α-halohydroxamate	product	yield (%)[b]
1	 2b	 3ab	82
2	 2c	 3ac	71
3	 2d	 3ad	77
4	 2e	 3ae	56
5	 2f	 3af	26
6	 2g	 3ag	N.R.
7	 2h	 3ah	76



[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.3 mmol), Na_2CO_3 (0.5 mmol) in HFIP (1.0 mL) for 2 h at room temperature. [b]Isolated yields.

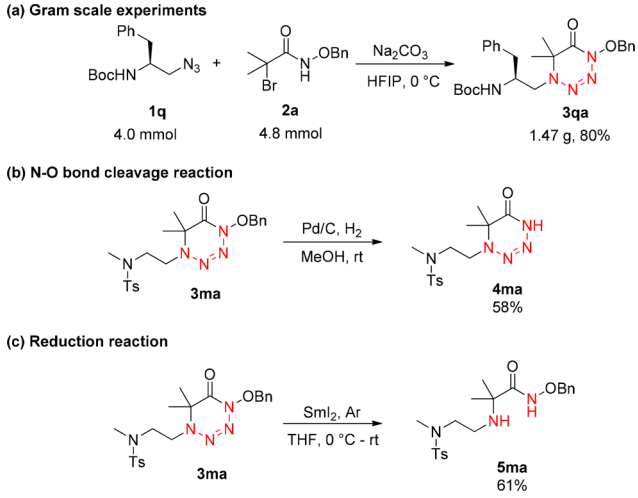
Product **3oa** with two 1,2,3,4-tetrazines was achieved in 86% yield bearing lower temperature and longer reaction time.

To demonstrate the potential generality of this innovative cycloaddition reaction, we then further expanded the substrate scope of azides with natural products and drug molecules. As shown in Scheme 3, azides with coumarin and amino acid moieties provided **3pa** and **3qa** in good yields. Lithocholic acid, as the simplest prototype of the bile acids, could successfully transformed to **3ra** in 80% yield. As a nonsteroidal anti-inflammatory drug, celecoxib is used to treat pain or inflammation caused by arthritis, ankylosing spondylitis, and menstrual pain.[20] Strikingly, compound **3sa** with both celecoxib and 1,2,3,4-tetrazine frameworks could be efficiently realized in 87% yield. The vitamin E derivative **1t** underwent cycloaddition with **2a** smoothly to deliver **3ta** in 77% yield. Given the importance of the components of cell membranes, we were pleased to find that cholesterol bearing azide readily participated in this reaction, offering **3ua** in 56% yield. The cyclization of zidovudine (AZT), a reverse transcriptase inhibitor used to treat HIV, delivered tetrazine **3va** in 41% yield.

After carefully checking the substrate scope of azides **1**, we then turned our attention to the substrate scope of α-halohydroxamates (Table 2). When the benzyl group was replaced with methyl, ethyl, and *tert*-butyl groups (**2b–d**), the corresponding products **3ab–ad** were realized in 71–82% yields. Cyclohexyl-substituted haloamide **2e** delivered **3ae** in 56% yield. When α-halohydroxamate with a monophenyl group was tested, **3af** was obtained in low yield with indefinable side reaction. Unfortunately, α-halohydroxamates bearing a monomethyl group rendered no product, probably due to the unstable azaoxyallyl cation intermediate. Interestingly, subjecting α-halohydroxamate containing vitamin E (**2h**) to the reaction conditions provided **3ah** in 76% yield.

To display the practicality and potential value of this novel [3 + 3] cycloaddition reaction, further studies were attempted as shown in Scheme 4. The reaction of **1q** with **2a** could be

Scheme 4. Further Study and Transformation of 1,2,3,4-Tetrazines



conducted on a gram scale without significant erosion in yield (**3qa**, 1.47g, 80% yield). Catalytic hydrogenation of **3ma** in methanol at room temperature afforded the N–O bond cleavage product **4ma** in 58% yield. Interestingly, the loss of dinitrogen product **5ma** could be formed in moderate yield by SmI_2-mediated reduction reaction.

In summary, we have developed a formal [3 + 3] cycloaddition reaction between azides and in situ formed azaoxyallyl cations. This method provides an efficient and practical pathway to synthesize 1,2,3,4-tetrazines in good to excellent yields under mild conditions, exhibiting good functional group tolerance and gram-scale ability. Notably, a series of biologically important molecules could be well compatible with this procedure, highlighting the potential value of this reaction. Further related studies utilizing the in situ generated azaoxyallyl cations in the construction of natural products and pharmaceutical molecules are 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.8b00280.

^1H and ^{13}C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1585564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: hyao@cpu.edu.cn; cpuhyao@126.com.
*E-mail: ajlin@cpu.edu.cn.

ORCID

Hequan Yao: 0000-0003-4865-820X
Aijun Lin: 0000-0001-5786-4537

Author Contributions

†X.X. and K.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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