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Communication

Ring opening [3 + 2] cyclization of azaoxyallyl cations with benzo[*d*]-isoxazoles: Efficient access to 2-hydroxyaryl-oxazolines

Yicheng He, Chao Pi*, Yangjie Wu, Xiuling Cui*

Department of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, China

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ABSTRACT

A selective ring-opening [3 + 2] cyclization reaction of benzo[*d*]isoxazoles with 2-bromo-propanamides has been developed. The azaoxyallyl cation intermediates are employed as C∼O 3-atom synthon to build oxa-heterocycles *via* the selectivity of suitable cyclization partners. This transformation provides rapid access to highly functionalized 2-hydroxyaryl-oxazolines under mild conditions and excellent regioselectivity.

1,3-Dipolar cycloadditions represent a powerful tool in organic chemistry because efficient and atom-economical method for constructing various heterocycles or carbocycles could be provided [1]. Among which, the azaoxyallylic cation **2** [2] generated *in situ* from α-haloamide **1** by elimination of hydrogen halide has been recently drawn considerable attention [3]. Initially, Jeffrey reported the synthesis of seven-member *N*-heterocycles *via* [4 + 3] cycloaddition of the azaoxyallylic cations with furan [4]. Since then, the [3 + m] cycloaddition of the azaoxyallylic cations **2** with cyclization partners [5] has been widely developed as a wise method to construct *N*-heteroaromatic compounds **4**, such as indole derivatives [6], carbonyl compounds [7] and sulfur ylides [8]. Theoretically, the azaoxyallylic cations **2** exist as two tautomers: amide form **2a** and imidate form **2b**. Chemists mainly focus on amide form **2a** as C∼N 3-atom synthon to afford azacycles **4**. However, the study on imidate form **2b** as C∼O 3-atom synthon to construct oxa-heterocycles is less developed [5b,5j,6d,7a,7e] because the corresponding product iminolactone take easily rearrangement to give lactams **4** [9]. We assumed that, imidate form **2b** of azaoxyallylic cations **2** could be obtained as a main tautomer under the suitable reaction conditions and react with suitable cyclization partners to give the oxacycles **5** (Scheme 1).

To verify this hypothesis, the reaction of 2-bromo-propanamides **1** and benzo[*d*]isoxazoles **3** [10] was chosen as the reaction substrates to synthesize 2-hydroxyaryl-oxazolines **5**, which is a privileged skeleton in a diverse array of biologically active molecules, such as antitumour, antibiotic and antitrypanosomally alkaloids [11]. The conventional approaches toward such a core suffer from multi-steps and harsh reaction conditions [12]. Thus, the development to efficiently build 2-hydroxyaryl-oxazolines from readily available starting materials in one pot manner under mild conditions remains significant challenge and highly desirable. Based on our research interest on construction of heterocycle [13], we explore herein a novel and effective base-mediated one-pot synthesis of hydroxyaryloxazolines **5** starting from α-haloamides **1** and benzo[*d*]isoxazoles **3** under mild and simple conditions *via* ring opening of benzo[*d*]isoxazoles, selective [3 + 2] cycloaddition and H-transfer cascade reaction. The significance of this protocol is not only due to its great potential for accessing a wide range of 2-hydroxyaryl-oxazolines but also the usage of the azaoxyallylic cations as the imidate **2b** tautomer of azaoxyallylic cation to construct oxa-heterocycles. During preparation of this manuscript, Feng reported similar work [14]. Compared to Feng's work, this method is advantageous with weak base and short reaction time.

We initiated our investigation on the model reaction of *N*-(benzyloxy)-2-bromo-2-methylpropanamide (**1a**) and benzo[*d*]-isoxazole (**3a**) to optimize various reaction parameters. The results are summarized in Table 1. The designed ring opening annulation was carried out in the absence of transition metal as a catalyst at room temperature for 0.5 h, providing **5aa** in 13% yield as the main product (entry 1). The structure was confirmed by single-crystal X-ray diffraction analysis and NMR spectra (Supporting inforamtion).

* Corresponding authors.
E-mail addresses: pichao@zzu.edu.cn (C. Pi), cuixl@hqu.edu.cn (X. Cui).

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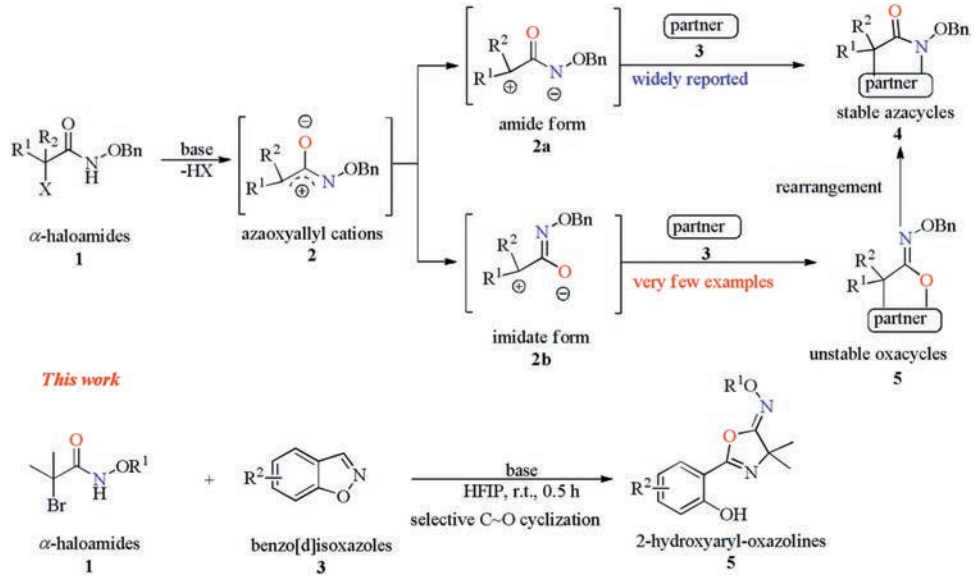
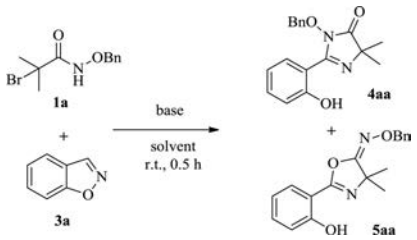


Scheme 1. Multitasking annulation modes of azaoxyallylic cations.

Table 1
Optimization of the reaction conditions.[a]



Entry	Base	Solvent	Yield (%)[b]	
			4aa	5aa
1	—	HFIP	—	13
2	KO^{t}Bu	HFIP	11	41
3	Cs_2CO_3	HFIP	13	66
4	Na_2CO_3	HFIP	15	85
5	K_2CO_3	HFIP	15	80
6	$KHCO_3$	HFIP	7	81
7	DMAP	HFIP	14	83
8	DBU	HFIP	14	58
9	NEt_3	HFIP	19	78
10	Na_2CO_3	Toluene	—	—
11	Na_2CO_3	MeCN	—	—
12	Na_2CO_3	H_2O	—	—
13	Na_2CO_3	DCE	trace	trace
14	Na_2CO_3	DCM	8	12
15	Na_2CO_3	TFE	20	16
16[c]	Na_2CO_3	HFIP	11	74
17[d]	Na_2CO_3	HFIP	10	69
18[e]	Na_2CO_3	HFIP	7	19

HFIP = hexafluoro isopropanol; DCE = 1,2-dichloroethane; TFE = 2,2,2-trifluoroethanol.

[a] If not further mentioned, the reaction carried out with **1a** (0.2 mmol) and **3a** (0.1 mmol) in the presence of base (0.4 mmol) in HFIP (1 mL) at room temperature for 0.5 h.

[b] Isolated yield.

[c] Base = 3.0 equiv.

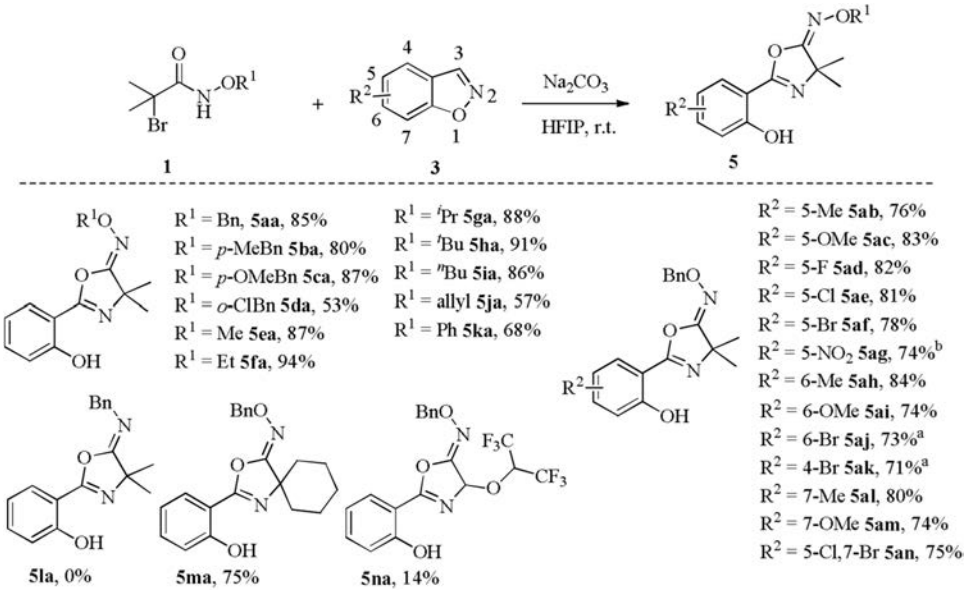
[d] **1a** = 0.15 mmol.

[e] 0 °C, 6 h.

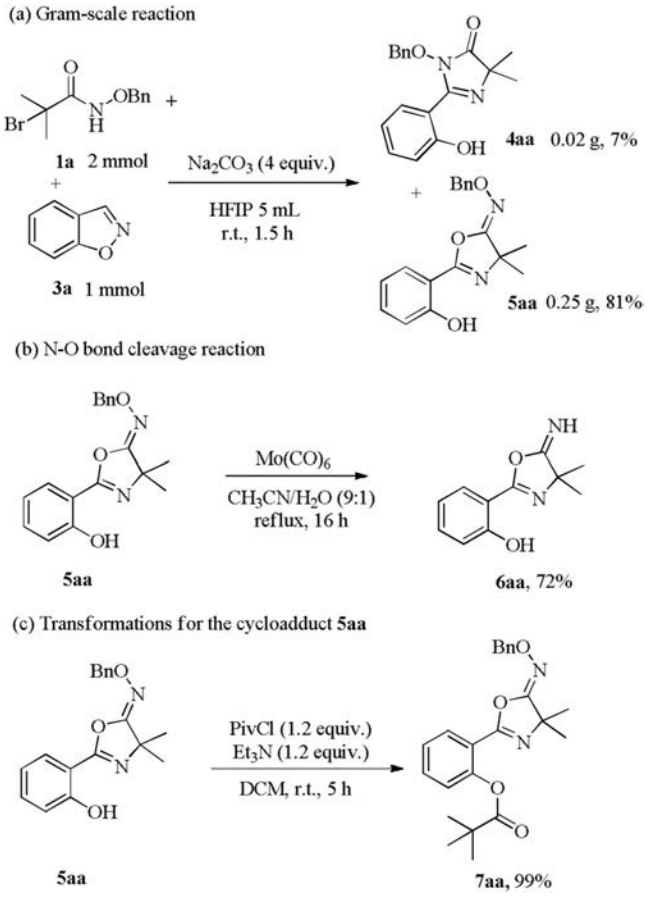
Considering the influence of base on the reactivity, we firstly used KO^{t}Bu as the base. To our delight, the desired product was isolated in 41% yield of **5aa** as well as 11% of **4aa** (entry 2). This encouraging result prompted us to investigate other commonly used bases (entries 3–9). Na_2CO_3 was proved to be beneficial than various inorganic (Cs_2CO_3, K_2CO_3 and $KHCO_3$) and organic bases (DMAP (*N*, *N*-dimethylpyridin-4-amine), DBU (2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine) and Et_3N (triethylamine)), affording product **5aa** in 85% yield (entry 3 *vs.* entries 2–9). Further screening solvent revealed that HFIP was proved to be optimal than others, such as toluene, MeCN, H_2O, DCE, DCM and TFE (entries 10–15), vastly suppressed the reactivity. It might be the HFIP plays a positive effect on the azaoxyallyl cation intermediates [15]. Moreover, with reducing the loading of **1a** or base, the yield of **5aa** decreased obviously (entries 16 and 17). When the reaction temperature decreased to 0 °C from room temperature, the target product was obtained in 19% yield (entry 18). Finally, the optimized reaction conditions (entry 4) were determined as follows: *N*-(benzyloxy)-2-bromo-2-methylpropanamide (**1a**) (0.2 mmol), benzo[*d*]isoxazole **3a** (0.1 mmol) and Na_2CO_3 (0.4 mmol) in HFIP (1 mL) at room temperature for 0.5 h.

With the optimized reaction conditions in hand, the applicability of this protocol was examined (Scheme 2). The effect of the substituents on the nitrogen atom of **1** was first examined. To our delight, electron-withdrawing or electron-donating groups (for example, -Me, -OMe, -Cl) on the phenyl ring at the aromatic alkoxy-substituents were well tolerated and gave the desired products in 53%–87% yields (**5aa-5 da**). Subsequently, we investigated aliphatic alkoxy-substituents to react with **3a**, including -Me, -Et, -^{i}Pr, -^{t}Bu, -^{n}Bn, -allyl, giving the desired products (**5ea-5ja**) in 57%–94% yield. Additionally, the reaction of *N*-phenyl-substituted 2-bromo-2-methylpropanamide **1k** with **3a** provided the corresponding product **5ka** in 68% yield. However, the expected product (**5la**) was not detected for the substrate with benzyl on the nitrogen atom. Satisfyingly, cyclohexylsubstituted haloamide **1m** reacted smoothly with **3a**, giving the desired product **5ma** in 75% yield. *N*-(Benzyloxy)-2,2-dichloroacetamide **1n** provided the unexpected product **5na** in 14% yield. Other mono-substituted haloamide were also tried as reactants, *e.g.*, monomethyl, monoethyl and monophenyl-substituted haloamide, no desired product was observed.

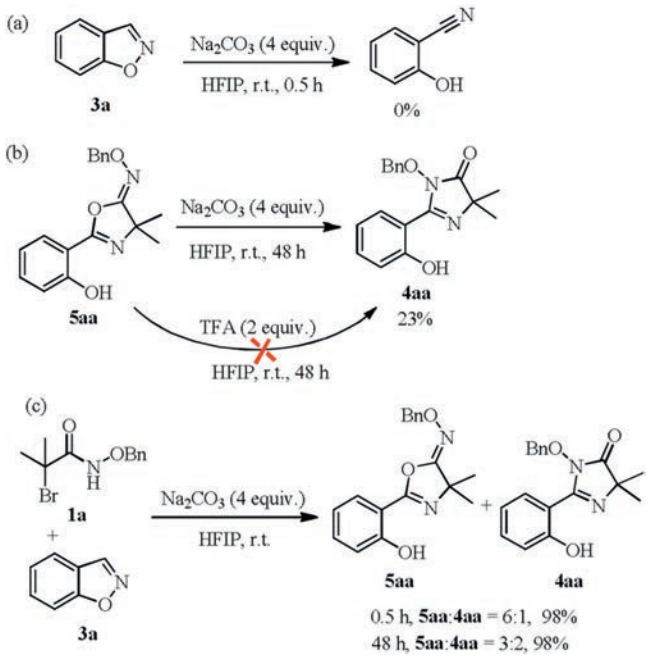
Furthermore, a range of benzo[*d*]isoxazoles were employed to probe the scope of the reaction. Satisfyingly, benzo[*d*]isoxazoles with electronic or steric effects groups proceeded smoothly with **2a** to give the desired products (**5ab-5an**) in 71%–84% yields.



Scheme 2. Extension of reaction scope. Reactions were carried out with 0.2 mmol of **1** and 0.1 mmol of **3** in the presence of 0.4 mmol of Na_2CO_3 in 1.0 mL of HFIP at room temperature for 0.5 h. Isolated yield. [a] 1 h. [b] 2 h.



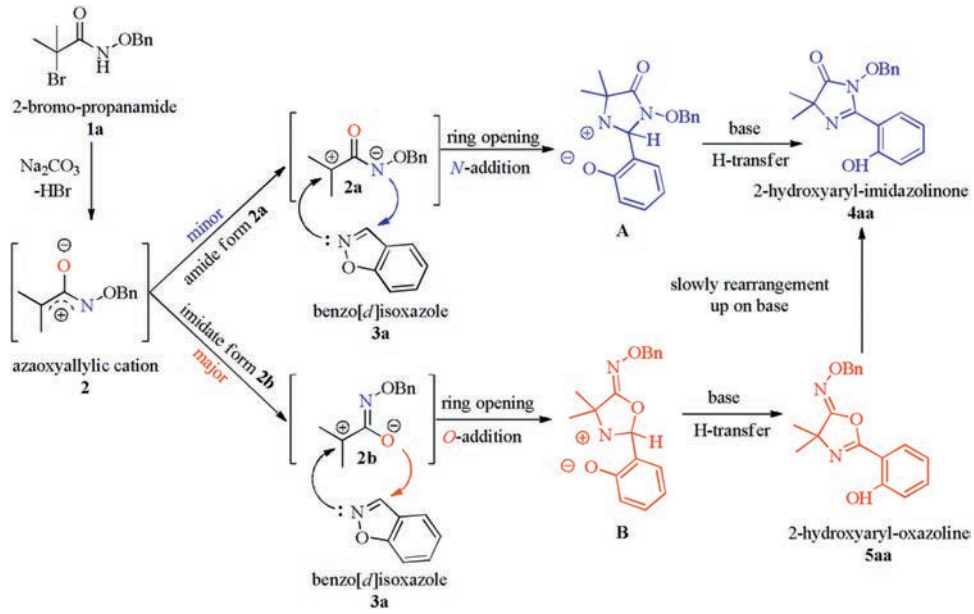
Scheme 3. Further study on [3 + 2] cycloaddition reaction between azaoxyallyl cations and benzo[*d*]isoxazoles.



Scheme 4. Mechanism study.

Electron-donating (-Me, -OMe) and withdrawing (-F, -Cl, -Br) groups at 5-position on the benzo[*d*]isoxazoles were readily coupled with **2a** to provide the corresponding products in 76%–83% yields (**5ab**-**5af**). We were delighted to find that the reaction of benzo[*d*]isoxazole with challenging groups (-NO_2) also afforded the desired product (**5ag**) in 74% yield. These results indicated that the electron density of benzo[*d*]isoxazole did not significantly affect this transformation. The 6-substituted substrates also showed excellent compatibility with various functional groups, such as -CH_3 (**5ah**), -OMe (**5ai**), -Br (**5aj**). In particular, substituents at both 4- and 7-position of **3** showed good reactivity with 71%–80% yields (**5ak**-**5am**), thus displaying tolerance of steric hindrance. Moreover, disubstituted benzo[*d*]isoxazole **3n** worked well with **1a** to provide the target product (**5an**) in 75% yield.

In order to showcase the robustness and practicality of this ring opening cycloaddition reaction, we carried out gram-scale reaction. As illustrated in Scheme 3a, **5aa** and **4aa** could be



Scheme 5. Plausible mechanism.

isolated in 0.25 g (81% yield) and 0.02 g (7% yield) under the optimized conditions, respectively. Cleavage of the N–O bond of **5aa** could be readily achieved through refluxing with $Mo(CO)_6$ in the mixture of MeCN/H_2O (9:1), and 2-(5-imino-4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenol **6aa** was obtained in 72% yield (Scheme 3b). The hydroxyl group of **5aa** could be converted to ester in the presence of PivCl (1.2 equiv) and Et_3N (1.2 equiv.) at room temperature for 5 h. The *tert*-butoxycarbonyl (Boc) group protected product **7aa** was obtained in 99% yield (Scheme 3c).

Some control experiments were investigated to clarify the reaction mechanism (Scheme 4). Initially, we wondered whether the cycloaddition reaction started from between salicylonitrile and azaoxyallylic cation. The model reaction was carried out under the optimal reaction conditions in the absence of **1a**. The substrate **3a** was not transformed to salicylonitrile (Scheme 4a). Then, when the product **5aa** was treated with base or acid, the 2-hydroxyaryl-imidazolinone **4aa** could be achieved in 23% yield with Na_2CO_3 and was not obtained with TFA, respectively (Scheme 4b). Additionally, the 2-hydroxyaryl-oxazolines **5aa** was transformed to 2-hydroxyaryl-imidazolinone **4aa** obviously by extending the reaction time from 0.5 h to 48 h under the optimal reaction conditions, indicating that the 2-hydroxyaryl-oxazolone **5aa** may obtained as the stable kinetically preferred product, further could slowly rearrange to **4aa** under certain conditions (Scheme 4c).

On the basis of the above results and previous reports, a plausible reaction mechanism is proposed in Scheme 5. Firstly, 2-bromo-propanamide **1a** was *in situ* transferred to azaoxyallyl cation intermediate **2** under weakly basic conditions. The electron-donating group (−OBn) is indispensable to stabilize this intermediate. The ensuing cycloaddition of benzo[*d*]isoxazole **3a** and azaoxyallyl cation **2** could occur through unevenly two routes. The minor tautomer amide form **2a** of azaoxyallyl cation **2** exhibits the nitrogen atom as nucleophile delivers the *N*-cyclization intermediate **A**, following a H-transfer cascade reaction to afford the product 2-hydroxyaryl-imidazolinone **4aa**. On the other hand, the major tautomer imidate form **2b** of azaoxyallyl cation **2** through processes of *O*-addition and *H*-transfer produces the desired *O*-cyclization 2-hydroxyaryl-oxazoline **5aa**. Additionally, due to their structure properties [9], the generated *O*-alkylated **5aa** could slowly rearrange to **4aa** under base condition.

In summary, we have reported a novel synthesis of 2-hydroxyaryl-oxazolines *via* regioselective ring-opening [3 + 2] cycloaddition reaction between azaoxyallyl cations and benzo[*d*]-isoxazoles, in which the imidate form intermediates (C∼O 3-atom synthon) from azaoxyallyl cations were employed as the major cycloaddition intermediates. This procedure provided an efficient route to synthesize 2-hydroxyaryl-oxazolines in good yields under mild reaction conditions, exhibiting good functional group tolerance and gram-scale ability. Further applications of this methodology to the construction of natural products and pharmaceutical molecules are currently underway in our laboratory.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.025.

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