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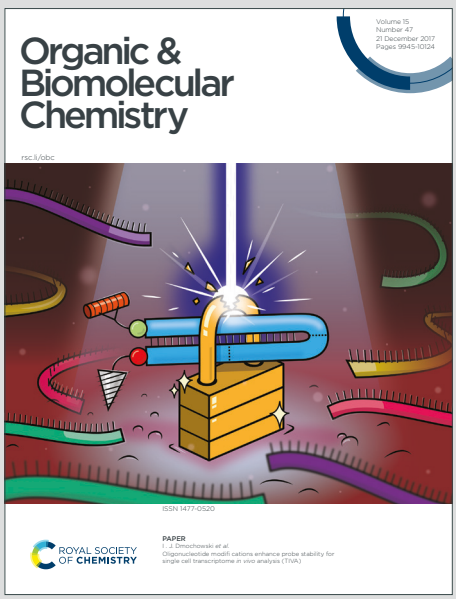

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COMMUNICATION

An Efficient Synthesis of Oxazolines via Cascade Reaction between Azaoxyallyl Cations and 1, 2-Benzisoxazoles

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A formal [3+2] cycloaddition reaction between the C and O terminals of the azaoxyallyl cations formed *in situ* and 1, 2-benzisoxazoles has been realized. This one-pot cycloaddition method provided an effective and practical pathway to s-ynthesize oxazoline in good yields under mild conditions. The titled products were observed unique fluorescent properties.

The oxazolines are important heterocyclic structure motifs in bioactive natural products and pharmaceuticals[1]. For example, the natural product DDM-838[2] was obtained from Mycobacterium tuberculosis, vulnibactin[3] served as iron chelators, and etoxazole[4] exhibited a very strong ovicidal activity against tetranycus urticae. In addition, they have also found applications in synthetic chemistry as valuable ligands[5] and exhibit tuneable luminescence properties[6] (Fig.1). Due to their biological and physical properties, oxazoline derivatives have received increasing attention from organic and pharmaceutical chemists. But developing more efficient, versatile and simple synthesis methods is still necessary.

In the past decade, α-halohydroxamates, a readily available and stable precursor of azaoxyallyl cations, has been widely developed as the key to new efficient synthesis of heterocyclic. In pioneering work, Jeffrey[7] et al. reported the intermolecular [3 + 4]-cycloaddition reactions of the azaoxyallyl with furans for the synthesis of heterocycles. Subsequently, a series of [3 + 3]-[8] [3 +2][9] [3 + 1]-[9k] and [2 + 4]-[10]cycloaddition reactions involved *in situ* formed azaoxyallyl cations were developed, in which most of the C and N terminals of azaoxyallyl cations were participated in the final bond formations. Only in few cases, the cycloaddition products with the C and O terminals of azaoxyallyl cations could be observed [Scheme 1 (1)].

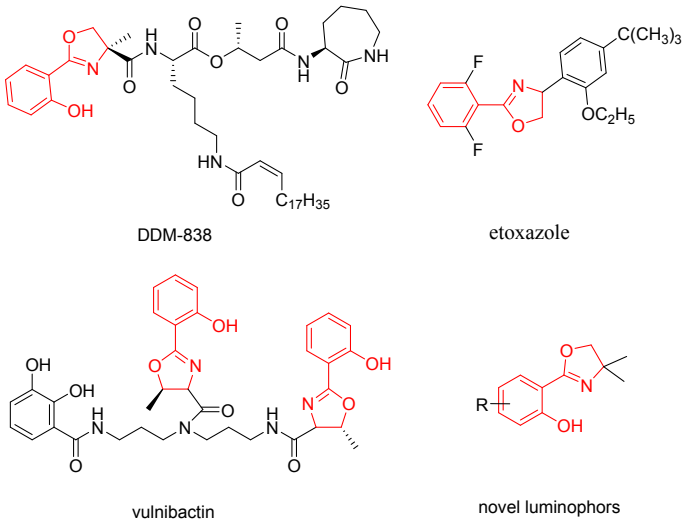

Fig. 1 Some compounds containing oxazoline ring

On the other hand, 1, 2-benzisoxazoles was also used to prepare various azaheterocycles based on the nucleophilicity of nitrogen atoms in the molecule. For example, Tang[11] proposed a [3 + 2]-cycloaddition reaction of Rh-catalyzed *N*-sulfonyl-1, 2, 3-triazole with 1, 2-benzisoxazoles. Recently, Liu[12] reported that *tert*-butyl propiolates and 1, 2-benzisoxazoles underwent [4 + 2]-cycloaddition by Au-catalysis produce 2-(2-hydroxyphenyl)-6*H*-1, 3-Oxazine-6-one derivatives [Scheme 1 (2)]. Inspired by these efforts, we envisioned that the *in situ* formed azaoxyallyl cations could be subjected to a [3 + 2]-cyclization reaction with 1, 2-benzisoxazoles. Surprisingly, X-ray crystallography (Fig. 2) revealed that cycloaddition occurred through 1, 2-benzisoxazoles with the C and O terminals of the azaoxyallyl cations rather than with the C and N terminals [Scheme 1 (3)].

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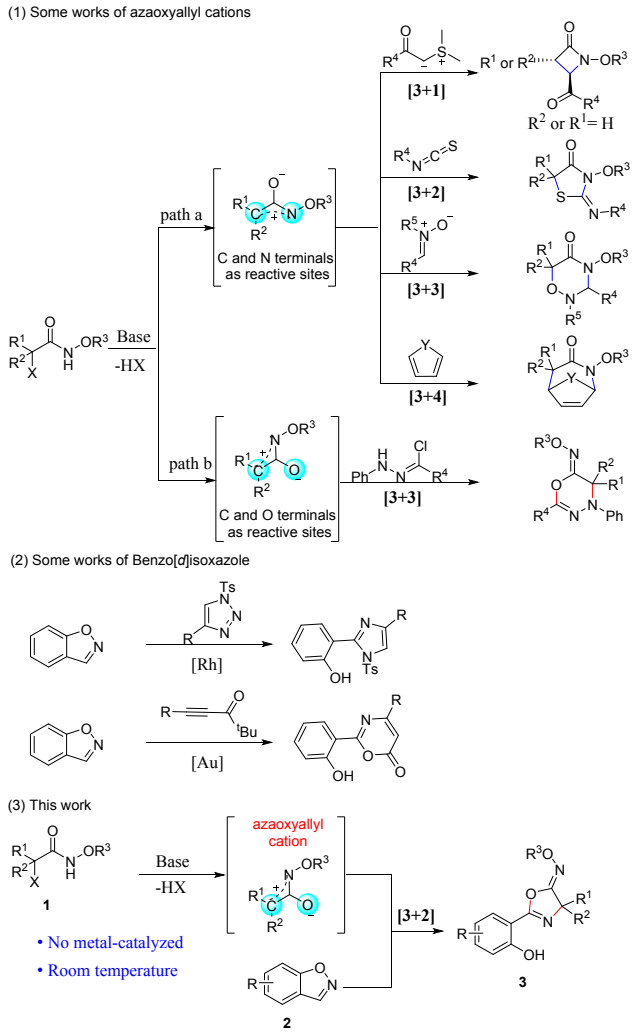


Scheme 1 Research background and assumptions

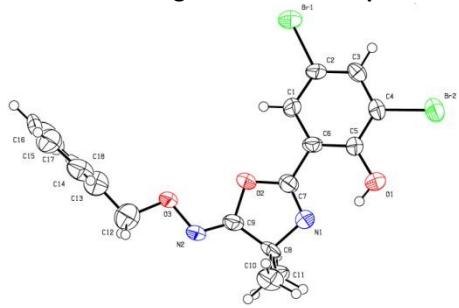
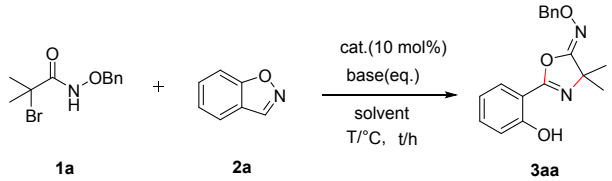


Fig. 2 X-ray crystallography of 3ao

Table 1 Optimization of reaction conditions[a]



Entry	Cat.	Base(equiv)	Solvent	T/℃,t/h	Yield[b,c](%)
1		Et_3N(2)	HFIP	25,3	74
2		DMAP(2)	HFIP	25,3	83
3		K_2CO_3(2)	HFIP	25,3	73
4		**Na_2CO_3(2)**	**HFIP**	**25,3**	**87**
5		$NaHCO_3$(2)	HFIP	25,3	39
6		CS_2CO_3(2)	HFIP	25,3	81
7		NaOH(2)	HFIP	25,3	79
8		KOH(2)	HFIP	25,3	55
9	CuI_2	Na_2CO_3(2)	HFIP	25,3	56
10	$CuCl_2$	Na_2CO_3(2)	HFIP	25,3	48
11	$Cu(OTf)_2$	Na_2CO_3(2)	HFIP	25,3	61
12		Na_2CO_3(2)	TFE	25,3	60
13		Na_2CO_3(2)	MeCN	25,18	25
14		Na_2CO_3(2)	Dioxane	25,18	29
15		Na_2CO_3(2)	THF	25,18	9
16		Na_2CO_3(2)	Toluene	25,18	NR
17		Na_2CO_3(2)	DCM	25,18	NR
18		Na_2CO_3(2)	DMF	25,18	NR
19		Na_2CO_3(2)	HFIP	0,3	83
20		Na_2CO_3(2)	HFIP	50,3	5
21		Na_2CO_3(1)	HFIP	25,3	34
22		Na_2CO_3(3)	HFIP	25,3	71
23[d]		Na_2CO_3(2)	HFIP	25,3	70
24[e]		Na_2CO_3(2)	HFIP	25,3	81
25[f]		Na_2CO_3(2)	HFIP	25,3	65

[a] The reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), base (0.4 mmol) in solvent (1.0 mL) for 3h at room temperature. [b] Isolated yields. [c] NR= no reaction. [d] 1 equiv of **2a** was used. [e] 2 equiv of **2a** was used. [f] **1a**:**2a**=1.5:1.

Initially, we selected *N*-(benzyloxy)-2-bromo-2-methylpropanamide **1a** and 1, 2-benzisoxazoles **2a** as model substrates (Table 1). The only product **3aa** was obtained under the organic bases Et_3N and DMAP in good yields 74% and 83% in HFIP, respectively (Table 1 entry 1-2). Then K_2CO_3, Na_2CO_3 and other inorganic bases were tried, the best yield of **3aa** (87%) can be isolated by using Na_2CO_3 (Table 1 entry 3-8). Since most of the reactions involved 1, 2-benzisoxazoles useing catalysts, several Lewis acids were tried. Unfortunately, no better result is produced (Table 1 entry 9-11). A brief screen of solvents showed that toluene, DCM, and DMF were unsuitable for this reaction, the yield of **3aa** in TFE was only 60% (Table 1 entry 12-18). The temperature was then further evaluated and high temperature only produced a trace amount of the **3aa** (Table 1 entry 19-20). Investigation on the feed ratios showed that 1.5 equiv of **2a** and 2 equiv of Na_2CO_3 were optimal (Table 1 entry 21-25).

After determining the optimized reaction conditions, we next examined the scope of 1, 2-benzisoxazoles substituted at aryl ring (Scheme 2). The corresponding [3 + 2]-cycloadducts were isolated in good to excellent yields. It was noted that the 1, 2-benzisoxazoles with electron-withdrawing groups result in higher yields. For example, the best yield of **3ab** (91%) was obtained. In addition, naphtha[2, 1-*d*]isoxazole was also suitable for this reaction to give **3an** in 80%. However, the 3-substituted 1, 2-benzisoxazoles did not produce the

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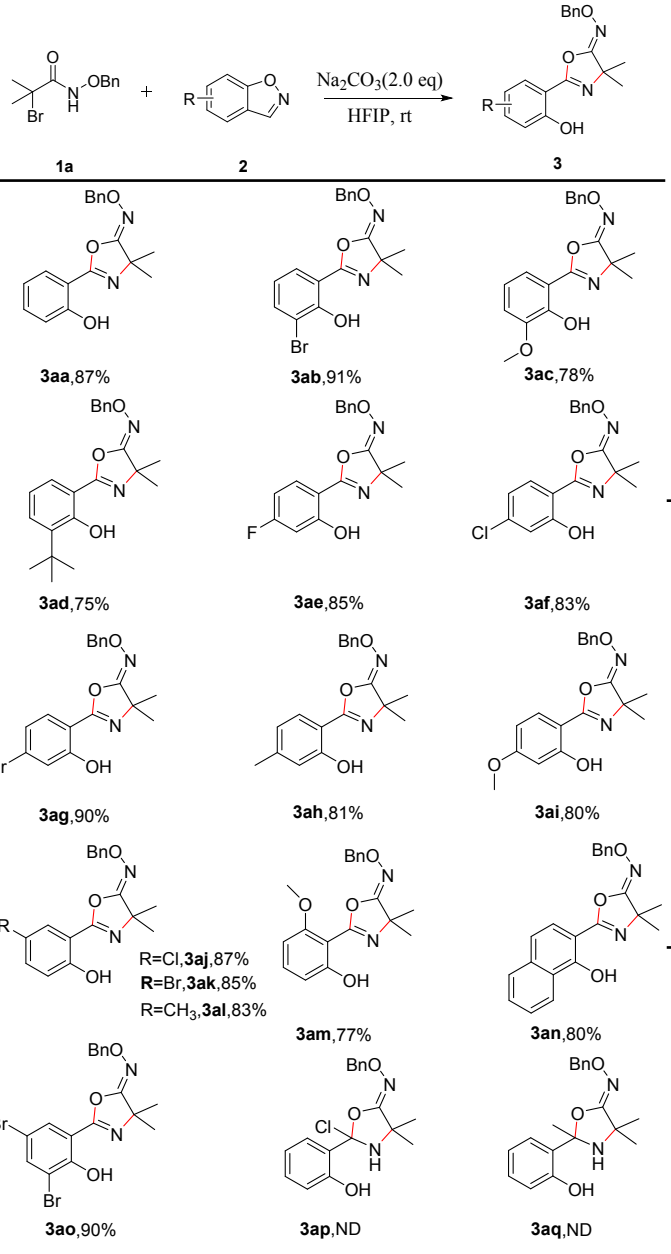
corresponding target products **3ap** and **3aq**. Then we turned to study the substrate range of α-halohydroxamates.

As shown in Scheme 3, acceptable yields were achieved when the benzyloxy group in α-halohydroxamates was replaced by its structural analogues, such as methoxy, ethoxy, allyloxy and *tert*-butoxy. However, no reaction occurred when the -OR^3 is changed from -OBn to -Bn. Fortunately, mono-alpha-substituted *N*-(benzyloxy)-2-bromopropionamide can successfully give product **3ag** with desired yield at relative high reaction temperature (50℃, 33%).

Scheme 2 Substrate scope of 1, 2-benzisoxazoless[a,b,c]

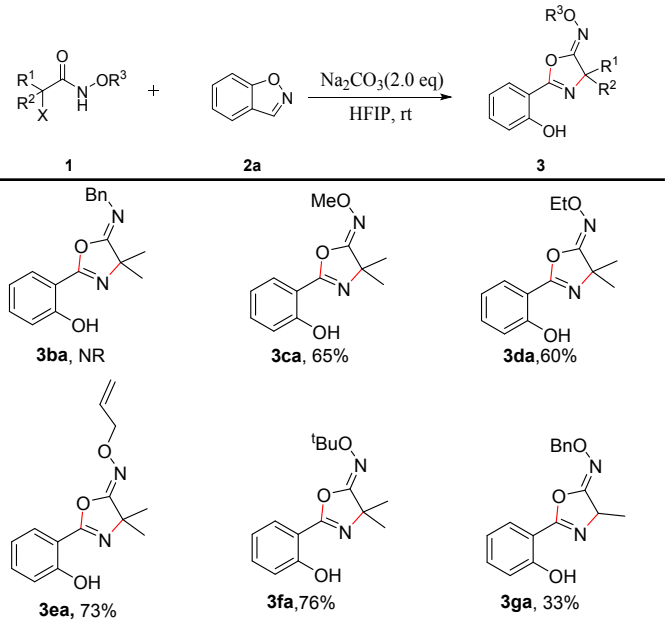


[a] Reaction conditions: **1a** (0.2mmol), **2** (0.3 mmol), Na_2CO_3 (0.4 mmol) in HFIP (1.0 mL) for 3 h at room temperature. [b] Isolated yields. [c] ND= no desired product was detected by TLC.

In order to display the practicability of the experimental method. We carried out a gram scale experiment under optimized conditions [Scheme 4 (a)], **3aa** was obtained in 1.04g (80%) without significant loss. According to the previous literature[8b, c, 9c, h, j], 3aa could be an intermediate obtained by rapid kinetic O-alkylation reaction, which may be rearranged into a thermodynamically favorable N-arylation product 4, however, only oxazole 3aa was observed in our reaction. Even if treated with TFA at room temperature for 3aa for 3 hours without any rearranged product formation [Scheme 4(b)], it finally implied that 3aa is a stable product of the cycloaddition reaction involving the C-O terminal.

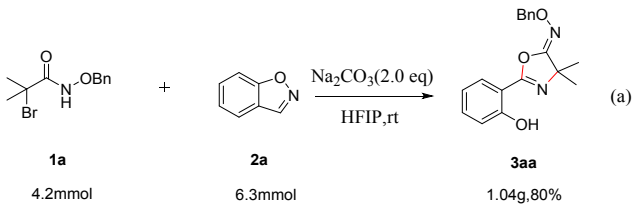
The possible reaction mechanisms are described in Scheme 5. At the beginning, azaoxyallyl cations were formed *in situ* from *N*-(benzyloxy)-2-bromo-2-methylpropanamide. Then an initial *N*-attack of 1, 2-benzisoxazole at azaoxyallyl cations to yield intermediate **A**, this *N*-attack arises from the potent nucleophilicity of the nitrogen atom. A subsequent cyclization intermediate **B**, finally readily aromatized because dissociation of the C–H proton from species **B** to give **3aa**.

Scheme 3 Substrate scope of α-halohydroxamates[a,b,c]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Na_2CO_3 (0.4 mmol) in HFIP (1.0 mL) for 3 h at room temperature or 50℃. [b] Isolated yields. [c] NR= no reaction.

Scheme 4. Related experiments



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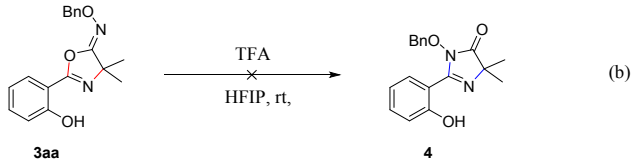
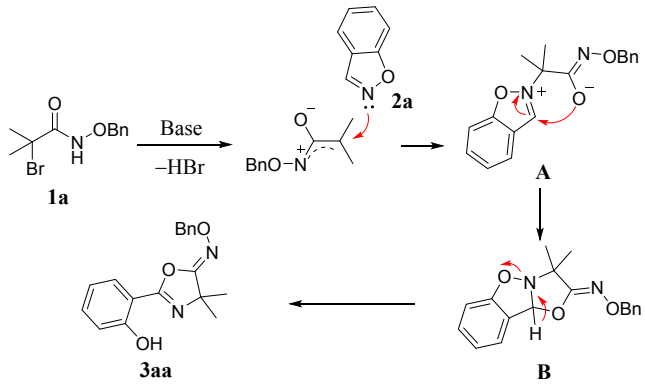


Scheme 5 Proposed mechanisms for the formation of 3aa



To investigate the synthetic utility, the **3aa** was treated with H_2/Pd in MeOH to afford oxime **5**. The products can be readily transformed into other interesting compounds due to the free hydroxyl group. For example, *O*-Michael addition product **6** was released when **3aa** was coupled with ethyl propiolate. (Scheme 6; see also Table S6 in the Supporting Information).

Interestingly, we noted that the product may have the ESIPT-based emission properties, and three selected phenols 3aa, 3ao and 3ai (Figure 3 and Table 2) were studied in dichloromethane because of the presence of an intramolecular hydrogen bond (H-bond) between the proton donor (–OH) and the proton acceptor groups in close proximity to each other in a molecule. The results of the graph show that the excitation and emission spectra of this series of compounds overlap declines, the Stokes shift is up to 20408 cm^{-1} , and the resolution of fluorescence analysis is much higher.

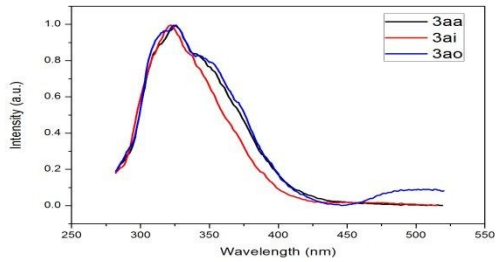
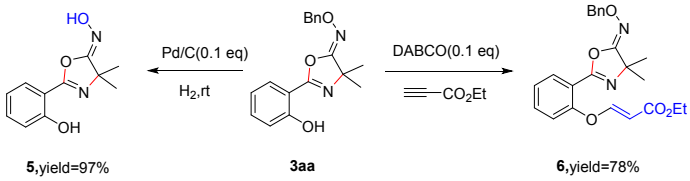


Figure 3. Normalized emission spectra of selected phenols in dichloromethane (c = 10^{-5} mol · L^{-1}).

Table 2. Emission properties of selected phenols

component	3aa	3ao	3ai
λ abs (nm)	267	266	267
λ em (nm)	326	325	326
Stokes shift (cm^{-1})	18868	18868	20408

Scheme 6. Gram-Scale and Synthetic Transformations



Conclusions

In summary, we have established a new [3+2]-cycloaddition reaction between the C and O terminals of azaoxyallyl cations with 1, 2-benzisoxazoles, which provides an effective and practical approach for the synthesis of oxazoline derivatives. The method has the characteristics of being gentle, simple and one-step. Further research is currently being conducted in our laboratory for the construction of drug molecules using *in situ* formed azaoxyallyl cations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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