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[3 + 2] Cycloaddition Reaction of in Situ Formed Azaoxyallyl Cations with Aldehydes: An Approach to Oxazolidin-4-ones

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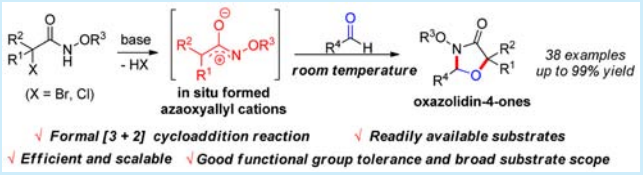
Supporting Information

ABSTRACT: A novel [3 + 2] cycloaddition reaction between in situ formed azaoxyallyl cations and aldehydes has been developed. This concise method allows the rapid formation of a number of oxazolidin-4-ones in high yields with good functional group tolerance at room temperature. Further transformation and late-stage modifications of drug molecules could also be achieved in good yields, highlighting the potential utility of the reaction.



The N,O-containing oxazolidin-4-ones are key structural motifs found in natural products and bioactive molecules with promising antimicrobial,[1] anticancer,[2] and antimigraine[3] activities, such as lipoxazolidinones A, B, and C and synoxazolidinones A, B, and C (Figure 1). Because of their bioactivities and medicinal value, oxazolidin-4-ones have received increasing attention from organic and pharmaceutical chemists in the past few decades.[4] Typical methods for the synthesis of oxazolidin-4-ones include cycloaddition reactions of oxaziridines with ketenes, azlactones, and ammonium enolates,[5] photoelimination reactions of α-keto amides,[6] domino *O*-alkylation/aza-Michael/retro-Claisen condensation reaction between enol ethers and α-bromoamido alcohols,[7] and condensation reactions between α-hydroxyamides and carbonyl compounds in the presence of acids under heating conditions.[8] Despite the fact that the aforementioned methods were of interest in constructing oxazolidin-4-ones, the development of a more efficient method with facile accessible substrates is still highly desirable.

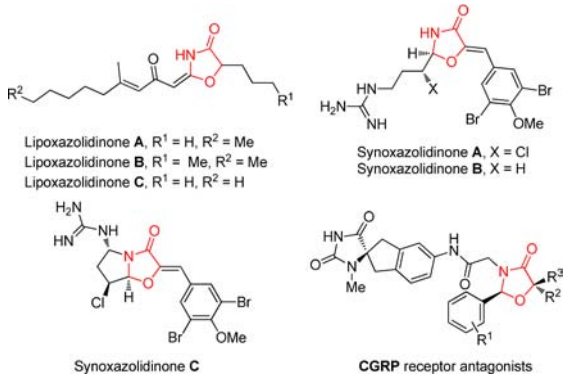
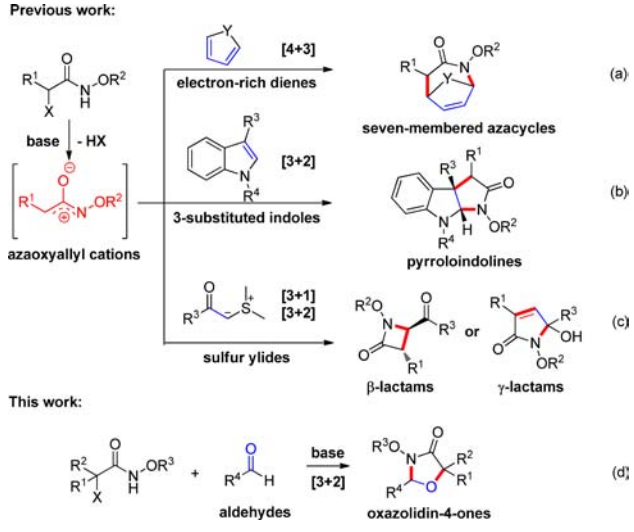


Figure 1. Selected examples of natural products and bioactive compounds with oxazolidin-4-one framework.

Recently, in situ formed azaoxyallyl cations, as newly designed versatile 1,3-dipoles, have been provided with unique chemical features for access to various heterocycles. In 2011, Jeffrey developed the first [4 + 3] cycloaddition reactions employing azaoxyallyl cations and cyclic dienes to construct seven-membered azacycles (Scheme 1a).[9] Subsequently, Jeffrey,

Scheme 1. Reactions of Azaoxyallyl Cations



Wu, and Liao realized [3 + 2] cycloaddition reactions between azaoxyallyl cations and 3-substituted indoles to synthesize pyrroloindolines independently (Scheme 1b).[10] Very recently, Chen reported that [3 + 1] and [3 + 2] cycloaddition reactions utilizing sulfur ylides as coupling partners reacted with azaoxyallyl cations for the synthesis of β-lactams and γ-lactams

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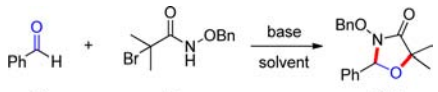
(Scheme 1c).[11] In contrast to these works with electron-rich dienes and indoles as coupling units, the [3 + 2] cycloaddition reaction of electron-deficient double bonds with azaoxyallyl cations has not been reported yet. To construct oxazolidin-4-ones through a concise pathway, we will herein explore the possibility of [3 + 2] cycloaddition reactions between in situ formed azaoxyallyl cations and ubiquitous aldehydes at room temperature (Scheme 1d).

We initiated our exploration by investigating the reaction of benzaldehyde **1a** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** (Table 1). Solvent screening indicated that no

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

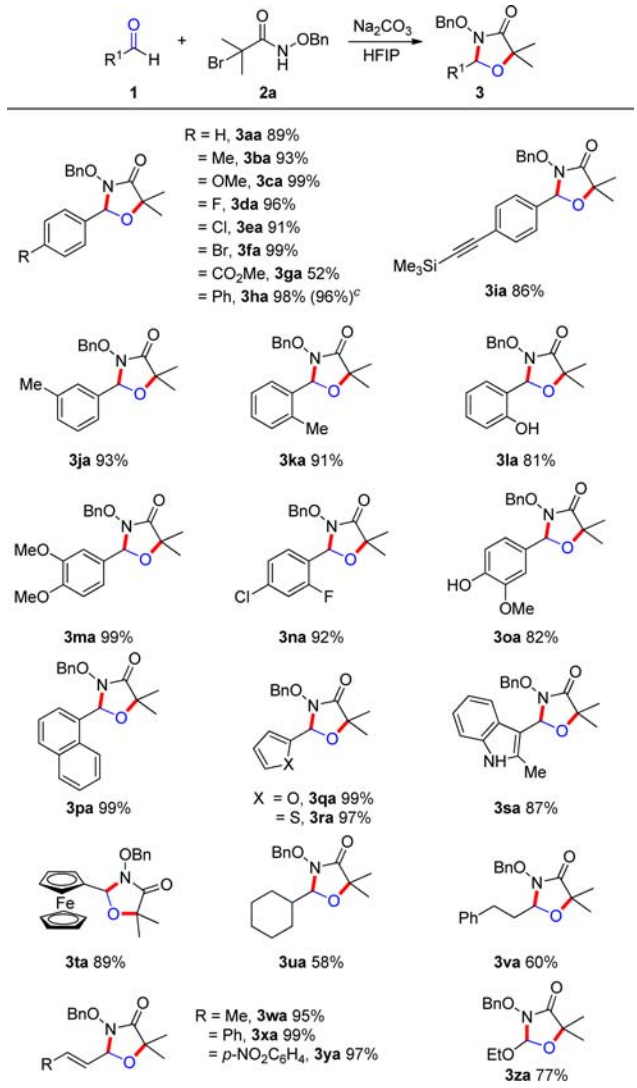
entry	base	solvent	time (h)	yield[b,c] (%)
1	Na_2CO_3	DMF	10	nr
2	Na_2CO_3	MeCN	10	nr
3	Na_2CO_3	DCM	10	nr
4	Na_2CO_3	THF	10	nr
5	Na_2CO_3	toluene	10	nr
6	Na_2CO_3	EtOH	10	nd
7	Na_2CO_3	TFE	10	46
8	Na_2CO_3	HFIP	2	74
9	$NaHCO_3$	HFIP	2	nr
10	NaOH	HFIP	2	51
11	K_2CO_3	HFIP	2	67
12	Cs_2CO_3	HFIP	2	trace
13	NaO^{t}Bu	HFIP	2	trace
14	Et_3N	HFIP	2	45
15	DMAP	HFIP	2	47
16[d]	Na_2CO_3	HFIP	2	86
17[e]	**Na_2CO_3**	**HFIP**	**2**	**89**
18[e]		HFIP	2	nr

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), base (3.0 equiv) in solvent (1.0 mL) at room temperature. [b]Isolated yields. [c]nr = no reaction; nd = no desired product was detected by TLC. [d]**2a** (1.20 equiv) was used. [e]**2a** (1.50 equiv) was used.

product could be formed in general organic solvents, such as MeCN, DCM, THF, toluene, DMF, and EtOH, in the presence of Na_2CO_3 as the base (entries 1−6). To our gratification, when 2,2,2-trifuoroethanol (TFE) was employed, the desired product **3aa** was obtained in 46% yield (entry 7), which demonstrated the effect of fluorinated solvent on the process of this [3 + 2] cycloaddition reaction.[12] Changing TFE to hexafluoroisopropanol (HFIP) gave a superior performance and afforded **3aa** in 74% yield (entry 8). Then various bases including inorganic and organic bases were examined (entries 9−15), while the yields could not be further improved compared with Na_2CO_3. Due to the recovery of some unreacted **1a**, we continued to investigate the substrate concentration (entries 16 and 17). Excellent yield (89%) could be achieved when the loading amount of **2a** was raised to 1.50 equiv (entry 17). Control experiments showed that no product was obtained in the absence of base (entry 18).

With the optimized conditions in hand, we next explored the reaction scope and generality of aldehydes (Scheme 2). Methyl, methoxyl, or halogen (−F, −Cl, −Br) groups at the *para*-position of the arylaldehydes afforded the desired products

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



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.375 mmol), Na_2CO_3 (3.0 equiv) in solvent (1.0 mL) for 2 h at room temperature. [b]Isolated yields. [c]4 mmol scale.

3ba−**fa** in 91−99% yields. The reaction became sluggish with an electron-withdrawing group at the *para*-position of the phenyl ring (**3ga**). (1,1′-Biphenyl)-4-carboxaldehyde delivered **3ha** in 98% yield. Moreover, **3ha** could be synthesized on a gram scale (1.435 g, 96% yield). Aryl aldehydes with (trimethylsilyl)ethynyl at the *para*-position afforded **3ia** in 86% yield. The cyclization with *m*-methyl- and *o*-methyl-substituted aryl aldehydes proceeded smoothly to offer **3ja** and **3ka** in 93% and 91% yields. The use of salicyl aldehyde led to the facile formation of **3la** in 81% yield. Benzaldehydes bearing disubstituted groups resulted **3ma**, **3na**, and **3oa** in 99%, 92%, and 82% yields. 1-Naphthaldehyde, heterocyclic aldehydes, and ferrocenecarboxaldehyde were also compatible, giving **3pa**−**ta** in 87−99% yields. Alkyl aldehydes afforded **3ua** and **3va** in 58% and 60% yields. Cycloaddition reactions with crotonaldehyde and cinnamaldehydes were also effective, delivering **3wa**−**ya** in 95−99% yields. Fortunately, ethyl formate could also offer **3za** in 77% yield.

With regard to α-halohydroxamates (Scheme 3), replacing the benzyl group with *tert*-butyl, ethyl, and methyl groups

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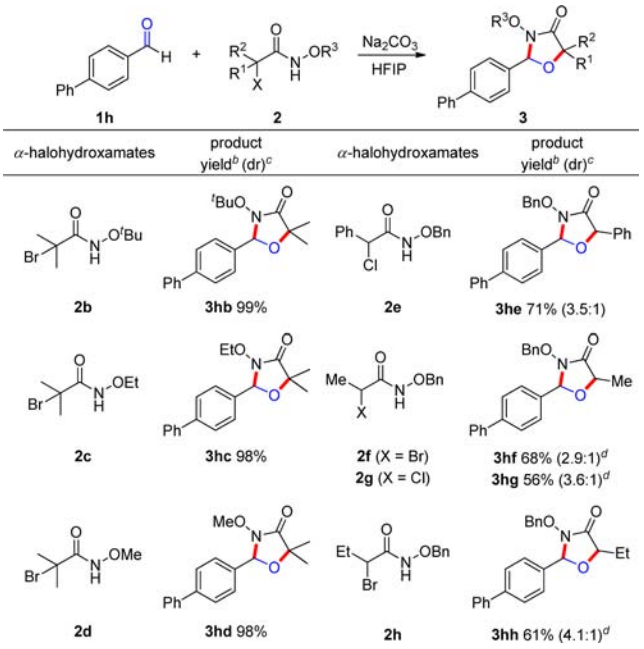
Scheme 3. Substrate Scope of α-Halohydroxamates[a]



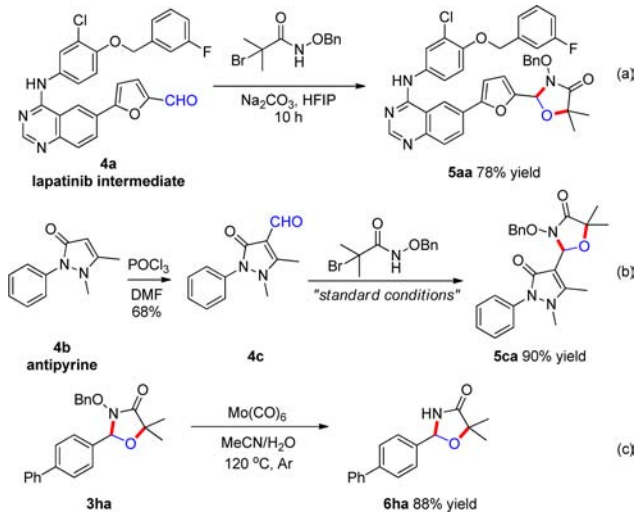
[a]Reaction conditions: **1h** (0.25 mmol), **2** (0.375 mmol), Na_2CO_3 (3.0 equiv) in solvent (1.0 mL) for 2 h at room temperature. [b]Isolated yields. [c]Diastereoisomeric ratio (dr) was determined by crude ^1H NMR analysis. [d]50 °C, 48 h.

delivered **3hb**–**hd** in excellent yields. The reaction of α-chloro hydroxamate with an α-phenyl group provided **3he** in 71% yield with 3.5:1 dr. By increasing the temperature to 50 °C and extending the reaction time to 48 h, α-halo hydroxamates with a monoalkyl group could afford **3hf**–**hh** in 56–68% yields with moderate diastereoselectivity (2.9:1–4.1:1).

In order to expand the utilities of our reaction, this innovative method was developed to modify complex drug molecules. As a dual EGFR/HER-2 inhibitor used to treat advanced or metastatic breast cancer, lapatinib has aroused wide interest from the chemical and medicinal community.[13] Herein, the oxazolidin-4-one motif could be incorporated into lapatinib intermediate **4a**, offering **5aa** in 78% yield (Scheme 4a). Antipyrine **4b** is an analgesic and antipyretic, and its derivatives have been investigated considerably.[14] The introduction of formyl group into **4b** offered substrate **4c**, which could be further transformed to antipyrine derivative **5ca** in 90% yield (Scheme 4b). The successful modification of drug molecules could be beneficial to improve the druggability and minimize adverse side effect. Then, the generated oxazolidin-4-one **3ha** was transformed as shown in Scheme 4c. *N*-Unprotected oxazolidin-4-one **6ha** could be easily synthesized by removing the phenylmethoxyl group via reflux with $Mo(CO)_6$ in the mixed solvents of MeCN and H_2O, which could be regarded as a precursor for conveniently synthesizing oxazolidin-4-one derivatives.

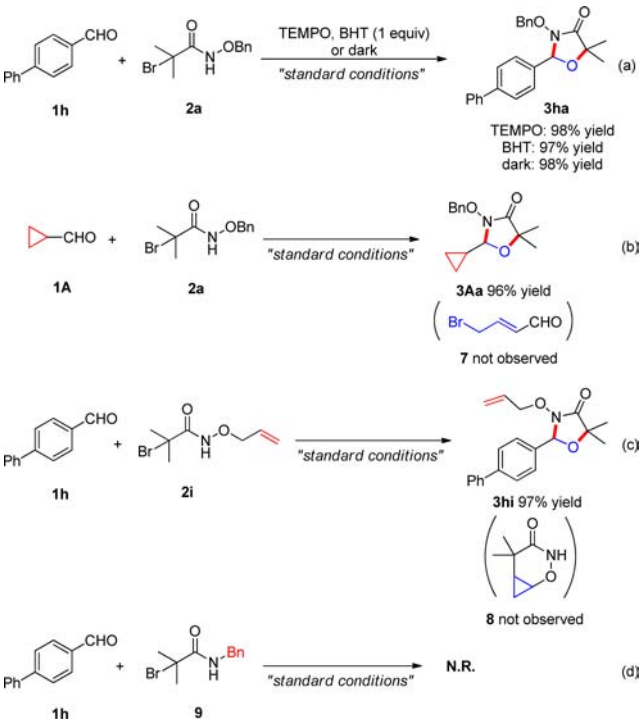
As observed in previous work, α-halohydroxamate **2a** underwent dehydrohalogenation to generate azaoxyallyl cationic intermediate, which was stabilized in HFIP by hydrogen bonding and/or dipole–dipole interaction.[9a,10b] To further demonstrate the mechanistic details of this formal [3 + 2] cycloaddition reaction, common radical scavengers TEMPO and BHT were introduced into the system, and these reactions were not restrained. This reaction could also perform well

Scheme 4. Late-Stage Modifications and Transformation



under dark reaction conditions (Scheme 5a). Cyclopropanecarboxaldehyde **1A** could react with **2a** smoothly to offer **3Aa**

Scheme 5. Control Experiments



in 96% yield rather than ring-opening product **7** (Scheme 5b), indicating that the radical process could be ruled out.[15] Moreover, *N*-(allyloxy)-2-bromo-2-methylpropanamide **2i** was prepared to further explore the reaction (Scheme 5c), and **3hi** was obtained in 97% yield without the formation of **8** through the intramolecular carbene insertion pathway.[16] Additionally, replacing the electron-donating group (–OBn) with a benzyl group (–Bn) failed to give the cycloadduct under standard conditions (Scheme 5d).

On the basis of the above results and previous work,[9a] a plausible mechanism was proposed as illustrated in Scheme 6. Under mild, weakly basic conditions, azaoxyallyl cation **A** is generated in situ, and the electron-donating group (–OBn) is

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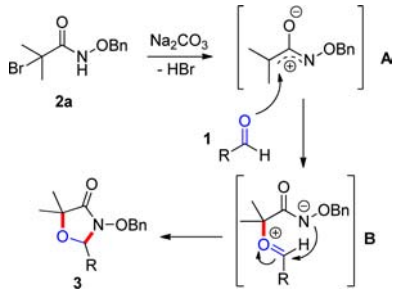
Scheme 6. Proposed Mechanism



indispensable to stabilize this intermediate. The following nucleophilic attack of **1** would deliver a zwitterion intermediate **B**. Eventually, the nitrogen anion undergoes intramolecular nucleophilic attack to form the final product **3**. On the other hand, this reaction could liberate the final product **3** through a concerted [3 + 2] cycloaddition reaction mechanism without going through intermediate **B**.

In summary, we have developed a formal [3 + 2] cycloaddition reaction between in situ formed azaoxyallyl cations and aldehydes to synthesize oxazolidin-4-ones. This concise procedure exhibited good functional group tolerance and gram-scale ability under mild conditions. Late-stage modifications of drug molecules could also be achieved in good yields, highlighting the potential utility of our reaction. Preliminary mechanism studies were conducted, and further studies of asymmetric catalytic versions are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02254.

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

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Notes

The authors declare no competing financial interest.

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