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Letter

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Access to 4-Oxazolidinones: A (3 + 2) Cycloaddition Approach

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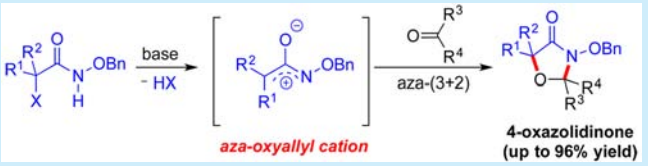
Supporting Information

ABSTRACT: The novel reactivity of *in situ* generated aza-oxyallyl cation intermediates with a variety of carbonyl compounds is reported to construct 4-oxazolidinones motifs with good yields and diastereoselectivities. This simple and efficient (3 + 2) cycloaddition method provides direct access to potential bioactive compounds.



4-Oxazolidinones are unique heterocyclic motifs present in a number of recently discovered antimicrobial natural products (Figure 1).[1−5] These natural products have been isolated from

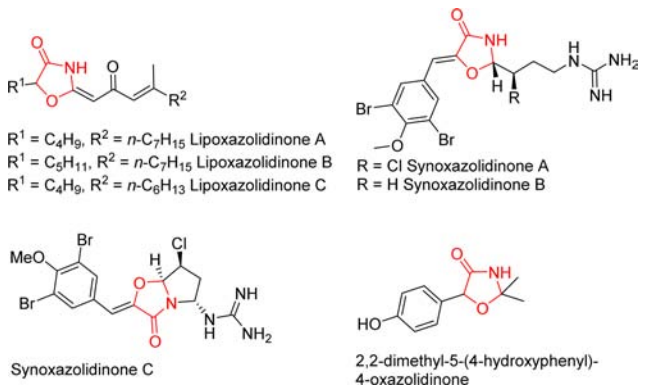
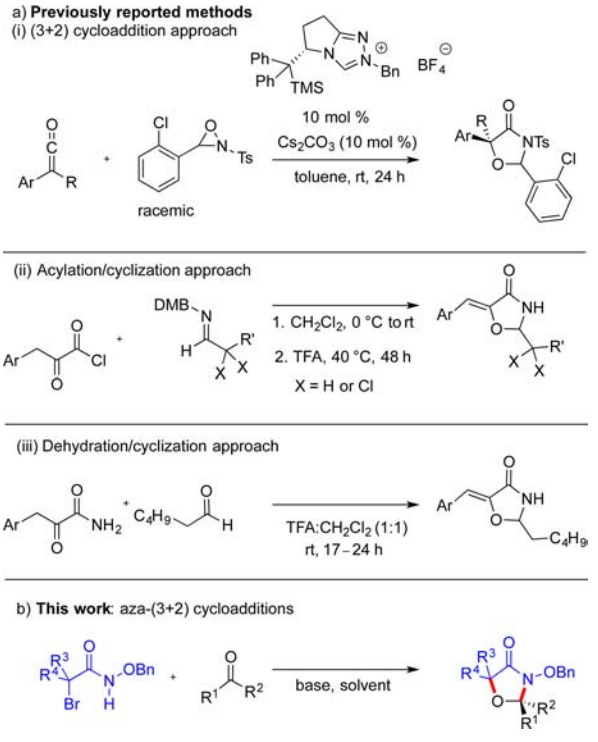


Figure 1. 4-Oxazolidinone natural products.

a variety of marine sources and share the common potent ability to inhibit the group of (Methicillin-resistant *Staphylococcus aureus*) MRSA strains of staph. MRSA is an infectious disease that plagues approximately 80 000 people per year and is commonly found to infect postoperative hospital patients.[6] Unfortunately, most current antibiotics are ineffective for the treatment of MRSA, stimulating research toward the discovery of a new anti-MRSA small molecule to combat this infectious disease. Our group became interested in a modular strategy to prepare these motifs from a formal (3 + 2) cycloaddition of aza-oxyallylic cations. Our and the Wu group followed by the Liao group recently uncovered that aza-oxyallylic cations efficiently undergo a formal (3 + 2) heteroannulation with 1,3-disubstituted indoles to afford pyrroloindolines.[7] While writing the manuscript, (3 + 1), (3 + 2),[8a] and (3 + 3)[8b] cycloaddition reactions of aza-oxyallyl cations to generate *β*-lactams, *γ*-lactams, and 1,11b-dihydro-[1,2,4]oxadiazino[3,2-*a*]-isoquinolin-2(3*H*)-ones derivatives have also been reported. The discovery of (3 + 2) heteroannulations of indoles with aza-oxyallyl cations prompted us to consider a cycloaddition reaction with a carbonyl reactant to deliver 4-oxazolidinone motifs in one step from simple starting materials. The bioactivity of these 4-oxazolidinone containing natural products has stimulated recent interest from the synthetic community. In 2010, Ye and co-workers established that 4-oxazolidinones could be prepared in enantiopure form through an organo-catalyzed reaction of aromatic oxaziridines and a ketene (Scheme 1 a, (i)).[9] Later, Pierce and co-workers developed the methods to prepare 4-oxazolidinones from *α*-ketoacid chlorides[10] or amides[11] with imines or aldehydes, respectively

Scheme 1. (3 + 2)-Cycloaddition Reactions of Aza-oxyallyl Cations with Carbonyl Compounds



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(Scheme 1a, (ii) and (iii)). This convergent method enabled the synthesis of a variety of potential anti-MRSA analogs of synoxazolidnones. Another recently reported method includes the Domino reaction of α-bromoaminoalcohol with enol-ethers.[12]

Our group has established that aza-oxyallylic cations can be generated in situ from α-halohydroxamates through a dehydro-halogenation reaction[13] or diaza-oxyallylic cations through an oxidative generation using hypervalent iodide reagents.[14] In both cases, we have demonstrated that the reactive aza- or diazaoxyallylic cations efficiently react with an indole reactant in a (3 + 2) manner[7,15] or a diene reactant through a (4 + 3) pathway.[12,13] Accordingly, we envisioned that generation of the aza-oxyallylic cation from dehydrohalogenation in the presence of a carbonyl reactant will would undergo a formal (3 + 2) heteroannulation to provide the desired 4-oxazolidinone motif. It is considered that the polarity of the carbonyl will efficiently react with the highly electrophilic aza-oxyallylic cation. Reported herein, is our study of the proposed reaction with aldehyde, ketone, ester, and amide reactants for the modular synthesis of this bioactive heterocyclic motif. Isolation of an imidate suggests a mechanism involving *O*-alkylation followed by rearrangement to the 4-oxazolidinone. While preparing a manuscript, Lin and co-workers also demonstrated a similar approach for the construction of 4-oxazolidinone using aldehyde reactants.[16]

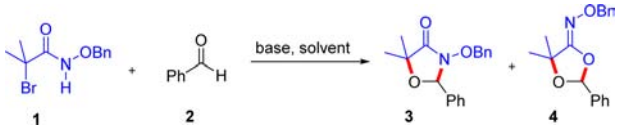
Our initial studies began with the optimization of the reaction of α-halohydroxamate **1** and benzaldehyde **2**. Our first attempts provided a trace amount of **3** of the product after 24 h of reaction time with solvolysis by TFE as a major product (Table 1, entry 1).[13a] Further optimization by switching the solvent to the less nucleophilic and more bulky HFIP solvent led to the isolation of the 4-oxazolidinone in good yield (entry 5). The rearrangement of the imidate intermediate to the 4-oxazolidinone will be discussed later in this letter. Reactions carried out with inorganic bases such as Na_2CO_3, K_2CO_3, and Cs_2CO_3 also provided good yield of products.

With the optimized conditions in hand we explored the substrate scope of the reaction with different aldehydes (Scheme 2). The reactions of aromatic (**3**, **6a–j**) and heteraromatic aldehydes **6k–l** efficiently provided the 4-oxazolidinone products in good to excellent yields. Electron-withdrawing groups in the *para* position substantially reduce the rate of reaction; however, electron-releasing groups in the *ortho* position enhance the reactivity. Saturated **6m**, unconjugated **6n**, and conjugated **6o–p** aldehydes were also found to be compatible with the reaction conditions, providing functionalized 4-oxazolidinones in good to excellent yields.

A study of the reaction with ester, amide, and ketone substrates demonstrated the versatility of this reaction, even with less reactive substrates (Scheme 3). The reaction with ethyl acetate efficiently provided the cyclic *ortho*-amide **8a** in good yield. Reactions with unsaturated lactones provided unique spirocyclic 4-oxazolidinones **8b** and **8c** in fair to good yield. DMF proved to be an excellent reactant, giving the amino *ortho*-amide in good yield. The reaction with acetone provided the stable imidate **8e** in excellent yield. Attempts to convert this imidate to the oxazolidinone under forcing conditions such as heat or acid (formic acid, trifloroacetic acid and concn HCl) only resulted in decomposition, although other ketones afforded desired products in good yield (**8f** and **8g**).

The reactions upon further exploration (Table 2) with the cyclohexyl substituted hydroxamate **9** were found to be accelerated to provide fair to excellent yields of products with aromatic, heteroaromatic, nonconjugated, and aliphatic aldehydes. However, primary amides **11** and **13** required an elevated temperature and a longer reaction time to provided 4-oxazolidinone products with moderate diastereoselectivity

Table 1. Optimization of the Cycloaddition Reaction of α-Halohydroxamate 1 with Benzaldehyde 2[a]

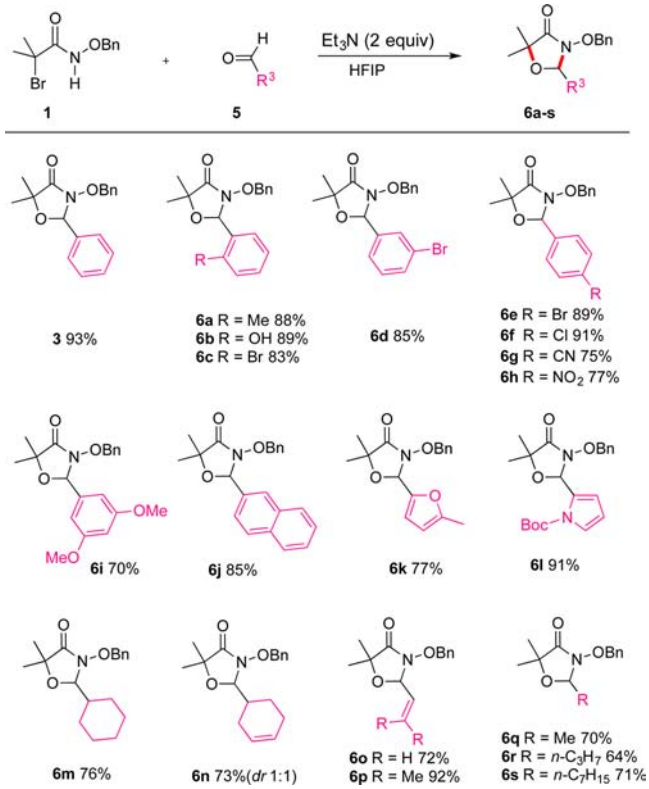


1 2 3 4

entry	base	solvent	3:4 (at 1 h)[b]	yield of 3[c] (%)
1	Na_2CO_3	TFE	1:1	>5
2	Na_2CO_3	HFIP	3:1	86
3	K_2CO_3	HFIP	3:1	92
4	Cs_2CO_3	HFIP	3:1	87
5	Et_3N	HFIP	3:1	93
6[d]	Et_3N	HFIP	3:1	75

[a]Reactions are carried out with α-halohydroxamate (1 equiv) with benzaldehyde (1.1 equiv) and base (2 equiv) dissolved in solvent (0.25 M) at 0 °C and stirred at room temperature up to 24 h. [b]Relative ratio from crude NMR analysis. [c]Isolated yield after complete conversion of **4** to **3**. [d]1.2 equiv of α-halohydroxamate **1**. TFE: 2,2,2-trifluoroethanol. HFIP: Hexafluoroisopropanol.

Scheme 2. Substrate Scope for the (3 + 2) Cycloadditions of Aza-oxyallyl Cationic Intermediates with Aldehydes[a]



[a]Reactions are carried out with α-halohydroxamate (1 equiv) with aldehyde (1.1 equiv) and base (2 equiv) dissolved in solvent (0.25 M) at 0 °C and stirred at room temperature until complete consumption of α-halohydroxamate starting material.

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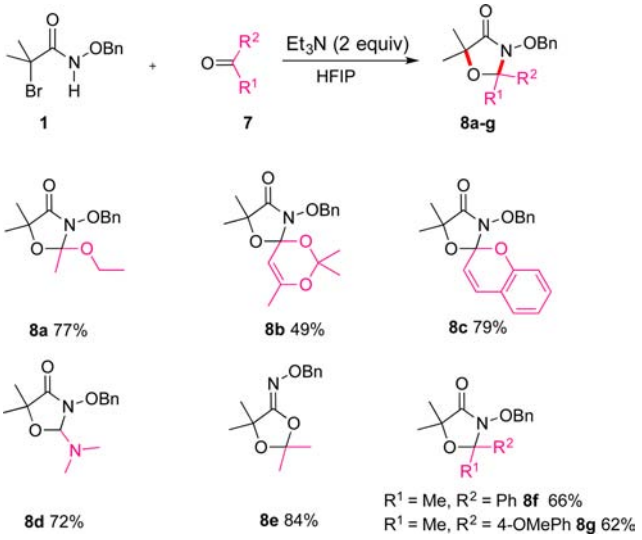
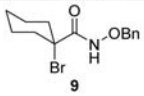
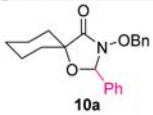
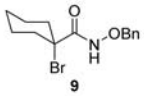
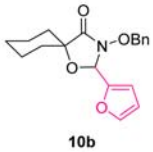
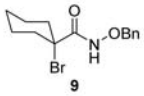
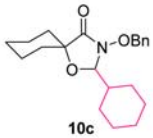
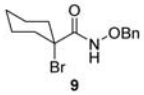
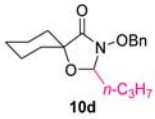
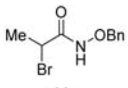
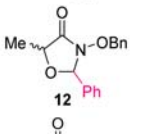
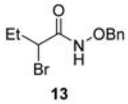
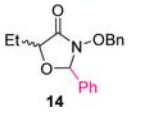
Scheme 3. Substrate Scope for the (3 + 2) Cycloadditions of Aza-oxyallyl Cationic Intermediates with Esters, Amides, and Ketones[a]



[a]Reactions are carried out with α-halohydroxamate (1 equiv) with the carbonyl substrate (1.0−10.0 equiv), base (2 equiv) dissolved in solvent (0.25 M) at 0 °C and stirred at room temperature until complete consumption of α-halohydroxamate starting material.

Table 2. Study of (3 + 2) Cycloadditions for Varieties of α-Halohydroxamates with Benzaldehyde[a]

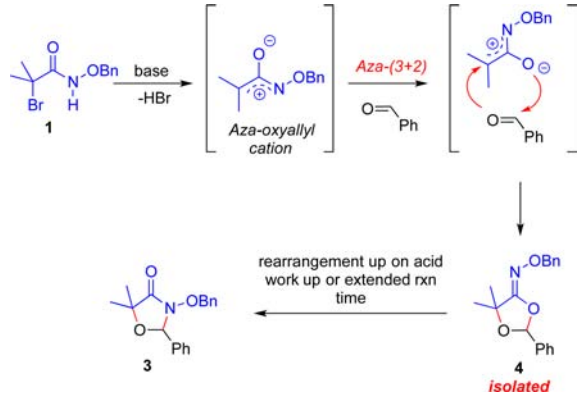
sn	haloamides	product	yield(%) (*dr*)[b]
1	 9	 10a	96
2	 9	 10b	73
3	 9	 10c	52
4	 9	 10d	47
5[c]	 11	 12	85 (3.7:1)
6[c]	 13	 14	70 (4.2:1)

[a]Reactions are carried out with α-halohydroxamate (1 equiv) with aldehyde (1.0−5.0 equiv) and base (2 equiv) dissolved in solvent (0.25 M) at 0 °C and stirred at room temperature until complete consumption of α-halohydroxamate starting material. [b]Diastereomeric ratio from crude NMR analysis. [c]At 70 °C.

(Table 2, entries 5 and 6) and good yield. This reactivity trend was consistent with our previous findings.[7a,13]

The isolation of the imidate products **4** and **8e** from the reactions and the apparent rearrangement to the 4-oxazolidinone products led to the following mechanistic hypothesis (Scheme 4). Consistent with the reports of Wu

Scheme 4. Proposed Mechanistic Pathway



and co-workers on oxyallyl cation[15] and aza-oxyallyl cation intermediates,[7b] we believe that the aza-oxyallylic cation undergoes a C−O annulation reaction to directly provide the imidate **4**. Wu and co-workers computationally provided support for the idea that the (3 + 2) reaction of oxyallylic and aza-oxyallylic cations with indoles proceeds by initial carbon−carbon bond formation and ring closure with the oxygen of the carbonyl followed by a rearrangement to the pyrroloindoline. Their computational results[7b,17a] were further supported experimentally by the isolation of an *O*-alkylated cycloadduct of the reaction of a 1,3-disubstituted indole with the haloketone, which provided the carbocycle fused indoline product, through an O to C rearrangement.[15] We therefore propose that the initial cycloaddition of an aza-oxyallyl cation occurs via C and O bond formation to provide the imidate **4**. This imidate then rearranges to the 4-oxazolidinone **3** upon extended exposure to the reaction conditions or via acid catalysis in the workup. It is apparent that substitution of the carbonyl reactant greatly changes how facile this rearrangement is. We observed that substituents that provide resonance stabilization to the cation rapidly rearrange to the 4-oxazolidinone products **3**, whereas less stabilizing substituents form more stable imidates, which require an acid catalyzed workup to force rearrangement (**6g−i**, **6m−s**, **10c−d**, **12**, **14**). The failed rearrangement of the acetone adduct **8e** suggests that the stability of the product dramatically slows the rearrangement. Additionally, consistent with our previous reports,[13] substrates without electron-releasing groups on the nitrogen failed to stabilize the aza-oxyallyl cation.

In order to address the viability of this reaction in the synthesis of N−H 4-oxazolidinone natural products, we explored the cleavage of the N−OBn bond. Here, we found that the reaction with SmI_2 in THF efficiently cleaved the N−O bond and provided the parent N−H substituted oxazolidinone in good yield (Scheme 5).

In conclusion, we have achieved a novel single step method to access 4-oxazolidinones by direct (3 + 2)-cycloaddition reactions of simple α-halohydroxamates and carbonyl compounds. Aldehydes, ketones, esters, and amides provide anticipated 4-oxazolidinones products in good to excellent

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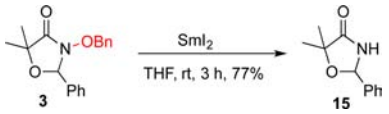
Scheme 5. N−O bond Cleavage Reaction of 3



yields. Further exploration of the method toward the natural products synthesis and bioactivity tests are presently under study.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03069.

Experimental procedures, tabulated characterization data, and copies of ^{1}H NMR 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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