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Graphical Abstract

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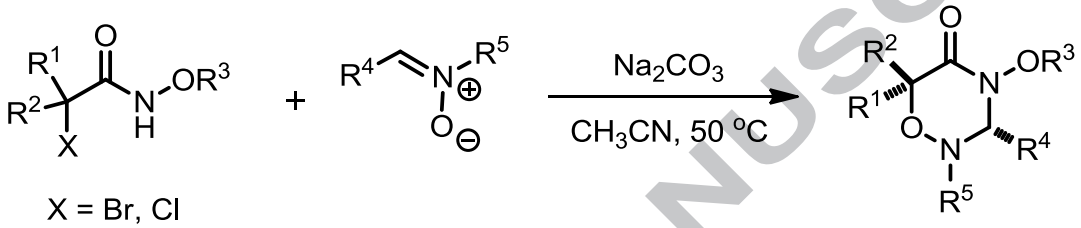
An efficient synthesis of 1,2,4-oxadiazinan-5-ones via [3+3] cycloaddition of *in situ* generated aza-oxyallyl cations with nitrones has been developed, The protocol features easy operation, excellent yields, excellent diastereoselectivities, broad substrate scope and good functional group tolerance.



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A Highly Diastereoselective [3+3] Annulation Reaction of Aza-oxyallyl Cations and Nitrones

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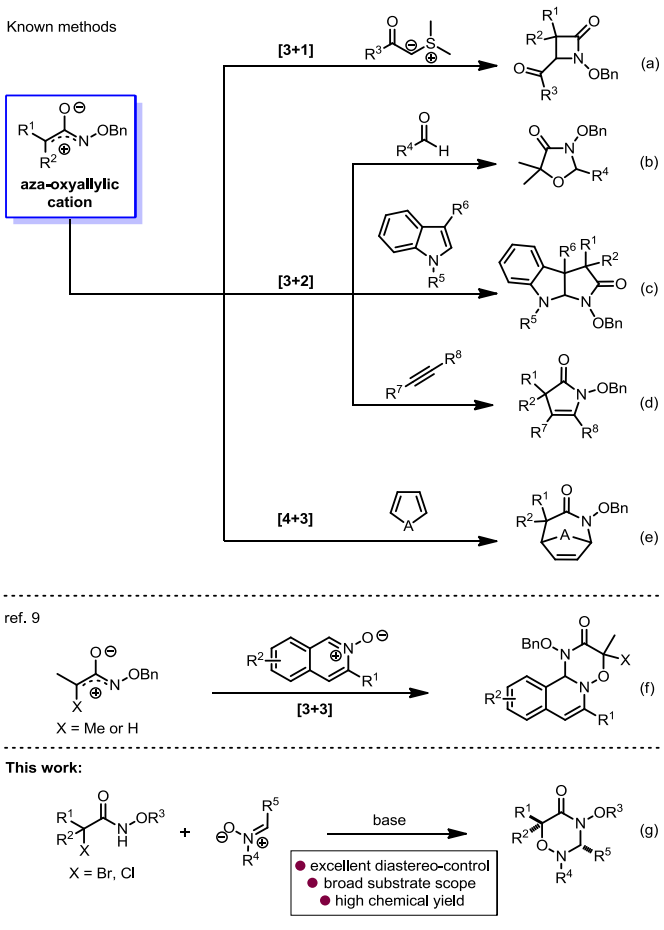
ABSTRACT

An efficient synthesis of 1,2,4-oxadiazinan-5-ones via [3+3] cycloaddition of *in situ* generated aza-oxyallyl cations with nitrones has been developed, The protocol features easy operation, excellent yields, excellent diastereo-control, broad substrate scope and good functional group tolerance.

The aza-oxyallylic cation intermediates had long been investigated since the Sheehan group reported it in 1960s[1] and following confirmed by Sakamoto *et al*.[2] Owing to its unique chemical properties, many efforts have been made to use these intermediates to rapidly construct medicinally important heterocycles[3]. In 2011, the Jeffrey group reported an elegant [4+3] cycloaddition reaction of aza-oxyallylic cations with dienes[4], resulting in a bridged bicyclic compound (Scheme 1e). Later on, the Jeffrey group and others discovered a novel [3+2] cycloaddition by utilizing aza-oxyallylic cations as intermediates to react with various substituted indoles, affording pyrrolindolines in good to excellent yields[5]. Recently, Wang, Lin and Jeffrey successfully uncovered a [3+2] cycloaddition of aza-oxyallyl cations to aldehydes respectively (Scheme 1b-c)[6]. Additionally, Xing and co-workers conducted the synthesis of 1,3-dihydro-2H-pyrrol-2-one derivatives by using a [3+2] cycloaddition of aza-oxyallylic cations and alkynes (Scheme 1d)[7]. Shortly after, Chen and co-workers reported [3+1] (Scheme 1a) and [3+2] cycloaddition reactions of azaoxyallyl cations with sulfur ylides to give β- and γ-lactam derivatives[8]. In contrast to other intensively studied cycloadditions of aza-oxyallylic cations, to date, the [3+3] cycloadditions of aza-oxyallylic cations received much less attention. There is an only example of [3+3] cycloaddition of azaoxyallyl cations reported by Wu *et al*. very recently (Scheme 1f).[9]

On the other hand, nitrones are useful synthons and used as versatile 3-units in [3+2][10] or [3+3][11] cycloaddition reactions[12] for the construction of densely functionalized five- or six-membered N,O-containing heterocycles[13]. Meanwhile, most nitrones are stable compounds that could be operated easily. As part of our interests on seeking efficient methods for heterocyclic synthesis,[14] we herein wish to report a practical procedure for making 1,2,4-oxadiazinan-5-ones through a formal [3+3] cycloaddition of

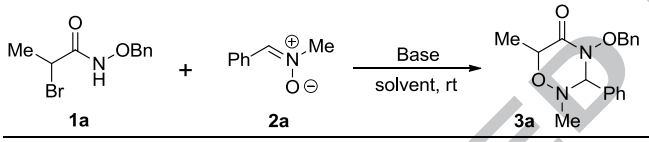


Scheme 1. Cycloaddition reactions of aza-oxyallyl cations.

nitrones with aza-oxyallylic cations under mild conditions (Scheme 1g).[15] Considering the easily preparation of azaoxyallyl cations and excellent diastereo-control of this process, we believe our method has developed a formal [3+3] cycloadditions.

The model reaction of *N*-(benzyloxy)-2-bromopropanamide **1a** and nitrone **2a** in the presence of Na_2CO_3 was initially investigated. As shown in Table 1, the solvent seems to play a critical role on reaction efficiency. CH_3CN allows the reaction proceeded smoothly to afford the corresponding 4-(benzyloxy)-2,6-dimethyl-3-phenyl-1,2,4 oxadiazinan-5-one **3a** in good yield and excellent diastereoselectivity (entry 7, 73%, >19: dr, 24 h). To our delight, elevating temperature to 50 °C yielded **3a** almost quantitatively in 3 h only (entry 8, 98%). Nevertheless, no product was achieved when the reaction was carried out in other solvents such as methanol, trifluoroethanol (CF_3CH_2OH), DCM, THF and DCM (entries 1-2, 4-6). Hexafluoroisopropanol (HFIP) could give the desired product **3a** in a moderate yield (65%), but only with a poor diastereoselectivity (entry 3, 1.6:1 dr). Further study showed that the base is also another critical factor for the reaction efficiency (entries 9-14). Organic bases (e.g. pyridine, DBU) and inorganic base (e.g. NaOAc) almost did not promote the reaction (entries 10, 12-14). Surprisingly, K_2CO_3, NaOH and TEA provided fair to moderate yields of **3a** (entries 9, 11, and 14, 75%, 32%, and 53%, respectively). Finally, the optimal conditions were achieved when the reaction was performed in the presence of Na_2CO_3 as base and CH_3CN as medium.

Table 1. Optimization of the reaction conditions.[a]

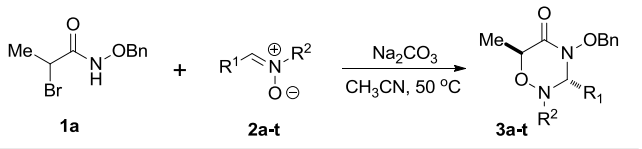


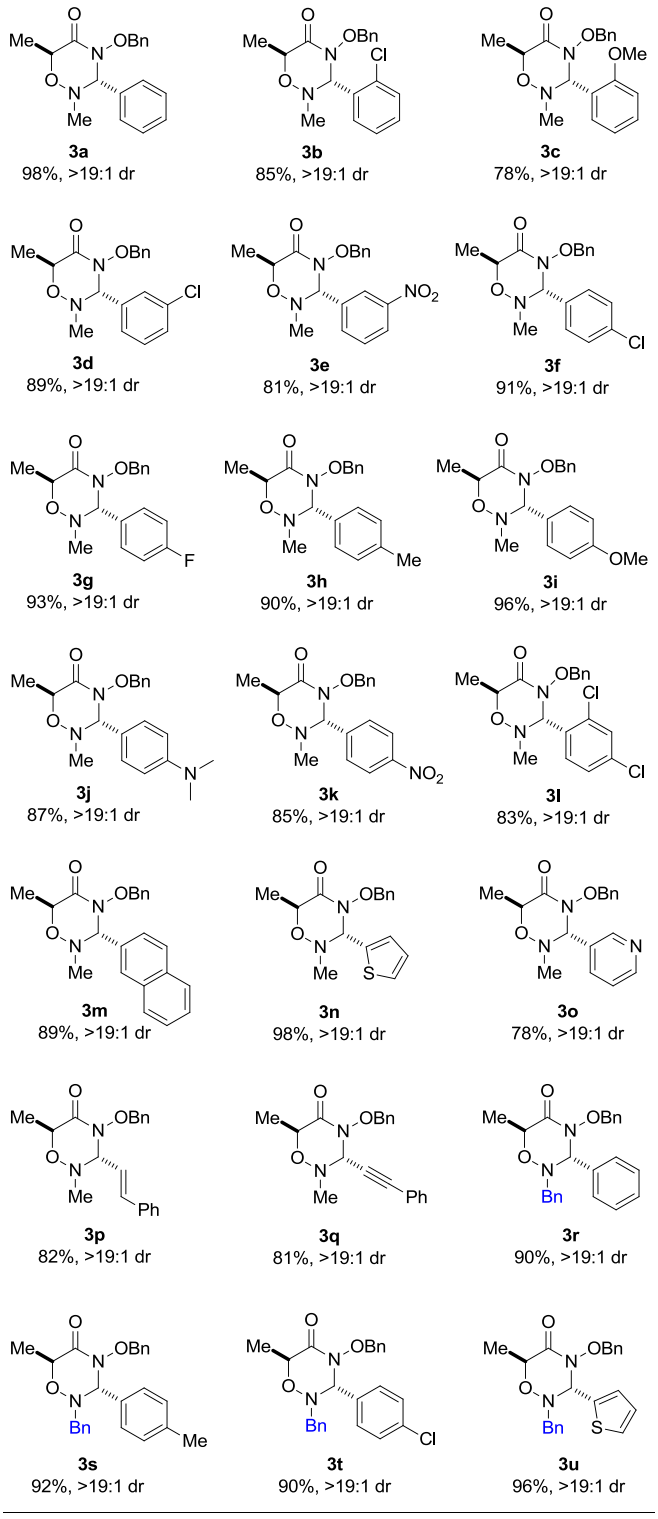
Entry	Base	Solvent	Time (h)	Yield (%)[b]	d.r.[c]
1	Na_2CO_3	MeOH	24	<5	-
2	Na_2CO_3	CF_3CH_2OH	24	<5	-
3	Na_2CO_3	HFIP	24	65	1.6:1
4	Na_2CO_3	DMF	24	<5	-
5	Na_2CO_3	THF	24	<5	-
6	Na_2CO_3	DCM	24	<5	-
7	Na_2CO_3	CH_3CN	24	73	>19:1
8[d]	**Na_2CO_3**	**CH_3CN**	**3**	**98**	**>19:1**
9	K_2CO_3	CH_3CN	24	75	>19:1
10	NaOAc	CH_3CN	24	<5	-
11	NaOH	CH_3CN	24	32	>19:1
12	pyridine	CH_3CN	24	<5	-
13	DBU	CH_3CN	24	<5	-
14	TEA	CH_3CN	24	53	>19:1

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.1 mmol), and base (2.0 mmol) in solvent (2 mL) was stirred at roomg temperature for a certain period of time. [b] Yield of isolated product. [c] Diastereomeric ratio. [d] 50 °C.

With the optimized conditions in hand, we next evaluated the generality of nitrones **2**. As indicated in Table 2, the substituent pattern and the electronic nature of nitrones **2** have limited effects on reaction conversion. In general, the corresponding products were obtained in good to high yields and with all excellent diastereoselectivities (**3a**–**k**, 78–98%, >19:1 dr). When nitrones beared 2-naphthyl, alkenyl, alkynyl or disubstituted pattern on phenyl ring, the corresponding products were obtained in high yields (**3l**–**m** and **3p**–**q**, 81–89%). Moreover, nitrones bearing a heterocyclic ring (e.g. 2-thiophenyl or 3-pyridinyl ring) could still afford the corresponding products in good to high yields (**3n** and **3o**, 98% and 78%, respectively). In addition, when *N*-benzyl group replaced *N*-methyl substituent on nitrones, excellent yields were still generally achieved (**3r**–**u**, 90–96%).

Table 2. Scope of nitrones.[a]



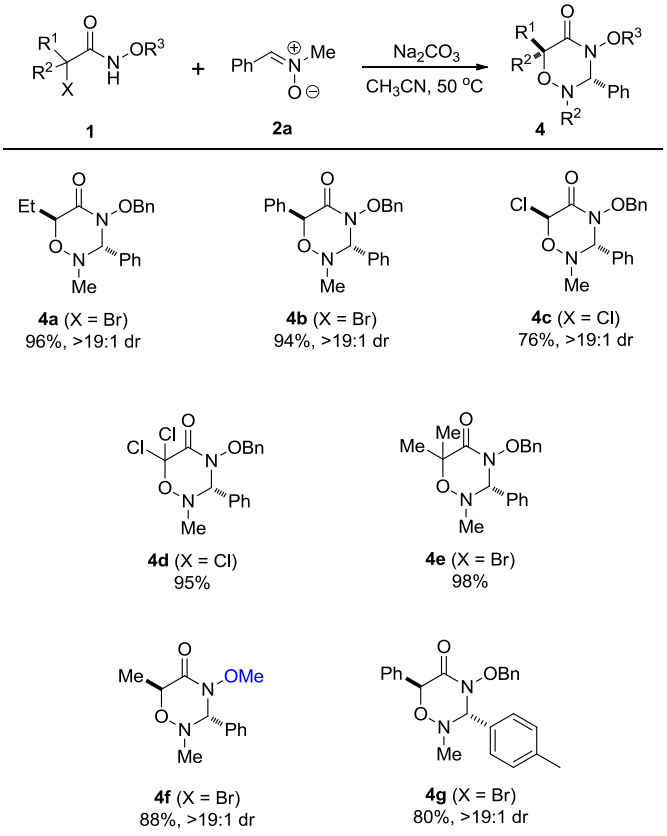


[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.1 mmol),

and Na_2CO_3 (2.0 mmol) in CH_3CN (2.0 mL) was stirred at 50 °C for 4-6 h. [b] Yield of isolated product.

We then turned our attention to examine the scope of α-halohydroxamates **1**. As shown in Table 3, all substrates displayed good performance and provided the corresponding products in moderate to high yields. When R^1 = H and R^2 = ethyl, phenyl or chloro group, reaction yielded the corresponding products **4a**–**c** in good to excellent yields (76–96%). When R^1 and R^2 were identical groups (e.g. chloro or methyl), the relative *O*-alkylhydroxamates provided excellent reactivity (**4d** and **4e**, 95% and 98%, respectively). When N-OBn was replaced by N-OMe, **4f** could still be achieved in a high yield and an excellent dr (Table 3). The relative configuration of products was assigned by X-ray single crystal analysis of **4g** (Figure 1).[16]

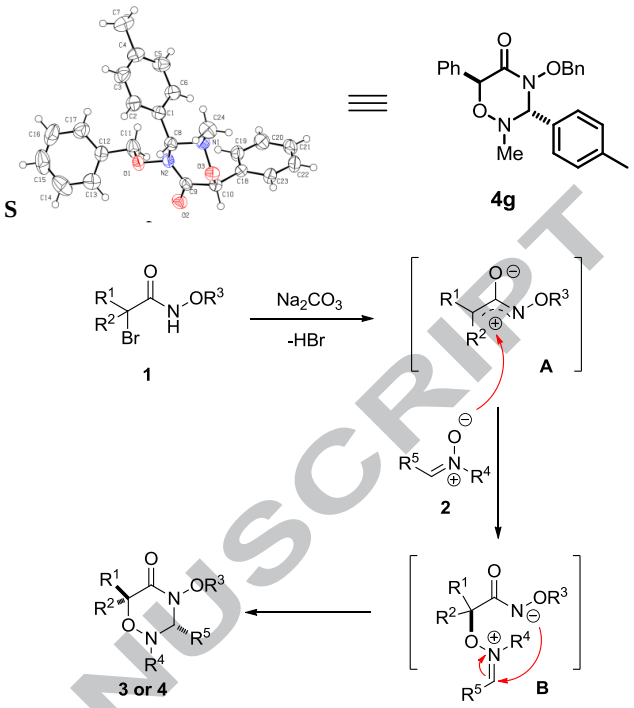
Table 3. Scope of α-halohydroxamates.[a]



[a] Reaction conditions: a mixture of **1** (1.0 mmol), **2a** (1.1 mmol), and Na_2CO_3 (2.0 mmol) in CH_3CN (2.0 mL) was stirred at 50 °C for 4-6 h. [b] Yield of isolated product.

On the basis of above experimental results, a plausible mechanism was proposed (Scheme 2). Under standard conditions, Na_2CO_3 promotes the formation of the intermediate azaoxyallyl cation **A**. The followed nucleophilic attack of nitrones **2** delivers the zwitterion intermediate **B**. Finally, the nitrogen anion undergoes intramolecular nucleophilic attack to generate final product **3** or **4**. The diastereomeric ratios of all cycloadducts were >19:1, suggested that the major *trans*-cycloadduct is favoured thermodynamically. Further investigation of enantiomeric control of this reaction is under way. Additionally, a concerted [3+3] cycloaddition mechanism cannot be completely ruled out.

Figure 1. X-ray single crystal analysis of **4g**.



In summary, we have developed an efficient [3+3] cycloaddition of nitrones to *in situ* generated aza-oxyallylic cations. This protocol provides a straightforward access to biologically important 1,2,4-oxadiazinan-5-ones derivatives in good to excellent yields under mild conditions. The further development of this cycloaddition process to other heterocycles is ongoing in our laboratory.

Acknowledgments

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Supplementary Material

Supplementary data associated with (experimental procedures and compound characterization data) this article can be found, in the online version.

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15. In the preparation of this manuscript, the Wang group reported a very similar work: Jia, D.; Li, D.; Lang, M.; Zhang, K.; Wang, J. *Adv. Synth. Catal.* **2017**, *359*, 3837. Unfortunately, relatively low disastereoselectivities were observed in their products (**4a–j**, Table 4). In sharp contrast, our reaction system provided excellent diastereo-control for all products (Table 3).
16. CCDC 1541516 (**4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Highlights

- excellent diastereo-control
- broad substrate scope
- high chemical yield