



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.

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The aza-oxyallylic cation intermediates had long been investigated since the Sheehan group reported it in 1960s¹ 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 dienes⁴, 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 and 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] cycloaddi-

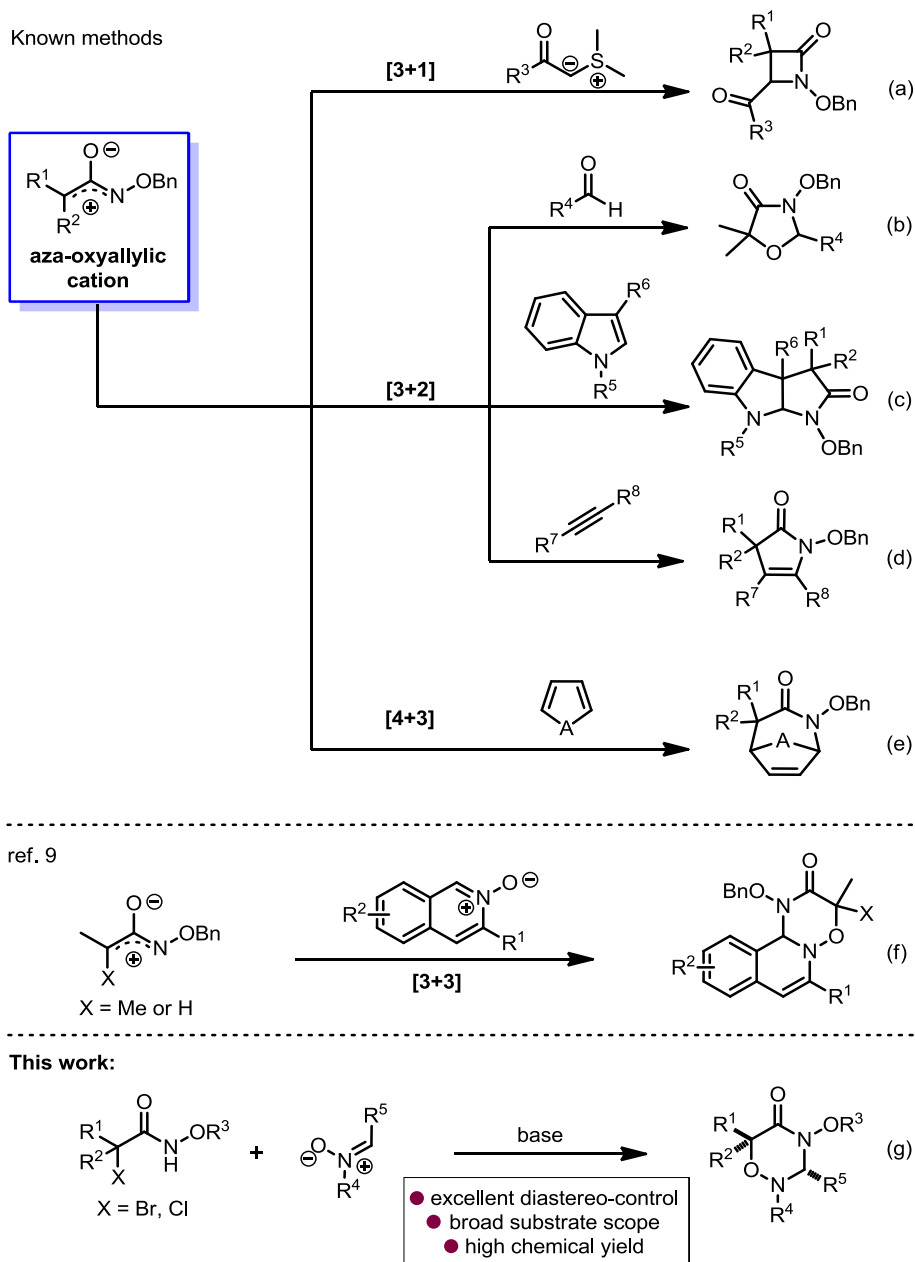
tion of azaoxyallyl cations reported by Wu et al. very recently (Scheme 1f).⁹

On the other hand, nitrones are useful synthons and used as versatile 3-units in [3 + 2]¹⁰ or [3+3]¹¹ cycloaddition reactions¹² 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 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 Na₂CO₃ was initially investigated. As shown in Table 1, the solvent seems to play a critical role on reaction efficiency. CH₃CN 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

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Scheme 1. Cycloaddition reactions of aza-oxyallyl cations.

reaction was carried out in other solvents such as methanol, trifluoroethanol ($\text{CF}_3\text{CH}_2\text{OH}$), 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.

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 bore 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 addi-

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