Efficient Synthesis of 1,2,4-Oxadiazine-5-ones via [3+3] Cycloaddition of In Situ Generated Aza-oxyallylic Cations with Nitrile Oxides

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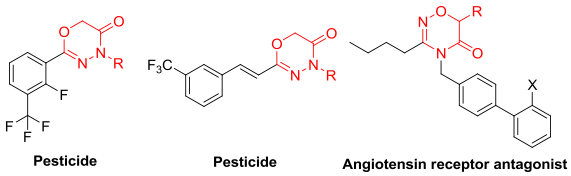
1,2,4-oxadiazin-5-ones were prepared via [3+3] cycloaddition of in situ generated aza-oxyallylic cations with nitrile oxides in good yields and excellent functional group compatibility. This efficient transformation is metal-free and is promoted by an inorganic base Cs_2CO_3. In addition, this reaction features simple-operation, mild conditions, and high regioselectivity.

Introduction

1, 2, 4-oxadiazin-5-ones are important class of heterocyclic structure motifs which exhibit interesting biological activities. For instance, 1, 2, 4-oxadiazin-5-one structure motifs are present in many pesticide molecules[1] and angiotensin receptor antagonists[2] (Scheme 1). The synthesis of these structure motifs have attracted significant attentions from the synthetic community due to their excellent biological properties.[3]

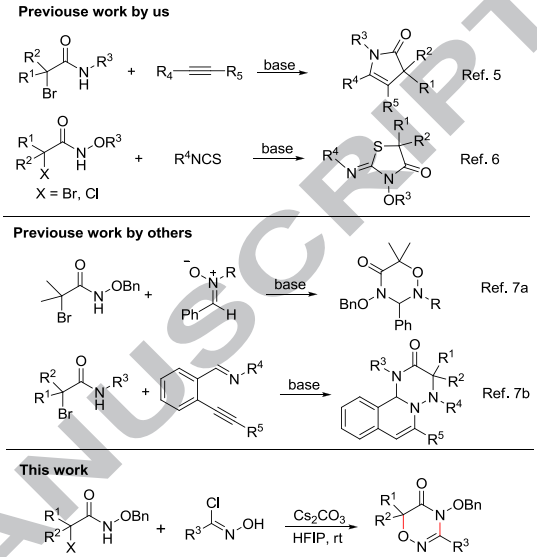


Scheme 1. 1,2,4-Oxadiazine-5-ones containng bioactive molecules

In the course of our research into the preparation of biologically important heterocyclic structures, we thought to utilize the [3+3] cycloaddition of aza-oxyallylic cations to construct the heterocyclic ring. Aza-oxyallylic cations, which are usually in situ generated from α-halohydroxamates in the presence of organic or inorganic bases, represent a class of useful and versatile synthons for organic synthesis. Recently, Aza-oxyallylic cations have become widely utilized in the synthesis of heterocyclic molecules via cycloaddition reaction.4 Last year, we reported efficient [3+2] cycloaddition reactions of aza-oxyallylic cations with alkynes5 and isothiocyanates6 for the synthesis of 1,3-dihydro-2H-pyrrol-2-ones and thiazolidin-4-ones respectively (Scheme 2). Herein, we would like to present our study on the synthesis of 1,2,4-oxadiazine-5-ones via [3+3] cycloaddition of aza-oxyallylic cations and nitrile oxides.

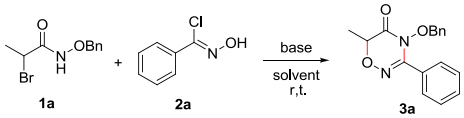
Scheme 2. Cycloaddition reaction with aza-oxyallylic cations

In 2017, Zhao and Wang independently reported [3+3] cycloaddition of azaoxyally cations and nitrones for a facile



access to 1,2,4-oxadiazinan-5-ones (Scheme 2).[7] Very recently, Cheng described a silver mediated [3+3] cycloaddition of *C,N*-cyclic azomethine imines with aza-oxyallyl cations for the synthesis of isoquinoline-fused triazines (Scheme 2).[8] In our work, we are interested in the utilization of nitrile oxides for the [3+3] cycloaddition with aza-oxyallylic cations.

Our investigation started from using α-bromohydroxamate **1a** and hydroximoyl chloride **2a** as the model substrates. Toluene and hexafluoro-2-propanol (HFIP) were employed as solvents. Different bases such as $NaCO_3$, K_2CO_3, $CsCO_3$, TEA, DMAP, NaOH were screened to identify the optimal base for the generation of both aza-oxyallylic cations and nitrile oxides. The reaction was conducted at room temperature or 50 °C for 2 to 24 hours. It was found that $CsCO_3$ in HFIP at rt for 2 hours gave the best yield (80%) of the [3+3] cycloaddition product 3a (entry 11, table 1). Triethyl amine in toluene produced the desired product in comparable yield (78%, entry 5, table 1) but required higher reaction temperature (50 °C). The optimal conditions we found are mild and operationally simple, meanwhile allowing us to efficiently access the novel 1,2,4-oxadiazine-5-one structure and construct both a C-O bond and a C-N bond within one pot.



Entry[a]	Base	Solvent	T/h	T/°C	Yield[b]
1	Na_2CO_3	Tol	24	50	25%
2	K_2CO_3	Tol	24	50	27%
3	Cs_2CO_3	Tol	24	50	36%

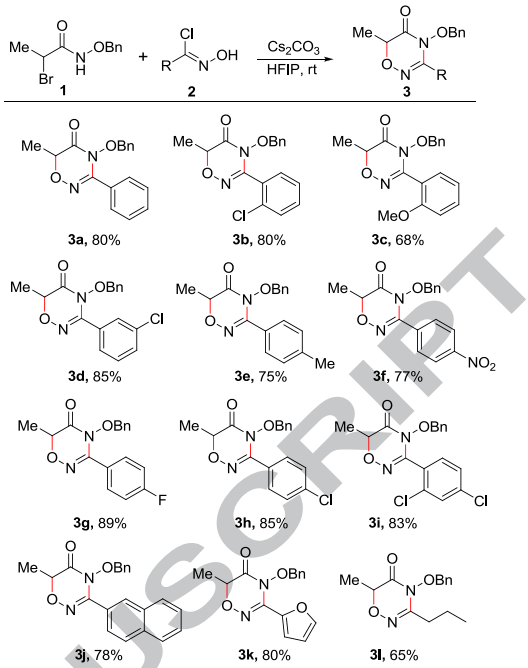
4	TEA	Tol	2	r.t.	40%
5	TEA	Tol	2	50	78%
6	DMAP	Tol	2	50	68%
7	TEA	HFIP	2	r.t.	51%
8	DMAP	HFIP	2	r.t.	56%
9	Na_2CO_3	HFIP	2	r.t.	68%
10	K_2CO_3	HFIP	2	r.t.	71%
11	Cs_2CO_3	HFIP	2	r.t.	80%
12	NaOH	HFIP	2	r.t.	45%

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.0 mmol), and base (2.1 mmol) in solvent (2 mL) was stirred at the set temperature for a certain period of time. [b]Yield of isolated product.

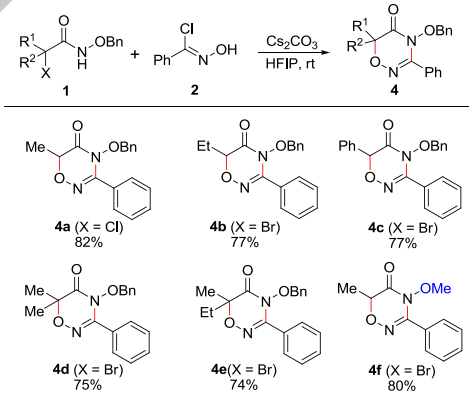
Table 1. Reaction optimization

With the optimal conditions in hand, we next proceeded the study of both the substrate scope and limitation of this transformation. First, we fixed a-bromohydroxamate **1a** as the precursor for aza-oxyallylic cation and varied the structure of hydroximoyl chloride **2** for the formation of a variety of nitrile oxides (Scheme 3). We found that this reaction has a very general substrate scope and excellent functional group compatibility. For the substituent on hydroximoyl chloride **2**, both aromatic rings including heteroaromatic rings and aliphatic chains are tolerated under the optimal conditions. Additionaly, both electron withdrawing groups and donating groups on the phenyl ring did not affect the reaction yields. For instance, halogens such as fluorine and chlorine at different positions of the phenyl ring all gave good to excllent yields. The usage of dichloro-substitued phenyl ring (**3i**) also provided good yield of the desired product. Electron donating groups such as methyl (**3e**) and methoxyl (**3c**) groups on the phenyl ring gave slightly lower reaction yields of the cycloaddition products.

Next, structures of α-halohydroxamate **1** were varied and N-hydroxybenzimidoyl chloride **2a** was used for the investigation of the substrate scope of the aza-oxyallylic cations (Scheme 4). It was found that the substituents at the alpha position of **1** tolerate both mono-substituted alkyl and aromaic groups such as ethyl (**4b**) and phenyl (**4c**) groups. More sterically hindered substituents at the alpha position did not affect the performance [3+3] cycloaddition reaction. For example, both α,α-dimethyl and α-methyl, α-ethyl substituted bromohydroxamates provided good yield of the cycloaddition products **4d** and **4e**. It is worth to mention that α-chlorohydroxamate can also be used to generate aza-oxyallylic cations as cycloaddition product **4a** was smoothly prepared by using α-chlorohydroxamate as the precursor. In addition, the substituent on the nitrogen of α-halohydroxamate can also tolerate methoxy group (**a**) and gave good yield.

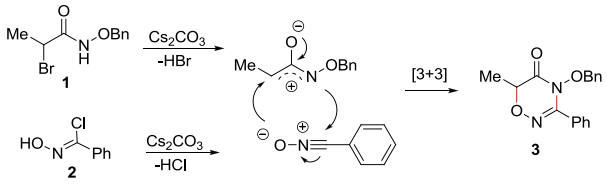


Scheme 3. Substrate scope of hydroximoyl chlorides



Scheme 4. Substrate scope of a-halohydroxamate.

In terms of the reaction mechanism, we believe that the use of base promotes the formation of the aza-oxyallylic cations from α-halohydroxamate and also nitrile oxides from hydroximoyl chlorides (Scheme 5). The [3+3] cycloaddition between aza-oxyallylic cations and nitrile oxides produces 1,2,4-oxadiazine-5-ones efficiently. The excellent regioselectivity of this reaction can be explained by both electronic nature and steric effect of both substrates.



Scheme 5. Substrate scope of α-halohydroxamate.

Conclusions

In summary, a highly efficient [3+3] cycloaddition reaction of in situ generated aza-oxyallylic cations and nitrile oxides were developed. Structurally fascinating and biologically important 1,2,4-oxadiazine-5-ones were prepared in good yields, mild reaction conditions, excllent functional group compatibility, and high regioselectivity.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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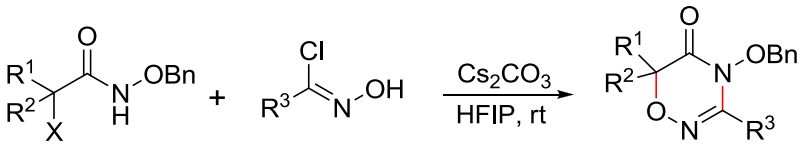
- Efficient synthesis of 1,2,4-Oxadiazine-5-ones derivatives
- [3+3] cycloaddition of *in situ* generated Aza-oxyallylic cations with nitrile oxides
- Easy operation, metal-free, good yields
- Broad functional group tolerance, excellent regioselelctivity



X = Br, Cl

18 examples
65-89% yield