



Synthesis of thiazolidin-4-ones via [3+2] cycloaddition of in situ generated aza-oxyallylic cations with isothiocyanates



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ABSTRACT

A highly efficient one-pot synthesis of thiazolidin-4-ones via [3+2] cycloaddition of aza-oxyallylic cations with isothiocyanates is developed. The aza-oxyallylic cations were generated in situ in the presence of a base. This cycloaddition reaction allows the rapid access to a variety of thiazolidin-4-one derivatives in mild conditions, good yield, and excellent functional group compatibility.

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Introduction

Thiazolidin-4-ones are unique heterocyclic structural motifs which have been identified with a wide range of biological activities, such as cardiovascular,¹ hypnotic,² and anticancer activities³ (Fig. 1). These important biological activities and intriguing heterocyclic structures attracted noticeable attention from the synthetic community, which led to the development of efficient methods for the synthesis of thiazolidin-4-one derivatives.⁴

During our continuous effort of developing efficient syntheses of bio-active heterocyclic compounds, we decided to take advantage of the [3+2] cycloaddition reaction of aza-oxyallylic cations to access thiazolidin-4-ones. After Jeffrey first reported the application of the aza-oxyallylic cation in [4+3] cycloaddition reactions, many research groups began to utilize aza-oxyallylic cations as the unique synthon for cycloaddition reactions in order to prepare heterocyclic molecules (Scheme 1). For instance, Lin and co-workers described a [3+3] cycloaddition of aza-oxyallylic cations with 2-alkenylindoles for the preparation of carbolinones.⁵ In 2016, Jeffrey reported a synthesis of 4-oxazolidinone by [3+2] cycloaddition of aza-oxyallylic cations with carbonyl compounds.⁶ Very recently, we communicated an efficient one-pot synthesis of 1,3-dihydro-

2H-pyrrol-2-one derivatives via [3+2] cycloaddition of aza-oxyallylic cations and alkynes.⁷ On the other hand, isothiocyanates have been extensively used in the [3+2] cycloaddition of aziridines for the synthesis of heterocycles.⁸ Thiazolidin-4-ones derivatives have been prepared by [3+2] cycloaddition reaction previously.⁹ While we are preparing our manuscript, a report of base-promoted [3+2] cycloaddition of azaoxyallyl cations with isothiocyanates appeared in the literature using hexafluoro-2-propyl alcohol (HFIP) as the solvent.¹⁰ Herein, we present our study on the [3+2] cycloaddition of in situ generated aza-oxyallylic cations and isothiocyanates for the synthesis of thiazolidin-4-one derivatives. It is worth mentioning that our work illustrated many examples with mono-substituted haloamides while the previous publications focus on geminal dimethyl-substituted haloamides.

Results/Discussion

We started our investigation for the optimal reaction conditions by choosing α -Bromoamide **1a** and isothiocyanatobenzene **2a** as the model substrate (Table 1). First, Na₂CO₃ was utilized as the base to produce aza-oxyallylic cations from α -Bromoamide **1a**. The corresponding aza-oxyallylic cation was expected to react with **2a** for the [3+2] cycloaddition. To our delight, CH₃CN was identified to be the best solvent (entry 1) which gave 93% yield of the desired [3+2] cycloaddition product **3a**. Other solvents including Toluene, Hexafluoroisopropanol (HFIP), CH₂Cl₂, DMF, CH₃OH, and THF all

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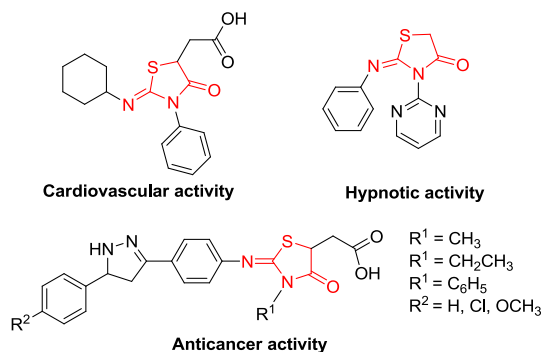
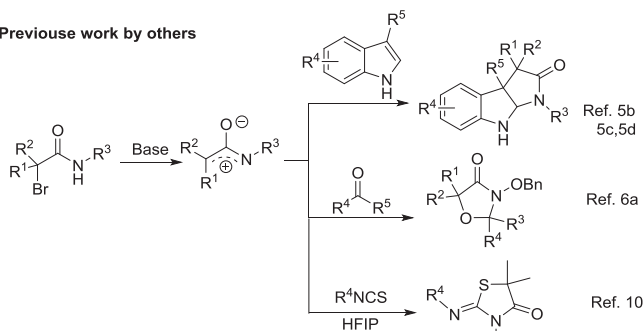
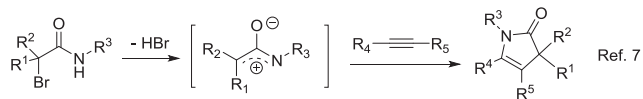


Fig. 1. Bioactive thiazolidin-4-ones.

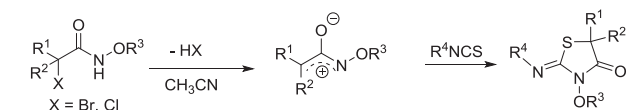
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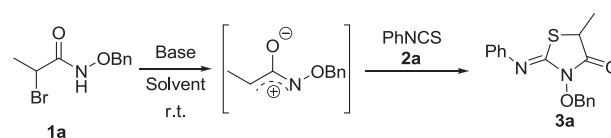
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Scheme 1. Previous work.

gave less yields (entries 2–7). Next, different bases such as Cs_2CO_3 , triethylamine, K_2CO_3 , NaOAc, NaOH were screened. It was found that all other bases gave less yield than Na_2CO_3 (entries 8–12) in the presence of the optical solvent CH_3CN . This efficient cycloaddition reaction was conducted at a mild condition at room temperature within short reaction time (4 h).

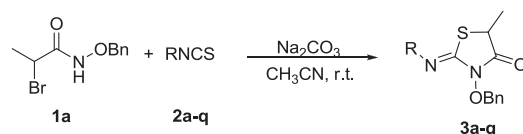
With the optimal conditions in hand, we began our study on the substrate scope and limitations of this reaction. As shown in Scheme 2, α -Bromoamide **1a** was utilized as the aza-oxyallylic cation donor. Concurrently, a variety of substituted aromatic and aliphatic thiocyanates were tested under the optimal [3+2] cycloaddition reaction conditions. Substituted isothiocyanatobenzene bearing either electron withdrawing or electron donating groups on the phenyl ring all gave good to excellent yields (entries **3a–l**). It is noticeable that strong electron withdrawing groups on the phenyl ring slightly decrease the yields of this reaction (entry **3j** and **3k**). Steric effect were also observed to influence the yields of the reaction. For example, *ortho*-substituted isothiocyanatobenzenes (entries **3b** and **3c**) showed lower yields than the corresponding *meta*- or *para*-substituted ones (entries **3b**, **3e**, **3h**, **3c**, **3d**, and **3f**). Additionally, the [3+2] cycloaddition reaction of thiocyanate with heteroaromatic substitute pyridine (entry **3m**) proceeded in good yield (89%). Several alkyl substituted thiocyanates

Table 1
Optimization of reaction conditions.^a

Entry	Base	Solvent	T/h	T/°C	Yield ^b
1	Na_2CO_3	CH_3CN	4	r.t.	93%
2	Na_2CO_3	Tol	4	r.t.	<5%
3	Na_2CO_3	HFIP	4	r.t.	65%
4	Na_2CO_3	DCM	4	r.t.	<5%
5	Na_2CO_3	DMF	4	r.t.	67%
6	Na_2CO_3	CH_3OH	4	r.t.	15%
7	Na_2CO_3	THF	4	r.t.	13%
8	Cs_2CO_3	CH_3CN	4	r.t.	76%
9	TEA	CH_3CN	4	r.t.	73%
10	K_2CO_3	CH_3CN	4	r.t.	81%
11	NaOAc	CH_3CN	4	r.t.	11%
12	NaOH	CH_3CN	4	r.t.	43%

^a Reaction condition: **1a** (1.0 mmol), **2a** (1.0 mmol), base (2.0 equiv.) in solvent (2 mL) for 4 h at room temperature.

^b Isolated yields.



Entry	R	Yield(%)	Entry	R	Yield(%)
3a		93	3i		85
3b		81	3j		79
3c		78	3k		76
3d		90	3l		86
3e		91	3m		89
3f		85	3n		90
3g		90	3o		70
3h		89	3p		78
			3q		87

Scheme 2. Substrate scope of isothiocyanates.

were also found to generate the [3+2] cycloaddition products in good yields (entries **3n–q**).

To confirm the structure of the thiazolidin-4-one product of this [3+2] cycloaddition reaction, we successfully obtained the X-ray

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