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[3 + 2] cycloaddition of nonstabilized azomethine ylides and 2-benzothiazolamines to access imidazolidine derivatives†

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A simple and practical method for the construction of 1,3,5-trisubstituted imidazolidine derivatives *via* [3 + 2] cycloaddition reaction has been developed. This reaction could smoothly proceed between nonstabilized azomethine ylides generated *in situ* and 2-benzothiazolamines to deliver a wide scope of differently substituted imidazolidines in high yields (up to 98%). The structure of one example was confirmed by X-ray single-crystal structure analysis.

Heterocyclic compounds are important structural motifs that are frequently discovered in natural products and biologically active molecules, with wide applications and potency in the field of medicinal chemistry.¹ Among them, the 2-aminobenzothiazole scaffolds, which contain a core of isothiourea motifs as a privileged scaffold, are ubiquitous in natural products, drugs and bioactive compounds.² Some examples of biologically active molecules and pharmaceuticals containing benzothiazoles are shown in Fig. 1. These compounds display a variety of important biological activities, such as anti-HIV, anticancer, antineoplastic and anticonvulsant activity, and so on.³

Due to their momentous and potent biological activities and structural diversifications, more organic and medicinal chemists have been significantly attracted to developing effective and advanced methodologies for the construction of benzazole scaffolds.⁴ The 2-benzothiazolamines could serve as alternative C4 synthons with various reaction partners in [4 + 2] cycloadditions for the straightforward and convenient access to 2-aminobenzothiazole scaffolds, and this type of reaction has been well established (Scheme 1a).⁵ By contrast, the 2-benzothiazolamines which acted as C2 synthons in cycloaddition reactions have been very limited.⁶ Therefore, the development of efficient cycloaddition between the 2-benzothiazolamines as C2 synthons and suitable reaction partners to provide diverse

functionalized heteroarenes molecules is always in great demand.

On the other hand, the 1,3-dipole cycloaddition is recognized one of the most efficient and powerful methods for building five membered heterocyclic rings from simple starting materials.⁷ In particular, the nonstabilized azomethine ylides generated *in situ* from *N*-benzyl-substituted compounds were a highly reactive intermediate with unsaturated compounds, such as activated alkenes,⁸ aromatic ketones,⁹ aromatic aldehydes,¹⁰ phthalic anhydrides,¹¹ imines,¹² cyano compounds¹³ or stable dipoles,¹⁴ to build various N-containing heterocycles *via* [3 + 2] or [3 + 3] cycloaddition reactions (Scheme 1b). Despite the progress were well developed *via* 1,3-dipolar cycloadditions employing nonstabilized azomethine ylides as the substrates, challenges still remain. Herein, we would like to present an effective process to furnish functionalized 1,3,5-trisubstituted imidazolidine derivatives *via* [3 + 2] cycloaddition strategy from 2-benzothiazolamines with nonstabilized azomethine ylides generated *in situ* (Scheme 1c). In contrast, the desired product was not obtained *via* [4 + 3] cycloaddition reaction.

Initially, we used 2-benzothiazolimine **1a** and *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl amine **2a** which could *in situ* form azomethine ylide in the presence of acid as model

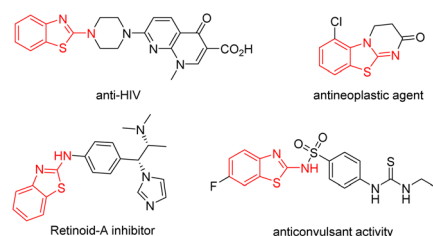


Fig. 1 Selected examples of biologically active compounds containing a 2-aminobenzothiazole scaffolds.

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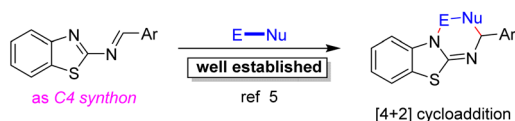
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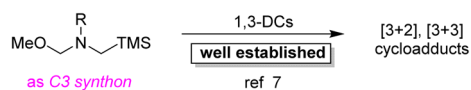
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs. CCDC 2182405 (**3h**). For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2ra04616d>



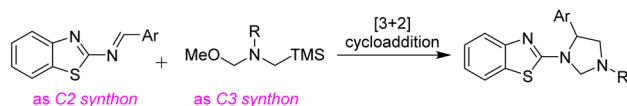
(a) Previous work of 2-benzothiazolines:



(b) Previous work of nonstabilized azomethine ylides:



(c) this work



Challenges: regioselective [3+2] versus [4+3] cycloaddition
high efficiency

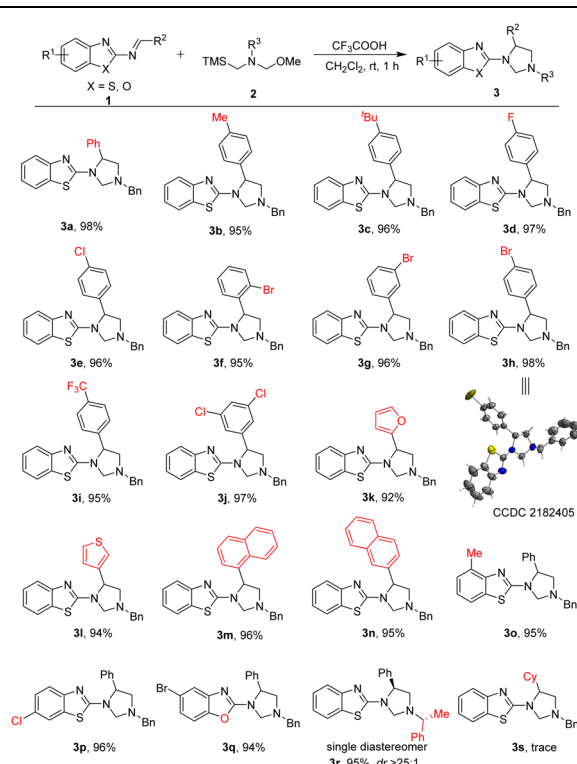
Scheme 1 Previous reports and our protocol.

substrates to optimize the reaction conditions. The results were shown in Table 1. The reaction could smoothly proceed to afford the [3 + 2] cycloadduct **3a** in 48% yield in CHCl₃ for 12 h under room temperature when used AcOH as the acid (entry 1, in Table 1). Subsequently, organic and inorganic acids were screened to improve the yield (entries 2–4, in Table 1). The results were found that the 1,3,5-trisubstituted imidazolidine **3a** could be provided in 90% yield using TFA as the addition (entry 3, in Table 1). Whereas the other acids were found to be the poor yields. Furthermore, in order to improve the yield of the product, a series of reactive solvents were also screened (entries

Table 1 Optimization of reaction conditions^a

Entry	Additive	Solvent	Time	Yield of 3a ^b (%)
1	AcOH	CHCl ₃	12	48
2	TfOH	CHCl ₃	12	51
3	TFA	CHCl ₃	3	90
4	HCl	CHCl ₃	12	20
5	TFA	CH ₂ Cl ₂	1	98
6	TFA	DCE	3	82
7	TFA	EtOAc	6	75
8	TFA	Toluene	12	70
9	TFA	MeOH	12	31
10	TFA	CH ₃ CN	3	71
11	TFA	Dioxane	12	59
12	TFA	Et ₂ O	12	46
13	TFA	THF	12	62

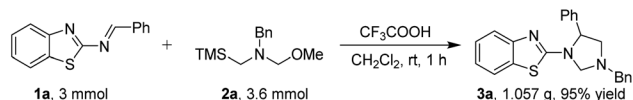
^a Reaction conditions: 2-benzothiazolimine **1a** (0.1 mmol, 1.0 equiv.), *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** (0.12 mmol, 1.2 equiv.), addition (0.01 mmol, 0.1 equiv.) and solvent (1.0 mL) in a test tube at room temperature. ^b Yield of the isolated product.

Table 2 Substrate scopes for the formation of 1,3,5-trisubstituted imidazolidine derivatives **3**^a

^a Reaction conditions: 2-benzothiazolimine **1** (0.1 mmol, 1.0 equiv.), *N*-alkyl amine **2** (0.12 mmol, 1.2 equiv.), TFA (0.01 mmol, 0.1 equiv.) and CH₂Cl₂ (1.0 mL) in a test tube at room temperature for 1 h. Yield of the isolated product.

5–13, in Table 1). The reaction could quickly transform and furnish the corresponding product in 98% yield for 1 h in CH₂Cl₂ (entry 5, in Table 1). Compared with CH₂Cl₂ solvent, the others solvents, such as DCE, ethyl acetate, toluene, MeOH, CH₃CN, dioxane, Et₂O and THF, led to decreased yields (entries 5–13).

After establishing the optimal reaction conditions, the scope and limitations of this [3 + 2] cycloaddition reaction for formation of 1,3,5-trisubstituted imidazolidines were examined. The results were shown in Table 2. Firstly, a wide range of 2-benzothiazolamines **1** with different electron properties and substitution patterns could be utilized as competent substrates in this [3 + 2] cycloaddition with nonstabilized azomethine ylides **2a**. The reaction worked well in the annulation affording the corresponding products **3a–3j** in excellent yields (95–98%) bearing either electron-donating or electron-withdrawing functional substituents including the different positions of the substituents on the benzene ring of R² group. It shows that the steric effect or electronic nature of R² group hardly effected the reactive efficiency. Additionally, the chemical structure of **3h** (CCDC 2182405[†])¹⁵ was unequivocally confirmed by X-ray crystallographic analysis (see ESI[†]). On the other hand, when the R² groups were heteroaromatic substituted group, such as 2-furanyl, 3-thienyl, 1-naphthyl and 2-naphthyl, the cycloaddition



Scheme 2 Gram-scale synthesis of product 3a.

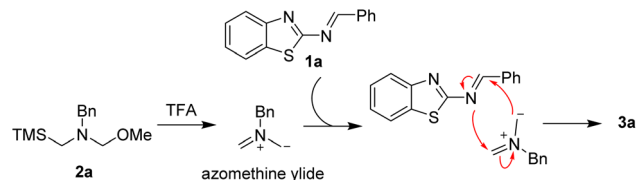
reaction were well tolerated and could also proceed smoothly without obvious interference to produce corresponding pyrazoles **3k–3n** in 92–96% yields. Meanwhile, substituted substrates at the C4 or C6-position of the 2-amino-benzothiazole, such as Me and Cl were also reacting smoothly to afford the corresponding products in 95%, 96% yields (**3o–3p**), respectively. Notably, the 2-benzoxazolimine as substrate also reacted smoothly with azomethine ylides **2a** to deliver the corresponding product **3q** in high yield (94%). Especially, when using (*R*)-nonstabilized azomethine ylide as the chiral substrate in the cycloaddition reaction, the reaction could proceed smoothly under the standard conditions to afford the corresponding chiral product **3r** in 95% yield as single diastereomer only. The chiral center was determined by NOESY analysis (see ESI†). Nevertheless, as for the R² group, when it was changed from an aryl group to an alkyl group, the reaction did not take place (**3s**). The possible reason may be due to the low activity of alkyl substituted substrate.

To further illustration and highlight the practical utility of the method for 1,3,5-trisubstituted imidazolidines, the gram scale experiments were performed. The reaction of 3 mmol of **1a** with 3.6 mmol **2a** proceeded smoothly under optimized condition for 1 h, producing the 1,3,5-trisubstituted imidazolidine **3a** (1.057 g) in 95% yield without an obvious loss of efficiency (Scheme 2).

On the other hand, we developed conditions to convert the bromine atom into phenyl group *via* Suzuki coupling of product **3h** with phenylboronic acid, which obtained product **4** in 65% yield (Scheme 3).

Based on the results presented in Table 2, a possible mechanism for this transformation is proposed to explain the reaction process in Scheme 4. First, the nonstabilized azomethine ylide from *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl amine **2a** is generated in the presence of TFA. Then, this nonstabilized azomethine ylide could react with 2-benzothiazolimine **1a** to obtain the desired product **3a** *via* [3 + 2] cycloaddition reaction.

In conclusion, we have developed a mild [3 + 2] cycloaddition reaction from nonstabilized azomethine ylides generated *in situ* with 2-benzothiazolamines. In this cycloaddition, 2-benzothiazolamines were used as C2 synthon. The method could offer a broad range of functionalized 1,3,5-trisubstituted



Scheme 4 Proposed mechanism.

imidazolidines in high yields (up to 98%) with high regioselectivity at room temperature. Additionally, the merits of our method are cheap starting materials, wide substrate scope, without metal catalyst. The synthetic utility and practicality were also highlighted by the gram-scale experiment and the synthetic transformation. The potential application of these 1,3,5-trisubstituted imidazolidines is under investigation in this laboratory.

Author contributions

The design of this protocol was carried out by K.-K. Wang and R. X. Chen. The manuscript was written through contributions of R. X. Chen and Z.-Y. Wang. The main experiments including synthesis of the target molecules were performed by K.-K. Wang and Y.-L. Li and J. Jing. The author of M.-Y. Wang conducted the large-scale preparation of the starting materials. All the authors analyzed the results and experimental data. K.-K. Wang participated in the modification of the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

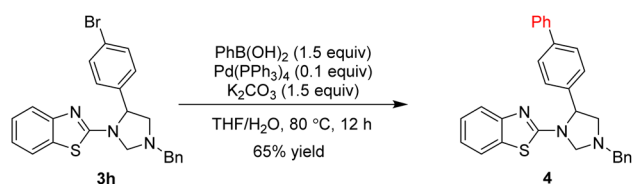
There are no conflicts to declare.

Acknowledgements

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Scheme 3 Transformations of product 3h.

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- 15 CCDC 2182405 for **3h**.†