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Cascade bicyclizations of *o*-alkynyl aldehydes with thiazolium salt: A new access toward poly-functionalized indeno[2,1-*b*]pyrroles

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Abstract

A new cascade bicyclization of *o*-alkynyl aldehydes with thiazolium salt is described, in which 25 examples of densely functionalized indeno[2,1-*b*]pyrroles are achieved in a functional-group-compatible manner. Thiazole carbenes generated in situ from thiazolium salt play dual roles as a reaction partner and as a NHC catalyst. The synthetic utility of these bicyclization reactions results in subsequent C–C bond-forming events to rapidly build up molecular complexity.

Graphical abstract

Polycyclic fused pyrroles are among the most ubiquitous heterocycles in nature and can often serve as “privileged structures” in medical and pharmaceutical chemistry owing to their biological activities, such as antibacterial, antiviral, anti-inflammatory, antitumoral and antioxidant activities.¹ Among these skeletons, a unique indenopyrrole motif commonly exists in natural alkaloids and has been represented by Strigolactam²; it shows a broad range of biological activities.³ These compounds are also widely employed as versatile building

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blocks in synthetic organic chemistry. With these attributes in mind, the scientific community devotes a great effort in finding new synthetic methods for the assemble of indenopyrrole and their structural analogues. A survey of the literature revealed that several synthetic methods for the construction of functional indeno[2,1-*b*]pyrroles have been developed, which involved zirconium-mediated coupling of benzyne, 1,3-butadiyne with acyl cyanides,⁴ the nucleophilic addition of β -lactam carbenes to 3,6-diphenyltetrazines,⁵ cyclization of phenylglutaric acids.⁶ Nevertheless, these methods are somewhat limited to harsh reaction conditions, the use of metal catalyst, and narrow substrate scope. Therefore, the exploration of a reliable and flexible access toward this family of heterocycles continues to be greatly valuable and challenging.

On the other hand, thiazole carbenes as *N*-heterocyclic carbene catalysts (NHC) in organic community have drawn considerable interest owing to their ability to catalyze various C-C formation reactions,⁷ transesterification,⁸ and Stetter reaction⁹ and their role as excellent ligands for transition metals. In particular, the beautiful applications of thiazole carbenes in the NHC chemistry have been widely studied over the past few decades, resulting in well-developed NHC-catalyzed procedures.¹⁰ However, in sharp contrast, the response to thiazole carbenes as a reaction substrate in insertion-bicyclization reaction remains to be unexploited although its great potential in the cycloaddition and multicomponent reactions.¹¹⁻¹² Due to the well-performance of the insertion of carbenes into alkynes toward cyclopropenes,¹³ we decided to introduce an alkyne moiety into the *ortho* position of formyl group in the phenyl ring. We reasoned that the alkynes could capture the thiazole carbenes through insertion reaction, and the formyl group would be converted into a suitable nucleophile *via* an umpolung process in the presence of thiazole carbenes, allowing intramolecular interaction forming important multifunctional aza-heterocycles. As a continuation of our project on bicyclization reactions,¹⁴ we became interested in thiazole carbenes insertion for heterocyclic synthesis. Herein we report the successful realization of this concepts *via* an unprecedented cascade bicyclization using readily available *o*-alkynyl aldehydes. Thiazole carbenes generated in situ from thiazolium salt play dual roles as a reaction partner as well as a NHC catalyst to construct a novel poly-functionalized indeno[2,1-*b*]pyrroles in a highly regioselective and functional-group-compatible manner (Scheme 1).

To develop metal-free conditions for the synthesis of indeno[2,1-*b*]pyrroles, we started our study by preparing *o*-alkynyl aldehydes in our laboratory according to the literature procedures.¹⁵ In order to optimize the reaction conditions, 2-(phenylethynyl) benzaldehyde **1a** and thiazolium salt **2a** in 1:1.2 ratio were investigated as model substrates using different bases for the synthesis of polyfunctionalized indeno[2,1-*b*]pyrroles **3a**. As shown in Table 1, without base conditions, the reaction did not proceed and the starting materials **1a** and **2a** were remained and recovered. The reaction of **1a** and **2a** afforded only a trace amount of product in the presence of Na₂CO₃ and *t*-BuOLi (1.0 equiv) in 1,4-dioxane at 120 °C for 4 h (entry 2 vs entry 6). The desired product **3a** was obtained in 43% yield under metal-free conditions using K₂CO₃ as a base promoter (entry 3). The use of Cs₂CO₃ gave a slightly lower yield (31%) (entry 4). The higher yield of product **3a** (58%) was isolated in the presence of Et₃N (1.0 equiv) (entry 5). Using other bases, such as *t*-BuOK, DBU and NaH,

the reaction efficiency was all decreased (entries 7-9). Taking Et₃N as the suitable base, we varied other parameters. Adjusting the amount of Et₃N to 2.0 equivalent at 120 °C proved more efficient, affording the expected product **3a** in 70% yield. Further lowering or raising of the amount of Et₃N and reaction temperatures ranging from 110 °C to 130 °C did not significantly change the yield (entries 10-14). Other solvents such as 1,2-dichloroethane (DCE), PhCF₃, acetonitrile (CH₃CN), DMF, EtOH, and toluene were inferior to 1,4-dioxane in terms of reaction yields.

With the optimal conditions in hand, we then set out to explore the scope of this reaction by conducting a variety of *o*-arylalkynylbenzaldehydes **1** to react with thiazolium salt **2a**; the results are summarized in Scheme 2. The variants of substituents on the arylalkynyl moiety like Me, MeO, F and Cl can be well-tolerated under the optimized conditions. Electronic effect of substituents on the arylalkynyl moiety affected the reaction efficiency. As shown in Scheme 2, substrate **1** carrying an electron-rich group such as Me and MeO showed lower reactivity than electron-withdrawing ones (**3b** and **3c** vs **3d** and **3e**). More sterically demanding 1,1'-biphenyl (1,1'-BiPh, **1f**) and 1-naphthyl (1-Np, **1g**) substituents were engaged in these NHC-catalyzed bicyclizations, affording the corresponding products **3f** and **3g** in 55% and 45% yields, respectively. Heterocyclic substituents, such as thiophenes, can be converted into the indeno[2,1-*b*]pyrroles, albeit with lower efficiency. This reaction also tolerated the substrates **1** bearing electron-poor Cl and F groups on phenyl ring directly linked to formyl group (R¹), and can smoothly proceed to give polysubstituted indeno[2,1-*b*]pyrroles **3i-3q** ranging from 45%-76% yields. Similarly, 2-(4-chlorophenylethynyl)nicotinaldehyde **1r** was successfully converted into the corresponding pyrrolo[2',3':4,5]cyclopenta[1,2-*b*]pyridines **3r** in 58% yield. Next, various thiazolium salt were investigated to examine the scope of NHC-catalyzed bicyclizations. We were pleased to find that different substituted thiazolium salt did not hamper this reaction process. Reactions of *N*-methyl thiazolium salt **2b** with substrates **1** involving arylalkynyl moieties attached by both electron-donating and electron-poor groups all worked well to give polysubstituted indeno[2,1-*b*]pyrroles **3s-u** in 47-60% yields. Alternatively, upon the treatment of substrate **1r** with thiazolium salt **2b** delivered *N*-methyl pyrrolo[2',3':4,5]cyclopenta[1,2-*b*]pyridines **3v** in 56% yield. Additionally, when *N*-benzyl substituted thiazolium salt **2c** was employed as a reaction partner and a NHC-catalyst, a significant drop in the yields were observed (30-38%), which may be ascribed to the relatively strong steric hindrance of benzyl group. The structure of product **3k** was unambiguously determined by single crystal X-ray diffraction (Fig. 1). Obviously, the present protocol provides a new and straightforward pathway for constructing polyfunctionalized indeno[2,1-*b*]pyrroles that are not easily assembled by other synthetic means.

On the basis of literature reports¹⁶ and from the observations of the experiment results, we believe that the nucleophilicity of thiazole carbenes plays a pivotal role in the success of the whole cascade reaction sequence. A reasonable mechanism for the present bicyclization reaction is shown in Scheme 3. The thiazol-2-ylidene **A**, generated in situ by the deprotonation of the thiazolium salt **2** at its most acidic position,¹⁷ reacted with the *o*-arylalkynylbenzaldehydes **1** to form enol intermediate **B** via umpolung process. The addition of thiazole carbenes **A** into C≡C bond of enol intermediate **B** delivers spirocycle

intermediate **C**.¹³ Afterward, the ring opening of cyclopropenes¹⁸ attacked by C-nucleophilic site may proceed to afford zwitterionic intermediate **D**,¹⁹ followed intramolecular H-transfer and subsequent elimination of thiazol-2-ylidenes **A** to give spirothiazole intermediate **F**. The intermediate **F** undergoes [3,3] rearrangement²⁰ to form **G**, which releases 3-hydroxypropanethioic *O*-acid **4**, detected by GC-MS, in the presence of base and aerobic conditions, to generate the final indeno[2,1-*b*]pyrroles **3**. Although the detailed mechanism of C-C bond breaking of intermediate **G** has not been fully elucidated at this point, it seems that a thiazole carbene addition reaction to the formation of the final aromatic indeno[2,1-*b*]pyrroles provides the driving force for [3,3] rearrangement and ring opening of cyclopropenes. These similar types of [3,3] rearrangement in the heterocyclic system²⁰ and ring opening of cyclopropenes¹⁶ have been reported, respectively.

Conclusions

In summary, we have developed an unprecedented cascade bicyclization reaction of *o*-alkynyl aldehydes with thiazolium salt, enabling a new NHC-catalyzed approach toward a wide range of functionalized indeno[2,1-*b*]pyrroles in a functional-group-compatible fashion. During this reaction process, thiazole carbenes generated *in situ* from thiazolium salt play dual roles as a reaction partner and a NHC catalyst. The reaction pathway may involve an umpolung, thiazole carbene addition and ring opening of cyclopropenes sequence. The annulation efficiency, flexible structural modification reliable scalability and as well as mild reaction conditions provide an invaluable access to structurally diverse indeno[2,1-*b*]pyrroles. Further study on the thiazole carbenes-catalyzed transformations is currently underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.
The ORTEP drawing of **3k**.

Scheme 1. Cascade bicyclizations toward indeno[2,1-b]pyrroles

Scheme 2.

Scope of the NHC-catalyzed bicyclization reaction. Yields of isolated products after column chromatography on silica gel are given. **1** (0.5 mmol) and **2** (0.6 mmol), Et_3N (1.2 mmol), 1,4-dioxane (5.0 mL), under an air atmosphere, 4 h.

Scheme 3. Mechanistic proposal

Table 1
Optimization of reaction conditions^a

Entry	Base (equiv) ^b	Solvent	T/°C	Yield ^c /%
1	-	1,4-dioxane	120	NR
2	Na ₂ CO ₃ (1.0)	1,4-dioxane	120	trace
3	K ₂ CO ₃ (1.0)	1,4-dioxane	120	43
4	Cs ₂ CO ₃ (1.0)	1,4-dioxane	120	31
5	Et ₃ N (1.0)	1,4-dioxane	120	58
6	<i>t</i> -BuOLi (1.0)	1,4-dioxane	120	trace
7	<i>t</i> -BuOK (1.0)	1,4-dioxane	120	21
8	DBU (1.0)	1,4-dioxane	120	15
9	NaH (1.0)	1,4-dioxane	120	13
10	Et ₃ N (1.5)	1,4-dioxane	120	64
11	Et ₃ N (2.0)	1,4-dioxane	120	70
12	Et ₃ N (2.5)	1,4-dioxane	120	69
13	Et ₃ N (2.0)	1,4-dioxane	110	51
14	Et ₃ N (2.0)	1,4-dioxane	130	57
14	Et ₃ N (2.0)	DCE	120	12
15	Et ₃ N (2.0)	PhCF ₃	120	41
16	Et ₃ N (2.0)	CH ₃ CN	120	trace
17	Et ₃ N (2.0)	DMF	120	trace
18	Et ₃ N (2.0)	EtOH	120	ND
19	Et ₃ N (2.0)	Toluene	120	45

^a Reaction conditions: 2-(phenylethynyl)benzaldehyde (**1a**, 0.5 mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**2a**, 0.6 mmol), solvent (5.0 mL), 4 h, under an air atmosphere.

^b The amount of bases is based on **2a**.

^c Isolated yield. NR = No Reaction. ND = No Detected.