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Metal-free aza-Claisen type ring expansion of vinyl aziridines: an expeditious synthesis of seven membered N-heterocycles†

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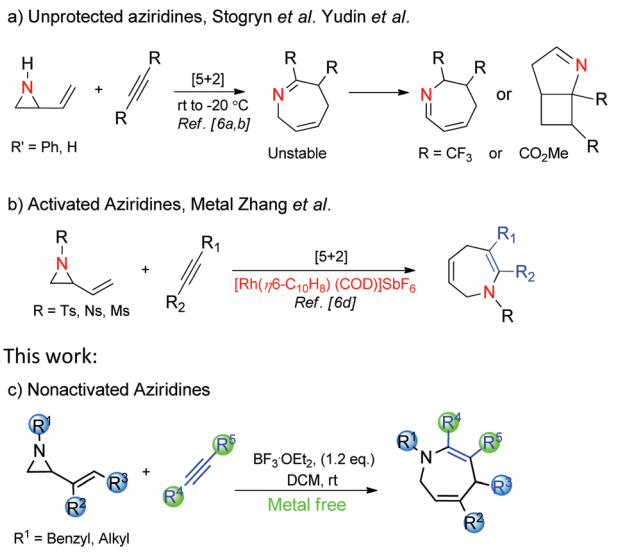
A metal-free approach for the synthesis of 7-membered aza-heterocycles has been developed by the intermolecular [5 + 2] cycloaddition of non-activated vinylaziridines and alkynes. This method has a broad substrate scope under mild reaction conditions to afford structurally diverse 7-membered N-heterocycles in high yield up to 92%.

Cycloaddition reaction is one of the most prominent, atom economical protocols for the construction of structurally complex carbocycles, heterocycles and natural products from readily available materials.[1] The cycloaddition strategy allows for multiple carbon–carbon or carbon–heteroatom bonds to be generated by the way of the ring expansion of the small ring system along with the involvement of additional functionality present in the substrate, which is tedious to achieve by conventional reactions.[1,2] Numerous reports are available in the literature describing the synthesis of relatively stable five and six membered cyclic compounds by a cycloaddition reaction.[2] However, there are relatively few reports on the assembling of a 7-membered ring especially N-heterocycles, by the cycloaddition strategy. This is due to its instability, nonbonding interaction, and the entropy factor. There is significant interest in developing an efficient and selective method to prepare 7-membered N-heterocycles (azepines), due to their presence as a core moiety in natural products and pharmaceuticals and their interesting biological profiles.[3] The 7-membered N-heterocycles, azepines, are also utilized as unique building blocks on which structurally complex molecules such as glucosepane and iboxyphylline are assembled.[4] However, very limited synthetic methods are available to access the azepine heterocycles. These include olefin metathesis,[5a–d] ring expansion,[5e,f] radical cyclisation,[5g–i] transition metal-catalyzed cyclisation,[5j–r] and metal-catalyzed cycloaddition (Scheme 1).[6–8] Among all available strategies, the metal-mediated hetero [5 + 2] cycloaddition is one of the good tools that lead to an azepine framework. Wender *et al.* did pioneering work for the synthesis of azepines by [5 + 2] cycloaddition of cyclopropyl imines and alkynes using $[Rh(CO)_2]Cl$ as a catalyst.[6e] However, these protocols require high temperature, high loading of a toxic metal catalyst, and the use of a specific directing group in the substrate. Recently, vinyl aziridine as a nitrogen-containing three membered ring along with an external functional group was used to access the larger N-heterocycles (Scheme 1). The highly strained three membered ring, the electron-withdrawing nature of nitrogen, and the presence of an external multiple bond make this substance to participate in various chemical transformations. Among them, the [3 + 2], [5 + 2] and [4 + 3] cycloaddition reactions of vinyl aziridines with alkenes and alkynes were a commonly used protocol for the synthesis



Scheme 1 Formal [5 + 2] cycloaddition of vinyl aziridines with alkynes.

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of pyrrolidine and azepine compounds. Zhang's group has reported the synthesis of azepines by [5 + 2] and [4 + 3] cycloaddition of vinyl aziridines with alkynes.[6d,7a] However, these methods require a very expensive and toxic transition metal catalyst and specific functionalities in the starting substrates such as benzo-fused activated aziridines with an electron-withdrawing group at the ring nitrogen and benzylic activation. The activated vinyl aziridine was decomposed under acidic conditions for [5 + 2] cycloaddition in the presence of Lewis acids such as $AgSbF_6$, $FeCl_3$, and $Sc(OTf)_3$, even though these conditions are well documented for the [3 + 2] cycloaddition reaction of phenylaziridines with alkynes.[6d] The ring expansion has a big disadvantage in that there is great difficulty generating the anion for initiation. Regardless of the method available, all aziridines used till date are "activated" bearing electron-attracting substituents at the ring nitrogen such as sulfones and phthalate, which are difficult to remove.[6,7] Moreover, the chemistry of "activated" aziridines is different not only in the ring strain energy but also in the method for achieving ring openings and ring transformations.[8] These rings are easily opened or rearranged without the assistance of any additional additive due to the highly activated aziridine ring with a narrow scope of regiochemical pathway.[8] Furthermore, introducing diverse groups at the ring nitrogen is highly limited. Therefore, utilization of "non-activated" aziridine[9b] provides an exceptionally good advantage in carrying out the reaction with structurally diverse starting materials. But its chemistry is tough to carry out owing to the intrinsic low reactivity of the ring opening reactions compared to those of the "activated" aziridine. Over the last three decades, our group has been highly engaged in exploring the chemistry of non-activated aziridines by ring opening, cyclisation and cycloaddition for synthesis of various natural products and heterocyclic compounds.[9]

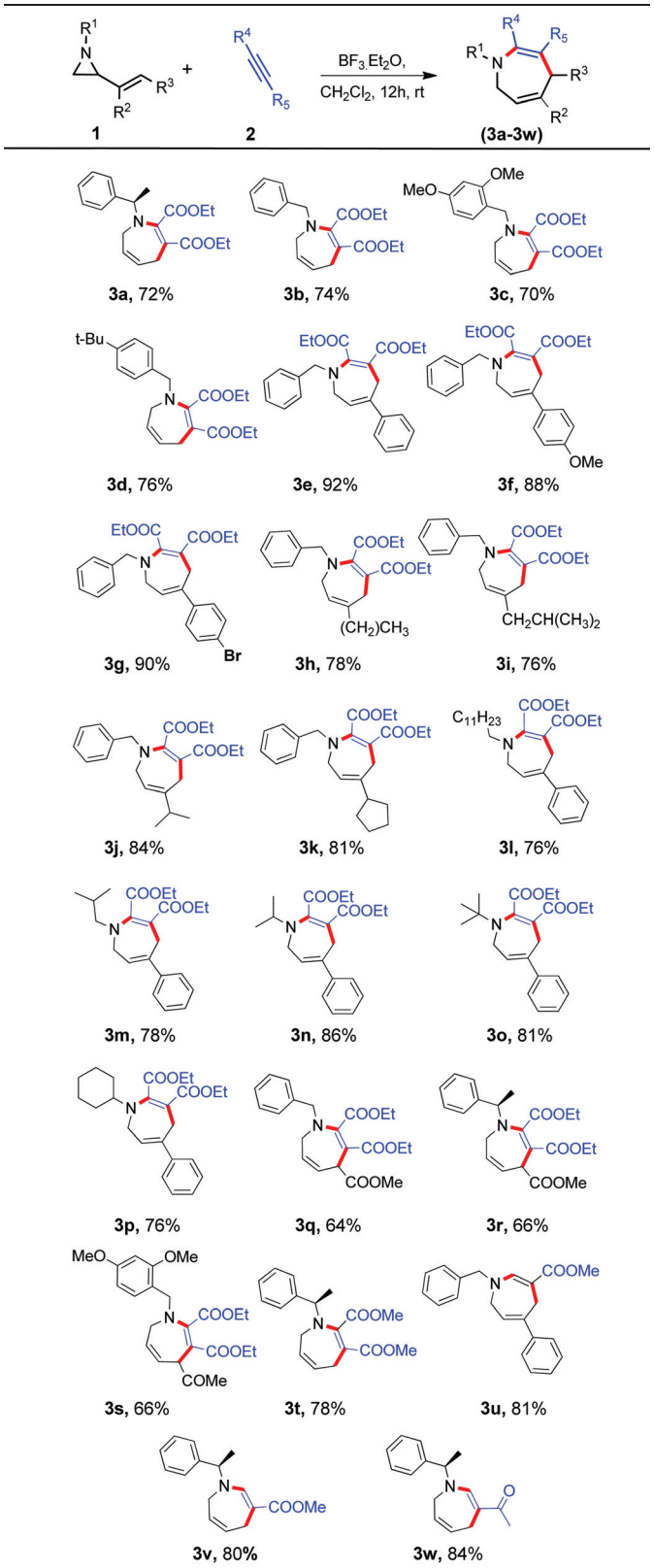
In this communication, we describe a metal-free and reliable synthetic method for the preparation of a 7-membered aza-heterocycle that starts from Lewis acid mediated formal [5 + 2] cycloaddition of non-activated aziridines with alkynes.[9b,10a] Mechanistically, this synthetic method is based on the aza-Claisen type rearrangement in association with a three membered aziridine ring leading to a [5 + 2] type electrocyclization. At first, a model reaction between vinyl aziridine **1a** and a diethyl but-2-ynedioate **2a** was carried out under various conditions by which two critical huddles were overcome: the proper activation of non-activated aziridines and the subsequent reaction with the counter alkyne leading to the aza-Claisen type rearrangement to give a 7-membered aza-heterocycle. All of the non-activated aziridines are relatively stable compared to the activated aziridines and less reactive toward almost all electron-rich nucleophiles.[9] Prior to the ring transformation, those non-activated aziridines should be activated by the use of various activators including Lewis acids. Among many previously known activators, $BF_3{\cdot}OEt_2$ is sometimes good for the ring transformation and the ring opening reaction, and it activates to a moderate extent without altering the substrate.[9c]

Initially a reaction of **1a** (1.00 mmol) and **2a** (1.5 mmol) with $BF_3{\cdot}OEt_2$ (1.2 mmol) under a nitrogen atmosphere in toluene for 12 hours gave rise to the desired 7-membered azepine **3a** in 62% yield. The yield was further improved by changing the solvents and it was found that the reaction produced the excellent yield of 72% by using CH_2Cl_2 as the solvent. The comparative studies using other Lewis acids such as $CeCl_3$, HBF_4, $FeCl_3$ and $HSbF_6$ did not improve the reaction yields. We have also attempted the reaction of **1a** and **2a** by use of a catalytic amount of $BF_3{\cdot}OEt_2$ (20 mol%). This resulted in a decrease in yield with most of the starting material unreacted. In the absence of a Lewis acid the reaction did not proceed at all. This demonstrates the crucial role of Lewis acids in this reaction (see, Table S1, ESI†).

Based on the optimized reaction conditions, the characteristics and the reaction scope were investigated to explore the synthesis of structurally diverse azepines with various aziridines and alkynes depicted in the reaction as starting materials (Table 1).

This synthesis takes advantage of the non-activated aziridines with diverse substituents at R^1. Several different electron-donating groups in R^1 such as phenyl ethyl (**3a**, **3r**, **3t**, **3v** and **3w**), benzyl (**3b**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3q**, **3s** and **3u**), dimethoxy benzyl (**3c**) and *p*-*t*-butyl benzyl (**3d**) in the aziridine ring nitrogen afforded the final products with the aforementioned groups in high yields without much change in reactivity. The alkyl chain represented by the dodecyl group in R^1 also gave rise to the product (**3l**) in 76% yield without any difficulty. All other cases with R^1 as the primary, secondary, and tertiary aliphatic group and cyclohexyl as the alicyclic group are more or less similar in the formation of products in the yield range of 76–86% (**3m**, **3n**, **3o** and **3p**). The phenyl substituent at R^2 drastically increased the reaction yield to 92% (entry **3e**). A similar result was obtained by starting with aziridine and other substituted phenyl groups at R^2 bearing 4-methoxy and 4-bromo substituents, which yielded the products **3f** and **3g** in 88% and 90%, respectively. The formation of the product in high yield with the aryl substituent R^2 stems from the stability of the starting material due to conjugation. In addition, the lowered transition state energy involving the bond-breaking step of the allylic weakened bond between N1 and C2 of the aziridine leading to the aza-Claisen type cycloaddition at ease. The reaction was explored further by taking R^2 as an alkyl substituent. The reaction proceeded smoothly with *n*-propyl (**3h**), isobutyl (**3i**), and isopropyl (**3j**) groups at R^2 which afforded the corresponding azepine in 78, 76 and 84% yields, respectively. Similarly, the aziridine having cyclic groups at R^2 such as cyclopentyl, also reacted well to create the product (**3k**) in 81% yield without any difficulty. In addition the reactions starting from aziridines having carboxylate and keto groups at R^3 are also coupled with the counterpart to produce the expected 7-membered aza-heterocycles (**3q**, **3r**, **3s**) in relatively low yield in the range of 64–66% yields, possibly due to the low activity of the olefin to make a new C–C bond to yield aza-heterocycles. As a counterpart of the aziridine, alkynes should be properly activated with carboxylates.

Table 1 Exploration of the substrate scope[a]



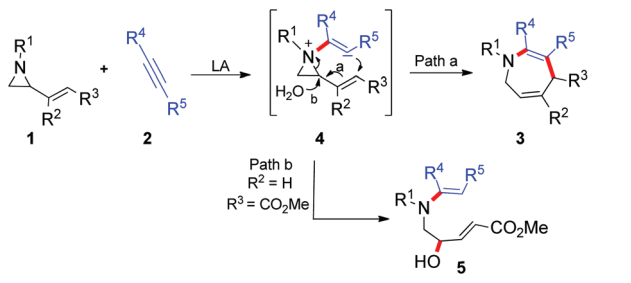
[a] Reaction conditions: The reaction mixture containing vinyl aziridine (1, 1.0 mmol), alkyne (2, 1.5 mmol), and Lewis acid (1.2 mmol) in the specified solvent (3.0 mL) was stirred at 25 °C. Yield reported refers to the isolated yield of compound **3**.

Therefore, we used diethyl but-2-ynedioate (**2a**) in most cases. However, ethyl but-2-ynoate (**2c**) with only one carboxylate was also a good partner to create the corresponding products (**3u** and **3v**) in 81 and 80% yields, respectively. Instead of the carboxylate, ethynyl methyl ketone (**2d**) was also reacted to give the product **3w** in 84% yield.

Interestingly, when we carried out the reaction with the starting aziridine (**2r**) bearing the carboxylate at R^3 we were able to isolate the by-product **5** in 10% yield, which provides us with a good clue regarding the reaction mechanism of the formation of 7-membered aza-heterocycles **3r** (Scheme 2). Even though the whole reaction scheme seems to proceed through [5 + 2] type cycloaddition to prepare 7-membered aza-heterocycles, the actual reaction mechanism is stepwise including Michael type addition and cyclization. At first, the electron-rich nucleophilic aziridine ring nitrogen as an advantage of non-activated aziridine was added to the alkynyl carboxylate as a good Michael acceptor, as we observed in our early study.[9c] The C–N bond formation leaves an anion at the α-position of carboxylate **4**, which is added to the vinylic position of aziridine at C2 with the formation of a new C–C bond generating 7-membered aza-heterocycles, as shown in Scheme 2. Thereby this reaction sequence appeared to be a [5 + 2] type cycloaddition, but the sequential reaction includes the Michael reaction and is followed by the aza-Claisen rearrangement. The initial adduct **4** with the newly formed C–N bond generated the acyclic product **5** in the presence of adventitious water or during the work-up with the expected regiochemical pathway as predicted on the basis of our early study. Once the initial adduct **5** was generated, the cycloaddition was retarded by relatively poor reactivity of the α-carbon bearing carboxylate, which gave rise to the acyclic ring opened product.

Furthermore, ring expansion and the bond formation with the breakage of the strained aziridine require relatively less energy[2i,10] compared to the corresponding cyclopropane[11a] and oxirane.[11b] The formation of an aziridinium ion exerting the ring expansion reaction is a key driving force that makes this pathway most valuable compared to the other hetero [5 + 2]-cycloaddition of vinyl aziridines. This is the reason why all hetero [5 + 2]-cycloadditions reported up to date have required metallic catalysts with activated aziridines as a starting substrate.

In conclusion, we have developed a novel strategy for metal-free synthesis of 7-membered aza-heterocycles by the inter-



Scheme 2 Plausible mechanism for aza-heterocycles.

molecular [5 + 2]-type-cycloaddition of non-activated vinylaziridines and alkynes with a broad substrate scope of both compounds under mild conditions. This method enables us to build structurally diverse 7-membered aza-heterocycles in high yield.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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