Heterocycles

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Hexafluoroantimonic Acid Catalysis: Formal [3+2+2] Cycloaddition of Aziridines with Two Alkynes**

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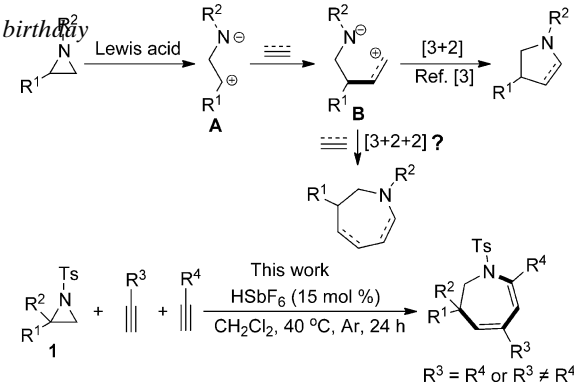
Dedicated to Professor Ming-Cai Chen on the occasion of his 60th birthday

Abstract: *A practical method for the synthesis of azepine derivatives, a typical seven-membered heterocyclic ring system, was developed and involves the use of hexafluoroantimonic acid to catalyze a formal [3+2+2] cycloaddition of aziridines with two alkynes. This method was applicable to two of the same or different terminal alkynes for the [3+2+2] cycloaddition with unactivated aziridines, and furnished the corresponding azepine derivatives in good yields with good levels of chemo- and regioselectivity. The mechanism was also discussed according to the results of the in situ HRMS and ^{1}H NMR analysis.*

The cycloaddition reaction has proven to be a powerful and straightforward synthetic tool for the atom-economical construction of cyclic compounds in modern organic chemistry.[1–4] In the cycloaddition field, an important strategy involving the use of the ring-openings of small strained rings as a key step, fascinates numerous researchers because it can be used to meet the synthetic demand of making bioactive natural products containing hererocyclic rings.[1–3] These cycloaddition processes allow the ring-opening of small strained rings and subsequent reaction with 2π components to construct various rings, specifically five- and six-membered rings, through [3+2] or [4+2] modalities. Particularly, cycloaddition reactions involving ring-opening reactions of strained aziridines have been widely applied in the construction of nitrogen-containing five-membered rings.[3] However, methods for the selective construction of larger nitrogen-containing rings, including nitrogen-containing seven-membered rings, are lacking.[4]

Generally, aziridines, a class of strained small heterocycles, are used as the precursors for both zwitterionic 1,3-dipoles (**A**; in the presence of Lewis acids; Scheme 1) and azomethine ylides (under irradiation or thermolysis) for [3+2] cycloaddition with 2π components such as alkenes and alkynes.[3] We reasoned that aziridines could undergo the [3+2+2] cycloaddition with two 2π components when the nucleophilicity of nitrogen anion in the intermediate **B** was reduced, thus enabling a subsequent electrophilic addition to another 2π component to form nitrogen-containing seven-membered rings. Herein, we report a new strategy to access the stable nitrogen anion in intermediate **B** using the superacid $HSbF_6$, thus triggering a new formal [3+2+2] cycloaddition of unactivated aziridines to two of the same or different terminal alkynes to construct azepine architectures (Scheme 1b). Such a reaction would be particularly valuable for the synthesis of azepine derivatives,[4,5] a typical seven-membered heterocyclic ring system, which are synthetically versatile compounds in synthesis and important skeletal units found in numerous natural products, potent pharmaceuticals, and peptidomimetics.[6]



Scheme 1. The cycloaddition of aziridines. Ts = 4-toluenesulfonyl.

We first investigated the proposed [3+2+2] cycloaddition reaction between 2-phenyl-1-tosylaziridine (**1a**) with phenylacetylene to optimize the reaction conditions (Table 1). Examination of a range of reaction temperatures, Brønsted acids, and solvents (entries 1–11) revealed the combination of the $HSbF_6$ as the catalyst and CH_2Cl_2 as the solvent at 40 °C to be most effective: treatment of **1a** with phenylacetylene and 15 mol% $HSbF_6$ in CH_2Cl_2 at 40 °C for 24 hours regioselectively afforded the desired azepine **2** in 76% yield (entry 1). The results demonstrated that the reaction temperature affected the reaction: the yield of **2** was reduced to 60% when the reaction was carried out at room temperature (entry 2). Of the amounts of $HSbF_6$ examined, it turned out that 15 mol% of $HSbF_6$ was perfect for the reaction (entries 1, 3, and 4). Notably, the absence of $HSbF_6$ resulted in no detectable amounts of **2** (entry 5). Subsequently, several

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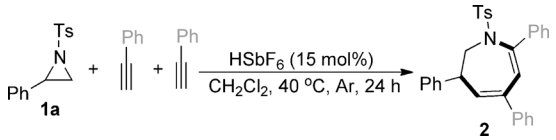
Table 1: Screening optimal reaction conditions.[a]



Entry	Variation from the standard conditions	Yield [%][b]
1	none	76
2	at room temperature	60
3	$HSbF_6$ (10 mol%)	58
4	$HSbF_6$ (30 mol%)	61
5	without $HSbF_6$	0
6	HOTf instead of $HSbF_6$	12
7	HOAc instead of $HSbF_6$	trace
8	HBF_4 instead of $HSbF_6$	6
9	CH_2ClCH_2Cl instead of CH_2Cl_2 for 48 h	52
10	toluene instead of CH_2Cl_2 for 48 h	trace
11	$MeNO_2$ instead of CH_2Cl_2 for 48 h	14
12[c]	none for 72 h	73

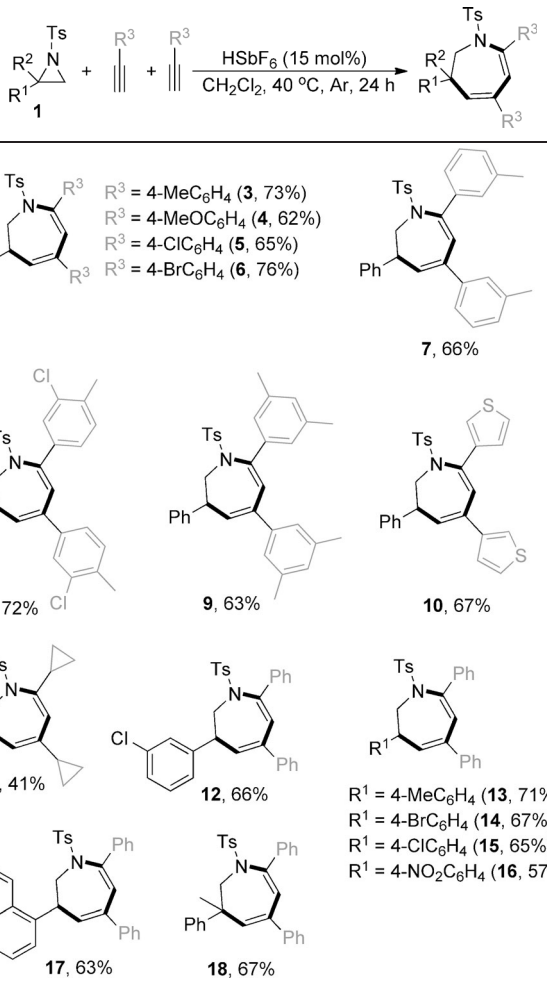
[a] Reaction conditions: **1a** (0.2 mmol), phenylacetylene (0.8 mmol), $HSbF_6 \cdot 6H_2O$ (15 mol%), and CH_2Cl_2 (2 mL) at 40°C under an argon atmosphere for 24 h. [b] Yield of isolated product. [c] **1a** (6 mmol, 1.638 g).

other Brønsted acids, such as HOTf, HOAc, and HBF_4, were tested (entries 6–8). Both HOTf and HBF_4 could catalyze the reaction, albeit in low yields after 24 hours (entries 6 and 8). However, HOAc had no effect on the reaction (entry 7). Screening revealed that the effect of solvents had a fundamental influence on the reaction (entries 1 and 9–11). While CH_2ClCH_2Cl was still an efficient solvent for the reaction (entry 9), both toluene and $MeNO_2$ displayed lower activity (entries 10 and 11). It is noteworthy that the reaction of 1.638 g (6 mmol) **1a** proceeds in good yield (entry 12).

With the standard reaction conditions in hand, the scope of this $HSbF_6$-catalyzed [3+2+2] cycloaddition reaction, with respect to aziridines reacting with two of the same terminal alkynes, was first exploited (Table 2). The standard reaction conditions were found to be compatible with a wide range of terminal alkynes, including aryl, heteroaryl, and aliphatic alkynes (**3**–**11**). Furthermore, several substituents, such as Me, MeO, Cl, and Br, on the aryl ring of alkynes were well tolerated (**3**–**9**). Alkynes having a *para*- or *meta*-methyl-substituted aryl group underwent the reaction with **1a** and $HSbF_6$ smoothly, thus providing the desired products **3** and **7** in 73 and 66% yield, respectively. Importantly, the halogens Cl and Br were tolerated under the reaction conditions, thereby facilitating additional modifications at the halogenated positions (**5**, **6**, and **8**). When using a dimethyl-substituted aryl alkyne, satisfactory yield was still achieved under the same reaction conditions (**9**). We were pleased to find that this [3+2+2] cycloaddition reaction was applicable to the preparation of the thiophen-3-yl-containing azepine **10** in 67% yield. Ethynylcyclopropane was also a suitable substrate for the reaction (**11**).

Gratifyingly, this catalyzed [3+2+2] cycloaddition protocol was subject to a variety of 1-tosylaziridines (**1**; Table 2, **12**–**18**). 2-(3-Chlorophenyl)-1-tosylaziridine, for instance, was successfully reacted with phenylacetylene and $HSbF_6$ to afford the product **12** in 66% yield. We were delighted to

Table 2: $HSbF_6$-catalyzed [3+2+2] cycloaddition of aziridines (**1**) with two of the same terminal alkynes.[a]

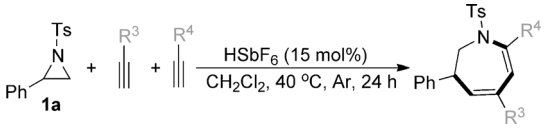


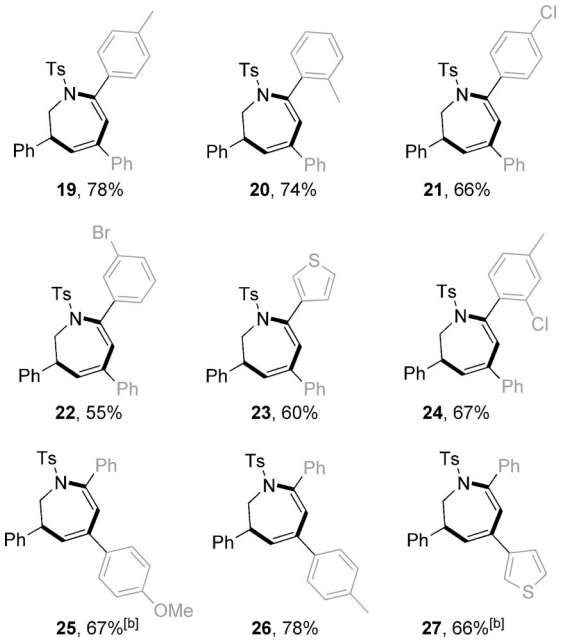
[a] Reaction conditions: **1** (0.2 mmol), alkyne (0.8 mmol), $HSbF_6 \cdot 6H_2O$ (15 mol%), and CH_2Cl_2 (2 mL) at 40°C under argon atmosphere for 24 h. Yields are those of the isolated products.

discover that a number of substituents, Me, Br, Cl, and NO_2, at the *para* position of the 2-aryl moiety were perfectly tolerated, thus resulting in the corresponding products **13**–**16** in moderate to good yields. Interestingly, the naphthalen-1-yl group could be readily introduced into the azepine structure (**17**). It was noted that 2-methyl-2-phenyl-1-tosylaziridine was also viable for the formation of the azepine **18** in 67% yield.

In light of the results described above, we next decided to examine the possibility of synthesizing azepines having different substituents at the 5- and 7-positions by using two different terminal alkynes (Table 3). As expected, the reaction of **1a** with two different terminal alkynes was successfully performed, thus furnishing the desired azepines **19**–**27** in moderate to good yields. For example, when **1a** was treated with phenylacetylene (the first alkyne) and 5 mol% $HSbF_6$ in CH_2Cl_2 at 0°C for 15 minutes, with subsequent addition of 4-methylphenylacetylene (the second alkyne) and 10 mol% $HSbF_6$ and an increase in the reaction temperature to 40°C for about 24 hours, 3,5-diphenyl-7-*p*-tolyl-1-tosyl-2,3-dihydro-1*H*-azepine (**19**) was delivered in 78% yield. It was noted that the same reaction conditions could be viable for the [3+2+2]

Table 3: [3+2+2] Cycloaddition of **1a** with two different terminal alkynes.[a]

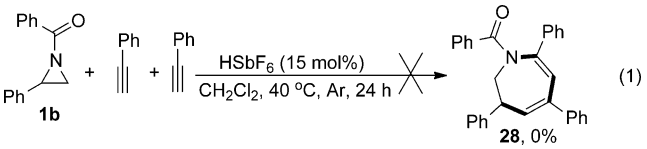


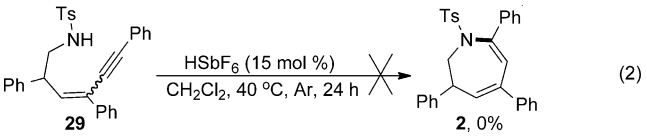


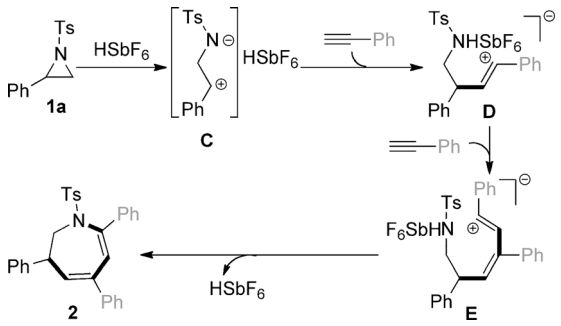
[a] Reaction conditions: a mixture of **1a** (0.2 mmol), the first alkyne (0.4 mmol), $HSbF_6 \cdot 6H_2O$ (5 mol%), and CH_2Cl_2 (2 mL) was stirred at 0 °C under an argon atmosphere. After 15 min, both the second alkyne (0.4 mmol) and $HSbF_6 \cdot 6H_2O$ (10 mol%) were added and the mixture was stirred at 40 °C for about 24 h. Yields are those of the isolated products. [b] The mixture of **1a** (0.2 mmol), the first alkyne (0.4 mmol), $HSbF_6 \cdot 6H_2O$ (5 mol%), and CH_2Cl_2 (2 mL) was first stirred at 15 °C under argon atmosphere for 30 min.

cycloaddition of **1a** with phenylacetylene and another alkyne, such as 2-methylphenylacetylene, 4-chlorophenylacetylene, 3-bromophenylacetylene, (2-thienyl)acetylene, or 2-chloro-4-methylphenylacetylene, thus leading to the corresponding azepines **20**–**24**, which have different substituents at the 7-position, in moderate to good yields. Interestingly, the substituent at the 5-position of the azepines could also be varied simply by the use of different alkynes the first step. Both phenylacetylene and 10 mol% $HSbF_6$ were added after 4-methoxyphenylacetylene reacted with **1a** and 5 mol% $HSbF_6$ in CH_2Cl_2 at 15 °C for 30 minutes, thus providing the 5-(4-methoxyphenyl)-substituted azepine **25** in 67% yield. When using 4-methylphenylacetylene or (2-thienyl)acetylene as the first alkyne, the corresponding 4-methylphenyl- and 4-(2-thienyl)-substituted azepines **26** and **27**, respectively, were also obtained in good yields.

However, phenyl(2-phenylaziridin-1-yl)methanone (**1b**) was unreactive for the [3+2+2] cycloaddition reaction [Eq. (1)]. To understand the mechanism, the reaction of the enyne **29** was carried out [Eq. (2)]. The results disclosed that **29** could not be converted into **2** under the standard reaction conditions, thus suggesting that the current reaction does not include an enyne intermediate.







Scheme 2. Possible mechanism.

Consequently, the working mechanism outlined in Scheme 2 was proposed on the basis of the present results and the literature reports.[3,7,8] Initially, the zwitterionic 1,3-dipole intermediate **C** is formed from the reaction of **1a** with $HSbF_6$,[3,8] with subsequent electrophilic addition to phenylacetylene to afford the intermediate **D**.[7,8] In this step, $HSbF_6$ can also serve to stabilize the nitrogen anion. Subsequently, **D** undergoes the second electrophilic addition to a second molecule of phenylacetylene to give the intermediate **E**.[8] Finally, dipolar cyclization of **E** gives the desired azepine **2**.

In summary, we have developed the first $HSbF_6$-catalyzed formal [3+2+2] cycloaddition of 1-tosylaziridines with two alkynes. This novel method provides a mild and general access to the azepine architectures with both excellent functional-group tolerance and good levels of selectivity control, thus representing a new [3+2+2] cycloaddition transformation using 1-tosylaziridines as zwitterionic 1,3-dipoles. Studies on the mechanism and applications of this formal [3+2+2] cycloaddition method in organic synthesis are currently underway in our laboratory.

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