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Tetrahedron Letters 45 (2004) 5011–5014
Tetrahedron Letters

Intramolecular cyclization reactions of aziridines with π-nucleophiles

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Received 10 February 2004; revised 30 April 2004; accepted 4 May 2004

Abstract—We have found that aziridines will react with a variety of π-nucleophiles in intramolecular cyclization reactions to produce nitrogen containing core structures found in a variety of bioactive molecules. These cyclizations are more general and facile than corresponding intermolecular reactions. We have examined the effects of ring size, π-nucleophile identity and substitution on this reaction.

The reactions of aziridines with nucleophilic reagents has and continues to be an excellent method for the introduction of an aminoethyl group. This type of reaction has been exploited with a variety of nucleophiles including heteroatom nucleophiles (e.g., azide, halide, alcohols, etc.) and carbon nucleophiles (e.g., organocuprate reagents, enolates, etc.).[1]

Among carbon nucleophiles, the use of π-nucleophiles to open aziridine rings has received little attention relative to other types of carbon nucleophiles. Milstein reported the first reaction between a π-nucleophile (benzene) and an aziridine ring.[2] This reaction was carried out at 170 °C in the presence of $AlCl_3$. More recent examples of such reactions have shown that only limited classes of either aziridines or π-nucleophiles readily undergo this reaction.[3–12] In general, either a highly reactive π-nucleophile (e.g., indole) or a 2-aryl aziridine is required for the reaction to proceed. Our own studies in this area have been directed at the use of allylsilanes to open aziridine rings in an intramolecular fashion.[13–16]

We report here our studies on a broader group of π-nucleophiles in intramolecular reactions with aziridines. This is the first report of intramolecular π-nucleophile cyclizations with aziridines using simple π-nucleophiles such as olefins and aromatic rings. These cyclizations are more general and facile than the corresponding intermolecular reactions and yield a variety of monocyclic and bicyclic nitrogen containing molecules. We have examined the scope of this reaction through examination of the substitution and connectivity of the π-nucleophile.

As with the intramolecular aziridine–allylsilane cyclization reactions, intramolecular π-nucleophile cyclizations should allow one to prepare several different types of products depending upon substitution patterns of the π-nucleophile and reaction conditions. As shown in Scheme 1, an initial nucleophilic attack of a π-system onto the aziridine, will generate a cationic intermediate (**3** via attack by an exocyclic π-bond or **2** via attack by an endocyclic π-bond). These intermediates can lead to regeneration of the π-system through elimination to form **4** or **7**. A bicyclic product (**5** or **6**) can also be obtained through trapping of the cationic intermediate by the sulfonamide.

These cyclization reactions should have great utility in the preparation of compounds that comprise the core structures of a variety of bioactive nitrogen containing molecules. Compounds such as **4** and **5** should be useful for the preparation of highly substituted pyrrolidine ring containing molecules. The pyrrolidine ring is commonly found in a number of biologically active molecules.[17,18] An attractive feature of the preparation of molecules

Keywords: Aziridines; Amines; Bicyclic heterocyclic compounds.
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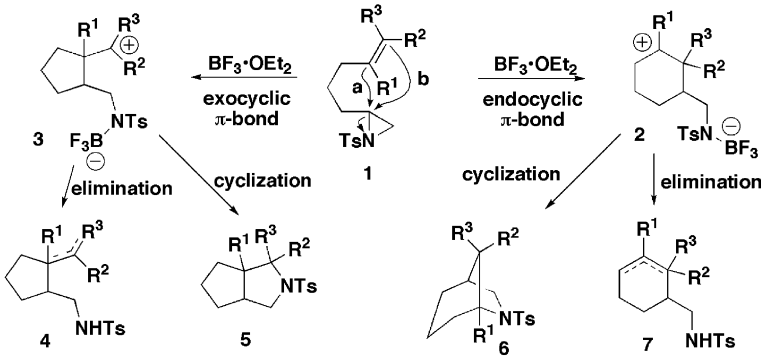
doi:10.1016/j.tetlet.2004.05.009



Scheme 1.

such as **5** is the ability to generate a quaternary carbon adjacent to the ring nitrogen. Azabicyclo [*x*.2.1]-systems such as **6** are found in a both natural products such as securinine[19,20] and aphanorphine[21] as well as unnatural biologically active molecules.[22–25] The cyclic methylamino substituted products such as **7** can be viewed as conformationally locked analogues of the arylethylamino pharmacophore found in central nervous system neurotransmitters such as dopamine, serotonin and norepinephrine.[26]

We have examined both aromatic rings and olefins as π-nucleophiles. The requisite aziridines were prepared as shown in Scheme 2. The primary method used for this study was a Suzuki-coupling route.[27] Hydroboration of olefinic aziridine **8** or **9**[16] followed by coupling to the appropriate aryl- or olefinic halide produces the aziridine **10** or **11**. The yields for the coupled products are shown in Tables 1–3.

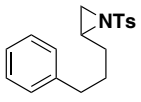
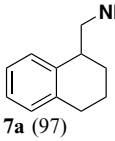
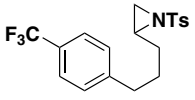
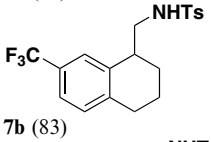
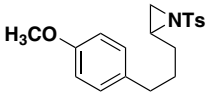
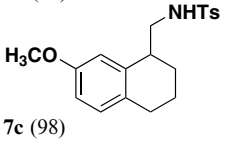
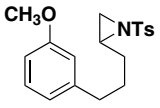
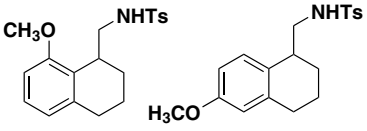
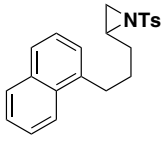
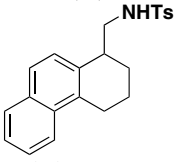
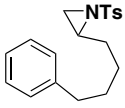
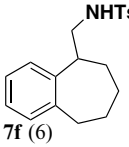
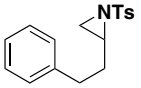
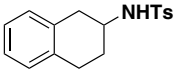
Some of the required aziridines could not be prepared using this method due to limitations in the aziridine substrate for the Suzuki-coupling reaction. These aziridines (**13a**–**c** and **15**) were prepared by a three step method[13] from either aziridine **12**[13] or **14**.[28] The aziridine ring was opened with a copper catalyzed Grignard reagent followed by desilylation and Mitsunobu ring closure to provide the requisite aziridines (**13** or **15**).

The aryl substituted aziridines were treated with 300 mol % of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C.[29] As shown in Table 1, the yields for this cyclization are generally quite high. With the exception of substrates **11a** and **13a**, all of these reactions were complete in less than 1 h. Although less Lewis acid could be used, the reaction takes much longer to go to completion. Both unsubstituted aromatic rings (**10a**,**e**) and those substituted with electron donating (**10c**,**d**) or electron withdrawing (**10b**) substituents provide the expected product in excellent yield. The cyclization of **10d** provides a 97% yield of both possible regioisomers in a 3:1 mixture.

The formation of the fused seven-membered ring **7f** occurred in 6% yield. Prolonged reaction times (5 days) and heating provided no improvements in yield.

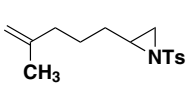
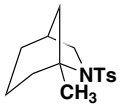
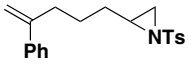
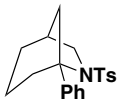
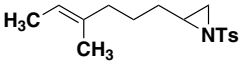
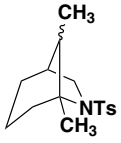
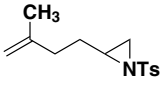
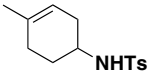
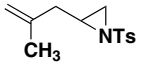
The reaction of **13a** provided tetrahydronaphthalene **16** in 45% yield. This product is not unexpected. Our previous examples of intramolecular cyclizations of aziridines with π-nucleophiles yield products in which nucleophilic attack takes place at the most substituted carbon of the aziridine ring (a 5-*exo* or 6-*exo*-cyclization).[13–15] However when the π-nucleophile is in the ring

Table 1. Arene–aziridine cyclizations

Starting material (% yield)	Product (% yield)
 **10a** (75)	 **7a** (97)
 **10b** (74)	 **7b** (83)
 **10c** (52)	 **7c** (98)
 **10d** (69)	 **7d**, 3:1 (97)
 **10e** (40)	 **7e** (88)
 **11a** (64)	 **7f** (6)
 **13a** (53)[a]	 **16** (45)

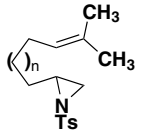
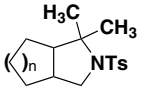
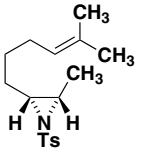
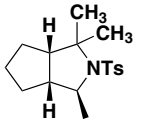
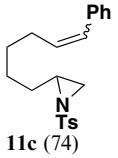
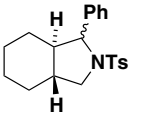
[a] Overall yield for three-step sequence from **12**.

Table 2. Endocyclic olefin–aziridine cyclizations

Starting olefin (% yield)	Product (% yield)
 **10f** (30)	 **6a** (71)
 **10g** (55)	 **6b** (63)
 **10h** (30)	 **6c** (75)
 **13b** (51)	 **17** (41)
 **13c** (62)[a]	 **6d** (72)

[a] Overall yield for three-step sequence from **12**.

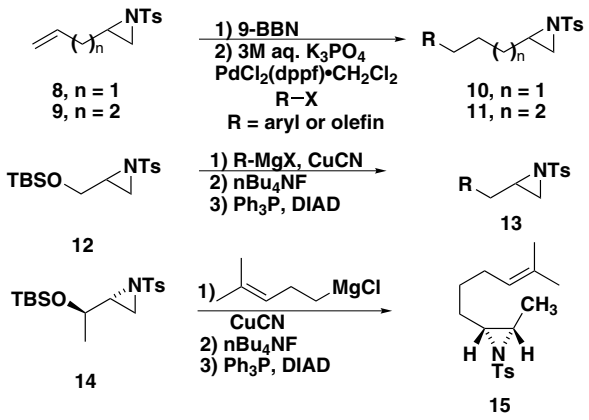
Table 3. Exocyclic olefin–aziridine cyclizations

Starting aziridine (% yield)	Product (% yield)
 **10i**, $n = 1$ (41) **11b**, $n = 2$ (70)	 **5a** (41) **5b** (75)
 **15** (33)[a]	 **5c** (75)
 **11c** (74)	 **5d** (9)

[a] Overall yield for three-step sequence from **14**.

being formed the 6-*endo*-cyclization products (e.g., **16**) are formed in preference to the 5-*exo*-cyclization product.[16,30–33]

Reactions of the aziridine ring with an endocyclic olefin (olefin in the ring being formed) are shown in Table 2. Treatment of these olefinic aziridines generally provided



Scheme 2.

a bicyclic product.[29] As shown in Scheme 1, two pathways are open to the cationic intermediate formed from the endocyclic π-nucleophile attack. When the π-nucleophile is an olefin, the sulfonamide nitrogen cyclizes onto the cationic intermediate (e.g., **2**) to provide the bicycle **6**. Both alkyl and aryl substitution on the endocyclic olefin provided sufficient stabilization of the cationic intermediates to provide bicyclic product (**6a** and **6b**) in moderate yield. In an effort to see if olefin geometry would be retained in this cyclization, substituted olefin **10h** was subjected to the usual reaction conditions. While the reaction proceeded in good yield, an approximately 1:1 mixture of the two diastereomers was obtained. Attempts to form larger ring systems were not successful.

The reaction of **13b** provided only cyclohexene **17** via a 6-*endo*-cyclization. As expected, none of the azabicyclo-[2.1.1]-octane ring system derived from the disfavoured 5-*exo*-cyclization was observed.

We also prepared and cyclized a one carbon shorter olefinic aziridine **13c**. We were quite pleased to see the formation of the bicyclo-[2.1.1]-system (**6d**) in 72% yield. This is a unique ring system that is difficult to prepare using other methods.

We next prepared and examined a series of tri and disubstituted exocyclic olefins.[29] The cyclization of compounds bearing two alkyl substituents on the terminus of the olefin (**10i**, **11b**) provided the expected cyclization products, **5a** and **5b** in good yield. This is especially exciting as it provides a route to ring systems containing a quaternary carbon adjacent to the ring nitrogen. These are in general difficult systems to prepare. The substituted aziridine **15** was also subjected to the usual reaction conditions to provide bicycle **5c** in good yield. The cyclizations of disubstituted olefins are not yet particularly successful as **11c** gave a 9% yield of the cyclized product **5d**. None of the olefinic products (e.g., **4**) were isolated from these reactions.

In summary, the intramolecular cyclization reactions of aziridines with a variety of π-nucleophiles appears to be a fairly general reaction. The formation of

six-membered rings either using arenes, endocyclic olefins or trisubstituted exocyclic olefins is a generally high yielding process going through a 6-*exo* cyclization. The corresponding 5-*exo* process using arenes or endocyclic olefins appears to be highly disfavoured with only the 6-*endo* products being formed. Only when an exocyclic olefin is the π-nucleophile is the formation of a five-membered ring is allowed. Further work to extend the scope and application of this reaction are in progress and will be reported in due course.

Acknowledgements

This work was supported in part by a grant from the NSF (CHE-9816208). We would also like to thank the Department of Chemistry and Biochemistry and the Office of the Vice-President for Research at Ohio University for support.

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