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Synthesis of substituted imidazolines via [3+2]-cycloaddition of aziridines with nitriles

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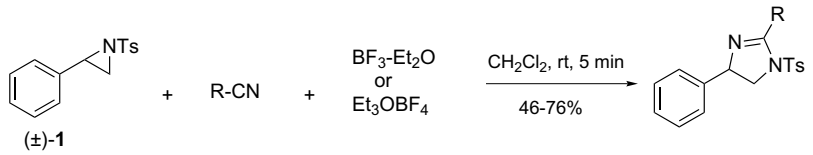
Abstract—An efficient synthesis of 2,4-disubstituted 1*H*-imidazolines from aziridines and nitriles in the presence of BF_3–Et_2O or triethyloxonium tetrafluoroborate has been described. The reaction proceeds via a [3+2]-cycloaddition reaction. Most of the nitriles successfully underwent cycloaddition reactions with aziridines even at room temperature in a very short time.

The synthesis of low molecular weight heterocyclic compounds with potential pharmacological properties has attracted considerable attention due to the need to identify active compounds by high-throughput screening of large combinatorial libraries. As a part of our program to develop small molecule libraries containing anti-inflammatory activity, we developed an efficient one-step synthesis of substituted imidazolines through the [3+2]-cycloaddition of aziridines with nitriles.

[3+2]-Cycloaddition of aziridines with dipolarophiles is a useful method for the synthesis of nitrogen-containing five-membered cyclic moieties.[1–8] Alkenes and alkynes have been used as dipolarophiles for the [3+2]-cycloaddition of aziridines.[2–8] Surprisingly, the utilization of nitriles as dipolarophiles for [3+2]-cycloaddition with aziridines has not resulted in an efficient entry to imidazolines,[9] which are known to exhibit a wide range of pharmacological activities. Imidazoline derivatives such as midaglizole, deriglidole and efaroxan are highly active anti-hyperglycemic agents.[10] Some derivatives have also been found to exhibit anti-inflammatory, antinociceptive, immunomodulating, anti-oxodant, antitumor, and anti-cancer activity.[11] We have studied the synthesis of substituted imidazolines in the presence of Lewis acids via [3+2]-cycloaddition reactions of aziridines with nitriles. Among the Lewis acids investigated, BF_3–Et_2O and triethyloxonium tetrafluoroborate were found to be the most efficient affording the substituted imidazolines in good yields (Scheme 1).

In the literature, most nitriles are known to be poor dipolarophiles for intermolecular [3+2]-cycloaddition reactions.[12] However, we observed that in the presence of 1 equiv of BF_3–Et_2O or Et_3OBF_4, most of the nitriles successfully underwent [3+2]-cyclization with aziridines even at ambient temperature in less than 5 min. When 10 mol% of the Lewis acid was used, the reactions were incomplete even after two days. Although the reaction was complete with the use of 20–50 mol% of the catalyst, the yields were poor. Thus, it became necessary to use stoichiometric amounts of BF_3–Et_2O or Et_3OBF_4 to



Scheme 1. [3+2]-Cycloaddition of 1-tosyl-2-phenylaziridine with nitriles in the presence of BF_3–Et_2O or Et_3OBF_4.

Keywords: Aziridine; BF_3–Et_2O; Triethyloxonium tetrafluoroborate; [3+2]-Cycloaddition; Imidazolines.
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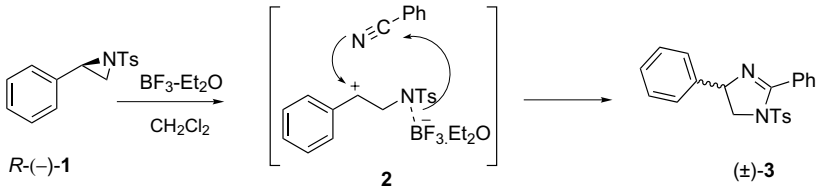
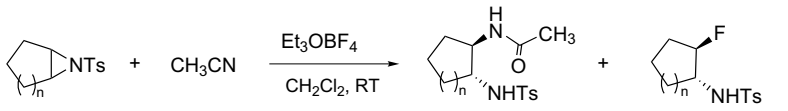


Scheme 2. Proposed mechanism for the [3+2]-cycloaddition of *N*-tosyl-(2*R*)-phenylaziridine with benzonitrile.



4 n = 1 **4a** 32% **4b** 30%
5 n = 2 **5a** 33% **5b** 30%

Scheme 3. Formation of the hydrolyzed α-acetamido β-sulphonamide products in the presence of Et_3OBF_4.

Table 1. [3+2]-Cycloaddition of 1-tosyl-2-phenylaziridine (±)-**1** with a variety of nitriles (R–CN) in the presence of BF_3–Et_2O or Et_3OBF_4

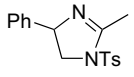
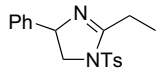
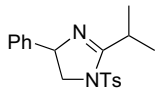
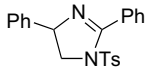
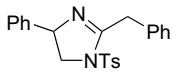
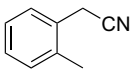
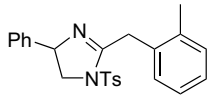
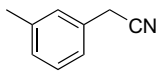
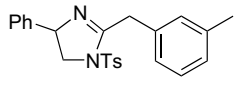
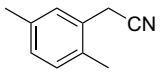
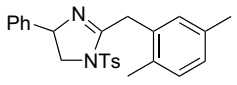
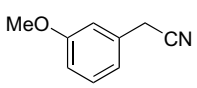
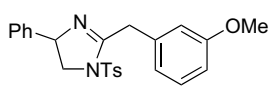
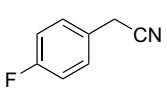
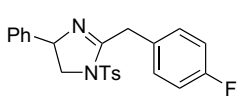
Entry	R–CN	Product	Yield (%)	
			BF_3–Et_2O	Et_3OBF_4
1	CH_3CN		75	74
2			72	72
3			76	74
4	PhCN		67	65
5			63	59
6			65	65
7			49	50
8			55	49
9			60	56
10			51	50

Table 1 (*continued*)

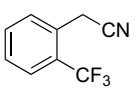
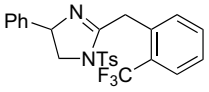
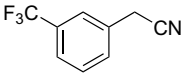
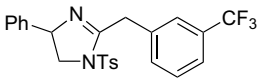
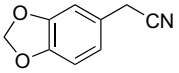
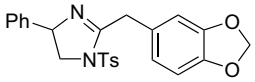
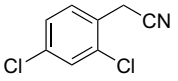
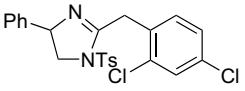
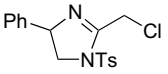
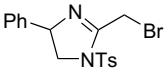
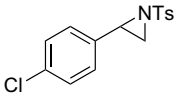
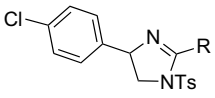
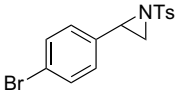
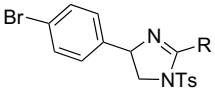
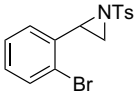
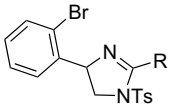
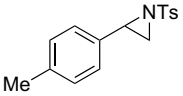
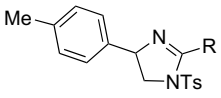
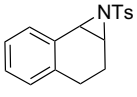
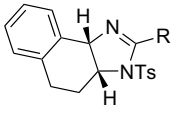
Entry	R–CN	Product	Yield (%)	
			BF_3–Et_2O	Et_3OBF_4
11			49	47
12			46	48
13			53	49
14			48	47
15			48	49
16			47	46

Table 2. [3+2]-Cycloaddition of nitriles with a variety of aziridines[a]

Entry	Aziridine	Product	Yield (%)	
			R = Me	R = Ph
1			52	59
2			54	60
3			52	55
4			51	54
5			54	56

[a] For all the reactions 1 equiv of BF_3–Et_2O was used, all reactions were complete in less than 5 min.

achieve good yields. It is proposed that the reaction involves a highly stabilized zwitterionic intermediate derived from the aziridine that undergoes cyclization with nitriles leading to the formation of an imidazoline. In order to substantiate this, a chiral aziridine *R*-(−)-**1** was prepared,[13] which on reaction with benzonitrile

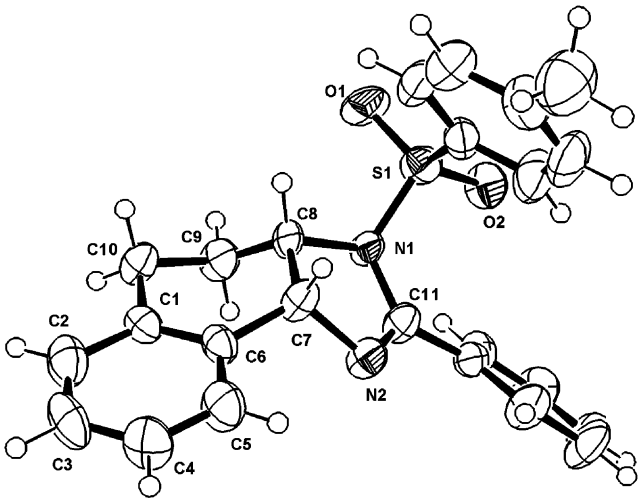


Figure 1. X-ray structure of tricyclic imidazoline (Table 2, entry 5, R = Ph).[17]

gave a racemic product **3** due to the formation of the benzyl carbocation **2**. This proved the participation of a zwitter ion as proposed in Scheme 2. Because of the stability of the benzyl carbocation, the cyclization is highly regioselective.

Both the Lewis acids BF_3–Et_2O and triethyloxonium tetrafluoroborate show similar reactivity in the [3+2]-cycloaddition reactions of aziridines with nitriles. In the presence of Et_3OBF_4, cyclopentene and cyclohexene aziridines underwent the [3+2]-cycloaddition reaction with acetonitrile but gave the hydrolyzed α-acetamido β-sulphonamide products after workup along with the fluorine-opened products (Scheme 3). BF_3–Et_2O gave a complex mixture for the same reaction. However, in the presence of BF_3–Et_2O and Et_3OBF_4, aryl substituted *N*-tosyl aziridines underwent the [3+2]-cycloaddition reaction with nitriles efficiently and gave imidazolines in moderate to good yields (Table 1).[14] High yields were obtained with aliphatic nitriles (Table 1, entries 1–3) whereas aryl nitriles gave only moderate yields of imidazolines. *Ortho*-substituted aryl nitriles were found to be more reactive than the *meta*-substituted nitriles (Table 1, entries 6, 7, and 8). Fluorinated aryl nitriles (Table 1, entries 10, 11 and 12) gave the cyclized products in moderate yields. Other functionalized nitriles such as TMSCN, benzoyl cyanides, and hydroxy cyanides gave complex mixtures of products, which could not be purified. However, chloro and bromo substituted acetonitriles gave the cyclized products in moderate yields (Table 1, entries 15 and 16).

The [3+2]-cyclization was then extended to a variety of aziridines with acetonitrile and benzonitrile (Table 2). In case of the aziridine derived from 1,2-dihydronaphthalene (Table 2, entry 5, R = Ph), a tricyclic imidazoline was obtained in modest yield. The structure of the product was determined by ^1H NMR and an X-ray crystal study (Fig. 1).[15] The imidazolines derived from acetonitrile slowly hydrolyzed to the corresponding α-acetamido β-sulphonamide on standing. In the presence of BF_3–Et_2O, *N*-Boc aziridines gave rearranged oxazolidin-2-ones without undergoing any [3+2]-cycloaddition reaction with nitriles.[16]

In conclusion, we have demonstrated an efficient one-step synthesis of substituted imidazolines in the presence of a Lewis acid via facile [3+2]-cycloaddition reactions of aziridines with nitriles in less than 5 min. We have also shown that most of the nitriles are good dipolarophiles undergoing [3+2]-cycloaddition with aziridines even under routine conditions. These imidazolines will find scope in the synthesis of various *N*-substituted compounds after the cleavage of sulphonamide and alkylation.[18,19]

General procedure: A solution of *N*-tosyl aziridine (1 mmol) in anhydrous dichloromethane (3 mL) and nitrile (1 mmol) was treated with freshly distilled $BF_3{\cdot}Et_2O$ (1 mmol) or Et_3OBF_4 (1 mmol, 1 M in DCM). After 5 min, saturated aqueous $NaHCO_3$ solution (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, then concentrated to give the crude product, which was purified over silica gel (30% EtOAc in petroleum ether) to give the substituted imidazoline.

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References and notes

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