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An efficient method for opening nonactivated aziridines with TMS azide: application in the synthesis of chiral 1,2-diaminocyclohexane†

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Abstract

A variety of *N*-substituted aziridines have been opened with TMS azide in MeCN at rt in the absence of any Lewis acid. The reaction was extended to the synthesis of (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexane.

Aziridines are versatile intermediates for the synthesis of nitrogen containing biologically active compounds.[1] Although these are nitrogen analogues of epoxides, reactivity of this strained heterocyclic ring system is less than that of epoxides and dependent upon the substitution on the nitrogen atom. Electron withdrawing groups on nitrogen enhance the reactivity of the ring and these compounds are termed as activated aziridines. A number of nucleophilic ring-opening reactions have been studied on activated aziridines with various nucleophiles, but studies on nonactivated aziridines (*N*-alkyl or aryl) have been restricted mainly due to their lack of reactivity and nonavailability of easy methods of synthesis. The ring-opening reaction of aziridines with nitrogen nucleophiles has special significance because the products are vicinal diamines which have varied applications in organic synthesis.[2] Recently, we have shown that nonactivated aziridines can be opened effectively with aromatic amines in the presence of a catalytic amount of $Sn(OTf)_2$ or $Cu(OTf)_2$ in a very short period of time and high yield.[3] We have also shown that activated aziridines can be opened with hydroxyl compounds in the presence of a catalytic amount of $Sn(OTf)_2$ or $BF_3{\cdot}OEt_2$.[4] These results encouraged us to use trimethylsilyl (TMS) azide for the nucleophilic ring opening of aziridines and apply the method in synthesis of chiral ligands.

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† We dedicate this paper with great respect to Professor K. K. Balasubramanian (I.I.T. Madras) on the occasion of his 60th birthday.

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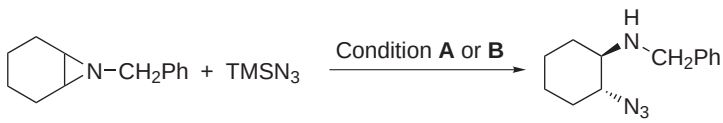
There are only a few reports on the ring opening of aziridines with $TMSN_3$. Yeung and co-workers reported the azidolysis of *N*-tosylaziridines with $TMSN_3$ in the presence of an imidochromium complex.[5,6] In this method, the reaction was too slow and the yields and regioselectivities were moderate. Later, Lectka et al. reported that certain transition metal and rare earth metal complexes catalyzed the azidolysis of *N*-benzoylaziridines.[7] It has recently been published that ring opening of activated aziridines by TMS azide can be triggered by the fluoride ion.[8] The above reported methods are compatible only with activated aziridines. Nonactivated aziridines are inert to these conditions. For example, Hou et al.[8] found that there is no reaction when the substituent on nitrogen is not strongly electron withdrawing (hydrogen or benzyl or even a Boc group).[9] This prompted us to look into the ring-opening reaction of nonactivated aziridines. In this paper we report our results of aziridine opening with $TMSN_3$ and its application in the synthesis of a useful chiral diamine.

At the outset, we carried out ring opening of *N*-benzylcyclohexyl aziridine with $TMSN_3$ in CH_2Cl_2 using 5 mol% of $Sn(OTf)_2$. The reaction was very effective as the ring-opened product was obtained in 98% yield. Under the same conditions $Cu(OTf)_2$ gave only 75% yield. The reaction was carried out in several solvents (Table 1) and it was observed that CH_2Cl_2 and MeCN both gave high yields of the ring-opened product except that the reaction was faster in MeCN. It was further observed that the reaction proceeded equally well in the absence of $Sn(OTf)_2$. In view of the above surprising results, the reaction was carried out on a variety of *N*-substituted aziridines in the presence and absence of the catalyst. In most of the cases, the absence of catalyst gave better results (Table 2). It was also observed that nonactivated aziridines reacted much faster than activated ones under the present experimental conditions (entry 9). In the case of cyclic aziridines, the stereochemistry of the ring-opened product was found to be *trans* from coupling constants of ring protons (entries 1–9). Phenyl substituted aziridines underwent reaction in a regiospecific manner, whereby azide ion attacked the benzylic position (entries 11 and 12). This is in contrast to the literature results where both regioisomers

Table 1

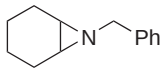
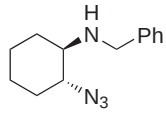
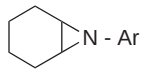
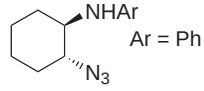
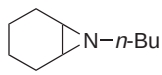
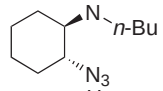
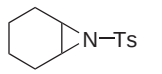
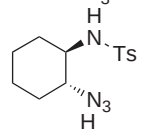
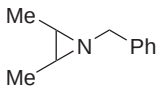
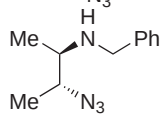
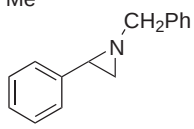
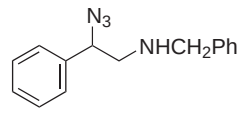
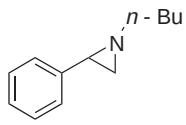
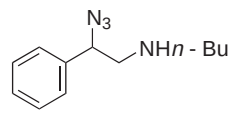
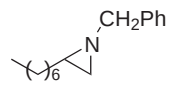
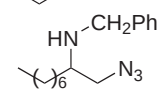
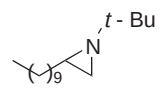
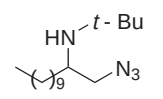
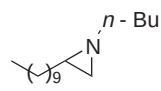
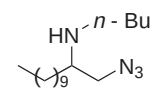


A = $Sn(OTf)_2$, Solvent, rt. **B** = Solvent, rt.

Solvent	Isolated yield (time)	
	Condition **A**	Condition **B**
CH_2Cl_2	98% (6 h)	99% (12 h)
Et_2O[a]	90% (24 h)	40%[b]
Benzene	85% (10 h)	90% (24 h)[a]
Hexane[a]	90% (16 h)	25% (30%)
MeCN	98% (2.5 h)	99% (2.5 h)

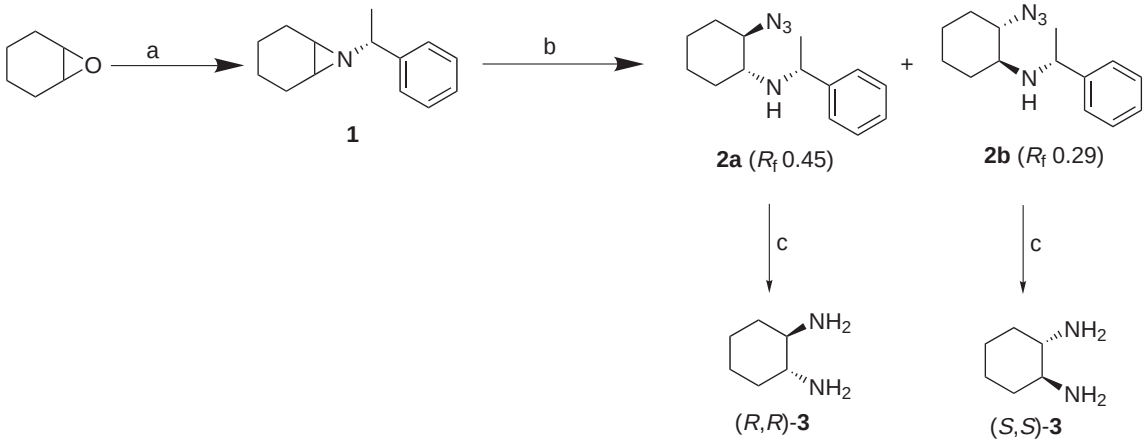
[a] Large excess of $TMSN_3$ needed for completion of the reaction.
[b] Reaction was not complete even after addition of excess $TMSN_3$.

Table 2
Cleavage of *N*-substituted aziridines with TMS azide in MeCN at room temperature

Entry	Aziridine	Azidoamine	Isolated Yield (Time)	
			5 mol % $Sn(OTf)_2$	No catalyst
1			98% (2.5 h)	99% (2.5 h)
2			98% (2 h)	98% (4 h)
3		Ar = C_6H_4-*p* -OMe	75% (1.5 h)	90% (1.5 h)
4		Ar = C_6H_4-*m*-Cl	75% (1.5 h)	94% (6 h)
5		Ar = C_6H_4-*o*-Me	82% (3 h)	91% (6 h)
6		Ar = 2-naphth	56% (2 h)	90% (4 h)
7		Ar = C_6H_4-*p*-Cl	92% (6 h)	90% (7 h)
8			58% (45 min)	70% (45 min)
9			30% (10 d)	70% (20 d)
10			71% (3 h)	70% (3.5 h)
11			60% (45 min)	83% (2 h)
12			62% (1 h)	92% (1 h)
13			88% (1 h)	93% (1 h)
14			78% (1 h)	82% (1 h)
15			88% (1 h)	93% (1 h)

were reported to be formed.[5,8] Acyclic terminal aziridines gave products resulting from terminal attack only, as has been observed in most of the azirdine-opening reactions by others.

In order to show the scope and utility of the above reaction, it was applied to the synthesis of a C_2 symmetric chiral diamine **3**, which is a very important ligand in asymmetric synthesis.[10] Cyclohexene oxide was converted into a chiral aziridine **1** by opening it with (*R*)-1-phenylethylamine and ring closure of the resulting amino alcohol by using diisopropyl azodicarboxylate and triphenylphosphine. The reaction of chiral aziridine **1** with TMS azide in MeCN at rt gave 90% yield of two distinctly separable (on TLC) diastereomers in a ratio of 4:1. The hydrogenation (20% $Pd(OH)_2/C$, H_2, 40 psi, rt) of the major diastereomer **2a**[11] (R_f 0.45; 10% EtOAc in hexanes) gave a diamine (*R*,*R*)-**3** {$[\alpha]_D$ of its HCl salt –9.7 (*c* 1.5, MeOH); lit.[12] $[\alpha]_D$ –9.4 (*c* 1.05, MeOH)} in 95% yield. Similarly, the minor diastereomer **2b** (R_f 0.29; 10% EtOAc in hexanes) provided the other enantiomer (*S*,*S*)-**3** (Scheme 1).



Scheme 1. (a) (i) *R*-(+)-1-Phenylethylamine, $LiClO_4$, MeCN, rt, 48 h, 95% yield; (ii) DIAD, Ph_3P, DCM, 0°C to rt, 7 h, 75% yield. (b) $TMSN_3$, MeCN, rt, 7 h, 90% yield (ratio of **2a** and **2b** = 4:1). (c) 20% $Pd(OH)_2/C$, MeOH, H_2, 40 psi, rt, 48 h, 95% yield

In conclusion, we have shown that nonactivated aziridines can be opened with TMS azide in high yield in MeCN in the absence of any Lewis acid. We have successfully used the method in the synthesis of an important chiral ligand in high yield.

Acknowledgements

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11. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92–1.36 (m, 4H), 1.36 (d, $J=6.6$ Hz, 3H), 1.58 (m, 2H), 1.73 (m, 2H), 2.02 (m, 1H), 2.39 (ddd, $J=10.7$, 10.5 and 4.2 Hz, 1H), 2.10 (ddd, $J=10.7$, 9.5 and 4.2 Hz, 1H), 3.94 (q, $J=6.6$ Hz, 1H), 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 24.32, 24.33, 30.5, 32.5, 56.6, 59.3, 66.3, 126.4, 126.7, 128.3, 146.9.
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