Ring Opening of Aziridines with Silylated Nucleophiles under Neutral Conditions

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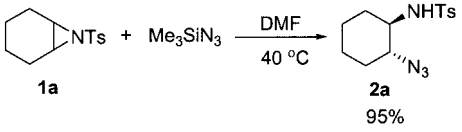
Keywords: Aziridine / Ring-opening / DMF / Silylated nucleophiles

Ring-opening of aziridines with silylated nucleophiles in DMF without any catalysts afforded the corresponding products in good to excellent yields under extremely mild reaction conditions.

The marked reactivity of aziridines toward ring opening and expansion is dependent upon their extremely strained ring structures. Among the procedures of ring opening of aziridines, the nucleophilic ring-opening reaction is one of the major routes to highly functionalized compounds.[1] Many ring-opening reactions of aziridines have been developed by using silylated nucleophiles.[2] Most of these methods are limited to the use of heavy and/or inexpensive metal-based catalysts such as a Lewis acid and frequently result in the formation of mixtures of regioisomers. Recently, we reported ring-opening reactions of aziridines with silylated nucleophiles triggered by tetrabutylammonium fluoride (TBAF) gave the corresponding products regioselectively in excellent yield.[3] It provides a facile and efficient procedure for the ring-opening reactions of aziridines and affords a practical access to the synthesis of 1,2-bifunctional compounds because of its efficiency and simplicity. Moreover, inspired by the results reported by Mukaiyama and Kobayashi[4] that Lewis bases are good catalysts for the silylcyanation of aldehydes with TMSCN, we found that Lewis bases (tertiary amines and phosphanes) were also efficient as catalysts in the ring-opening reactions of aziridines with silylated nucleophiles.[5] Very recently, another example of using Lewis bases as catalysts in the ring openings of aziridines with trimethylsilylated nucleophiles was reported by Minakata.[6] The ring opening of *N*-tosylaziridines with trimethylsilylated nucleophiles, catalyzed by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (20 mol-%), led to the production of β-functionalized sulfonamides in good yields.[6] However, the catalyst loading is high (20 mol-%) and reactions usually needed 24–100 hours for completion. On the other hand, although this amine-catalyzed reaction of aziridines with TMSX (X = CN, N_3, Br, and I), was readily opened by cyanide, azide, bromide, and iodide in the presence of a catalytic amount of TMEDA to give the desired compounds in good yields, strangely, ring opening of aziridines with the silyl chloride under the conditions did not proceed at all to recover the starting material.

Meanwhile, Kobayashi et al. have reported that allyltrichlorosilanes are activated by neutral organic molecules such as *N*,*N*-dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) to undergo allylation of aldehydes[7] or *N*-acylhydrazones[8] without the use of any metal catalyst. These organic molecules were proven to coordinate to allyltrichlorosilanes to form hypervalent silicon compounds[9] that react with electrophiles in a stereospecific manner. Inspired by these results, we found that, without any catalysts, the reaction of aziridine **1a** with trimethylsilyl azide also proceeded smoothly in DMF to afford the corresponding product in high yield (95%) (Scheme 1). The *anti*-stereochemistry of the product **2a** was confirmed by the coupling constant for two cyclic methine hydrogen atoms in the *trans*-positions.[3] The resulting product has the potential for serving as good building blocks for the preparation of vicinal diamines.[3]



Scheme 1. Reaction of aziridine **1a** with trimethylsilyl azide in DMF.

To demonstrate the generality of this method, without optimization of the reaction conditions, we next investigated the scope of this reaction and the results are summarized in Table 1. The operation is simple: silylated nucleophile (1.0 equiv.) was added to a solution of substrate **1** (0.25 mmol) in DMF (2.0 mL). The reaction mixture was stirred at 40 °C for a period of time (3–10 hours). After the reaction was completed monitored by TLC, the mixture was washed with water and extracted with ethyl acetate. The

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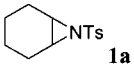
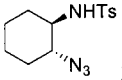
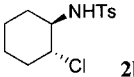
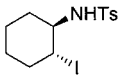
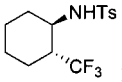
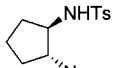
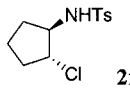
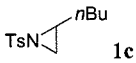
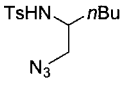
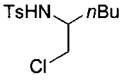
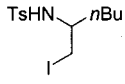
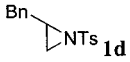
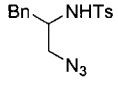
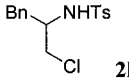
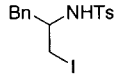
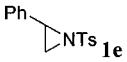
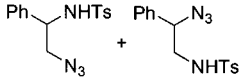
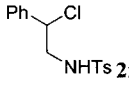
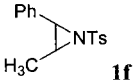
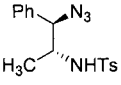
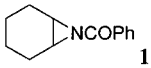
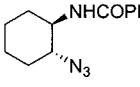
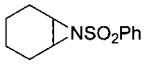
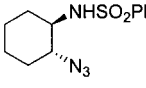
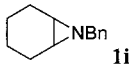
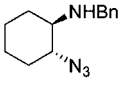
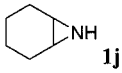
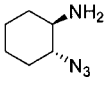
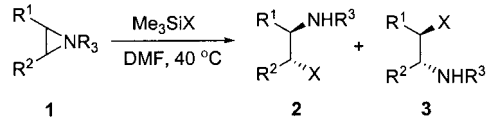
Table 1. Ring-opening of aziridines **1** with silylated nucleophiles in DMF.

Entry	Aziridine	Me_3SiX	Product	Time (h)	Yield (%)[a]
1	 **1a**	Me_3SiN_3	 **2a**	3	95
2	**1a**	Me_3SiCl	 **2b**	8	79
3	**1a**	Me_3SiI	 **2c**	9	62
4	**1a**	Me_3SiCF_3	 **2d**	12	–
5	 **1b**	Me_3SiN_3	 **2e**	18	87
6	**1b**	Me_3SiCl	 **2f**	8	93
7	 **1c**	Me_3SiN_3	 **2g**	3	89
8	**1c**	Me_3SiCl	 **2h**	8	90
9	**1c**	Me_3SiI	 **2i**	16	68
10	 **1d**	Me_3SiN_3	 **2j**	18	72
11	**1d**	Me_3SiCl	 **2k**	8	85
12	**1d**	Me_3SiI	 **2l**	16	84
13	 **1e**	Me_3SiN_3	 **2m/3m** (24/76)	3	91
14	**1e**	Me_3SiCl	 **2n**	8	61
15	 **1f**	Me_3SiN_3	 **2o**	6	81
16	 **1g**	Me_3SiN_3	 **2p**	12	93
17	 **1h**	Me_3SiN_3	 **2q**	12	90
18	 **1i**	Me_3SiN_3	 **2r**	12	–
19	 **1j**	Me_3SiN_3	 **2s**	12	–

[a] Isolated yield based on aziridine **1**.

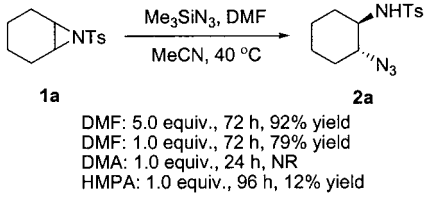
organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography column on silica gel afforded the corresponding product (Scheme 2).



Scheme 2. Ring-opening of aziridines **1** with various silylated nucleophiles in DMF.

This condition has proved to be useful for ring openings of a range of aziridines **1** with electron-withdrawing groups attached on the nitrogen atom (Table 1). In most of the cases, the reactions proceeded very clean and the desired products were afforded in good to excellent yields. Trimethylsilyl azide, as well as trimethylsilyl chloride and iodide are all suitable partners. However, no product was detected at all when trimethyl(trifluoromethyl)silane reacted with aziridine **1a** (Entry 4). In the case of unsymmetrically substituted aziridines **1c** and **1d**, completely regioselectivity with the attack of nucleophile on the less substituted aziridine carbon was observed. For the substrates **1f**, as previously reported, the attack of nucleophile was on the benzyl position due to electron effect. And also, it is reasonable that regioselectivity is not as specific as others when aziridine **1e** was employed as the substrate. Furthermore, the reactivity of aziridine was reduced according to the decreased electron-withdrawing ability of the substituent on the nitrogen atom of aziridine. For example, no reaction took place when compounds **1i** and **1j** were employed as substrates (Entries 17 and 18). For the role of DMF in the reactions, according to the precedent reports, we believe that DMF coordinates to trimethylsilyl compounds to form hypervalent silicon compounds,[8,9] which undergo further nucleophilic ring openings.

Further studies of solvent screening showed that only DMF was the best choice of solvents. The reaction of aziridine **1a** with trimethylsilyl azide also proceeded smoothly at room temperature although prolonged reaction time was needed (93% yield, 16 h). Moreover, 1.0 equiv. of DMF could push the reaction to go to completion (79% yield, 72 h, Scheme 3) when the solvent was changed to MeCN. However, no product was detected when DMA was employed. Addition of HMPA retarded the reaction.



Scheme 3.

In conclusion, we have discovered ring-opening reactions of aziridines with silylated nucleophiles in DMF without any catalysts proceeded highly efficient, which provided a general and convenient way to prepare a variety of 1,2-bifunctional compounds. The advantages of this method include good substrate generality, extremely mild reaction conditions, and experimentally operational ease. Desymmetrization of *meso*-aziridines with silylated nucleophiles by using chiral DMF analogues is under investigation in our laboratory.

Experimental Section

General Procedure for Reactions of Aziridines 1 with Silylated Nucleophiles: The silylated nucleophile (1.0 equiv.) was added to a solution of substrate **1** (0.25 mmol) in DMF (2.0 mL). The reaction mixture was stirred at 40 °C for a period of time indicated in Table 1. After the reaction was completed (monitoring was done by TLC), the mixture was washed with water and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography column on silica gel afforded the corresponding product. The data of products was identical with the literature reports.[3,5,6,10] Selected examples are given below.

***N*-(2-Azidocyclohexyl)-4-methylbenzenesulfonamide (2a):**[3] Colorless liquid. IR (film): $\tilde{\nu}$ = 3273, 2940, 2863, 2100, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.45 (m, 4 H), 1.60–1.80 (m, 2 H), 1.95–2.15 (m, 2 H), 2.45 (s, 3 H), 2.90–3.00 (m, 1 H), 3.00–3.10 (m, 1 H), 4.80 (br. d, J = 6.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H) ppm. MS: m/z = 295 [MH^+]. HRMS: $C_{13}H_{18}NO_2S$ [M – N_3]$^+$ 252.1058, found 252.1070.

***N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfonamide (2b):**[3] White solid with m.p. 100–102 °C. IR (film): $\tilde{\nu}$ = 3255, 2947, 2869, 1922, 1596 cm^{-1}. ^1H NMR (400 M Hz, $CDCl_3$): δ = 1.20–1.40 (m, 3 H), 1.55–1.75 (m, 3 H), 2.10–2.30 (m, 2 H), 2.40 (s, 3 H), 3.10–3.20 (m, 1 H), 3.60–3.70 (m, 1 H), 4.85 (br., 1 H), 7.30 (d, J = 8.0 Hz Hz, 2 H), 7.80 (d, J = 8.2 Hz Hz, 2 H) ppm. MS: 289 (M^+, ^{37}Cl), 287 (M^+, ^{35}Cl). $C_{13}H_{18}ClNO_2S$ (289.81): calcd. C 54.26, H 6.26, N 4.87; found: C 54.55, H 6.26, N 4.71.

***N*-(2-Iodocyclohexyl)-4-methylbenzenesulfonamide (2c):**[10] ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.32 (m, 3 H), 1.61–1.71 (m, 3 H), 2.16–2.27 (m, 2 H), 2.43 (s, 3 H), 3.24–3.27 (m, 1 H), 3.99–4.01 (m, 1 H), 5.01–5.02 (d, J = 6.2 Hz, 1 H), 7.26–7.31 (m, 2 H), 7.8 (d, J = 8.3 Hz, 2 H) ppm.

Acknowledgments

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