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Lewis Base Catalyzed Ring Opening of Aziridines with Silylated Nucleophiles

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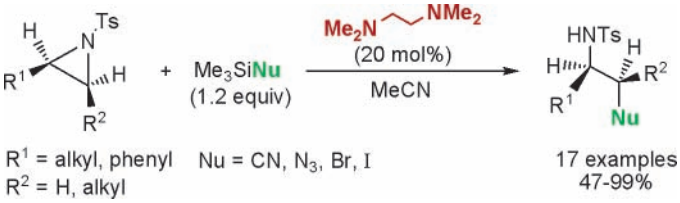
ABSTRACT



The ring opening of *N*-tosylaziridines with trimethylsilylated nucleophiles, catalyzed by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, led to the production of *β*-functionalized sulfonamides in good to excellent yields with high regioselectivity.

Aziridines are very useful synthetic intermediates for the synthesis of functional materials and biologically active compounds.[1] For this reason, in previous studies, we developed some facile synthetic methods for producing aziridines through the introduction of an N1 unit to alkenes.[2] The reactivity of aziridines toward ring opening and expansion is dependent upon their extremely strained ring structures. Among the procedures of ring opening of aziridines, a nucleophilic ring-opening reaction is one of the major routes to highly functionalized compounds.[3] Ring-opening reactions of aziridines have been developed using silylated nucleophiles.[4] 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. Hou and co-workers reported on the ring opening of aziridines with silylated nucleophiles, triggered by the presence of tetrabutylammonium fluoride (TBAF).[5] In the reaction, ammonium cyanide, derived from trimethylsilyl cyanide (TMSCN) and TBAF, acts as a nucleophile for the ring opening. While Lewis acid catalyzed ring-opening reactions, the regioselectivity of which are difficult to control, are based on the activation of aziridines, Hou's method probably involved the generation of a rather strong nucleophile (cyanide, azide, etc.) from TMSNu, similar to

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(5) Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344−1348.

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the Sakurai−Hosomi reaction.[6] In an attempt to better control the regioselectivity of such reactions, we focused on the activation of silyl reagents with a Lewis base catalyst (Figure 1). Although Mukaiyama and Kobayashi[7] originally reported

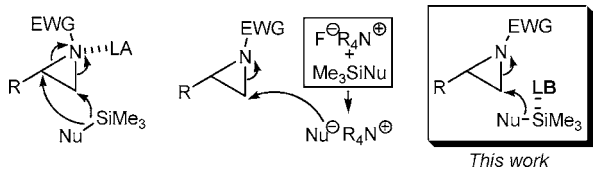
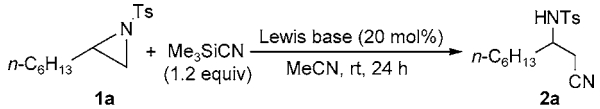


Figure 1. Representative modes of the ring opening of aziridines with TMSNu.

that Lewis bases are good catalysts for the silylcyanation of aldehydes with TMSCN, there are no examples of the ring opening of aziridines in which a combination of silyl compounds and Lewis base catalysts are used. From these points of view, we report on the Lewis base-catalyzed regioselective ring opening of aziridines with trimethylsilyl cyanide, azide, and halides. The resulting products have the potential for serving as good building blocks for the preparation of vicinal diamines and β-amino acids.

Although an initial reaction of aziridine **1a** with TMSCN in acetonitrile at room temperature did not proceed at all, when triethylamine (20 mol %) was added to the system ring-opening product **2a** was obtained in 63% yield after workup (Table 1, entries 1 and 2). When *N*-methylpyrrolidine

Table 1. Lewis Base Catalyzed Ring Opening of an Aziridine with TMSCN: The Effect of Lewis Bases



1a **2a**

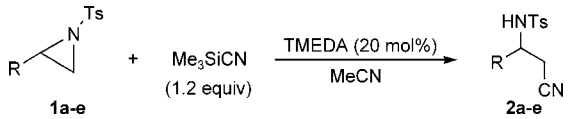
entry	Lewis base	yield (%)	recovery of **1a** (%)
1	none	0	100
2	Et_3N	63	27
3		75	0
4	Me_2N NMe$_2$	83 (76)[a]	0
5	MeO OMe	0	91
6	Me_2P PMe_2	78	0

[a] TMEDA: 10 mol %.

or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was employed, the starting material was completely consumed and **2a** was produced in good yields (Table 1, entries 3 and 4). Since TMEDA contains two Lewis basic sites, 10 mol % of the base was used to produce **2a** in 76% yield. While 1,2-dimethoxyethane was not effective, 1,2-bis(dimethylphosphino)ethane readily promoted the reaction (Table 1, entries 5 and 6). Tertiary amines and a phosphine were also found to function as catalysts for the ring opening. Among these, amines are inexpensive and commercially available and would be promising reagents for asymmetric reactions in our future studies. For the above reasons, TMEDA was selected for use in the ring opening of other aziridines.

The ring opening of **1a** was attempted with 20 mol % of TMEDA at room temperature, using a range of solvents, including acetonitrile, toluene, dichloromethane, and THF. Of these, only acetonitrile resulted in a complete conversion within 24 h. The ring opening of 2-substituted *N*-tosylaziridines was investigated under optimized conditions, and the results are shown in Table 2.

Table 2. TMEDA-Catalyzed Ring Opening of 2-Substituted *N*-Tosylaziridines with TMSCN



1a-e **2a-e**

entry	aziridine	R	*T* (°C)	time (h)	yield (%)
1	**1a**	n-C_6H_{13}	rt	24	83 (**2a**)
2	**1b**	CH_2Ph	rt	24	84 (**2b**)
3	**1c**	s-C_4H_9	60	48	93 (**2c**)
4	**1d**	Ph	rt	64	47[a] (**2d**)
5[b]	**1e**	CH_2OH	60	18	88[c] (**2e**)

[a] Recovery of **1d**: 19%. [b] TMSCN: 2 equiv. [c] Including 48% of *O*-silylated ring-opening product (R = CH_2OSiMe_3).

As described above, aziridines **1b** as well as **1a** were readily converted to the corresponding ring-opening products in good yields with complete regioselectivity (Table 2, entries 1 and 2). When the reaction of *sec*-butyl-substituted aziridine **1c** was examined at these conditions (rt), the reaction proceeded rather slowly (70% yield after 120 h, 25% recovery of **1c**). At a temperature of 60 °C, however, the rate of the reaction increased, affording **2c** in 93% yield (Table 2, entry 3). Although the efficiency of the reaction of **1d** could be improved, a complete regioselective ring opening was observed (Table 2, entry 4). In the case of nonmetallic and metal salt-promoted reactions, the product that opened at the benzylic position was mainly produced as a mixture of two regioisomers.[8] In contrast to this known behavior, the regioselectivity induced by the present method is perfect and similar to the case where strong nucleophiles are used. The method was also found to be applicable to the

(7) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537−540.

(8) For recent examples, see: (a) Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 5295−5300. (b) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 1691−1694. (c) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Reddy, P. V.; Harshavardhan, S. J. *Synthesis* **2004**, 1854−1858. For successfully controlled examples, see: (d) Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1314−1317. (e) Furuta, Y.; Kumamoto, T.; Ishikawa, T. *Synlett* **2004**, 362−364.

ring opening of a hydroxylated compound, giving the corresponding product, including the *O*-silylated ring opening compound, in good yields (Table 2, entry 5).

With an acceptable result for the ring opening of 2-substituted aziridines catalyzed by TMEDA in hand, the method was extended to 2,3-disubstituted aziridines. When the bicyclic aziridines **1f** and **1g** were treated with TMSCN in the presence of TMEDA at 60 °C for 24 h, the yields of the ring-opening products were moderate, especially for **1g**. Since the starting aziridine **1g** was recovered, the progress of the ring opening of **1g** was monitored by ^{1}H NMR (Figure 2). The spectral data indicated that **1g** and **2g** were present

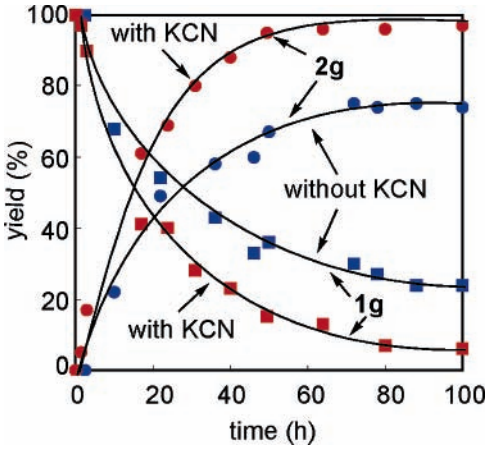


Figure 2. Time course for the ring opening of **1g** at 60 °C, without KCN vs with KCN (1 equiv).

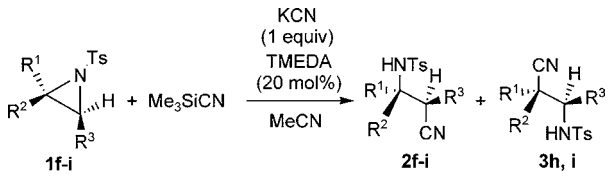
as an equilibrium mixture and, as a logical offshoot, the addition of KCN improved the efficiency of the reaction, giving the desired **2g** in quantitative yield. Quite recently, many examples of the ring opening of three-membered heterocycles have appeared, but reactions of 2,3-dialkyl-substituted unfused aziridines are rare.[9] The ring opening of 2,3-*cis*-dialkyl-substituted aziridine **1h** failed to proceed at all, even at 100 °C, in the absence of KCN. The presence of KCN enabled the ring opening of **1h** and **1i** in good yields, giving a mixture of regioisomers, where the stereoselectivity was completely controlled to afford a sole diastereomer (Table 3).

This amine-catalyzed reaction of aziridines with TMSCN is applicable to other silylated nucleophiles, $TMSN_3$ and TMSX, as shown in Table 4. Alkyl-substituted *N*-tosylaziridines, such as **1a** and **1b**, were readily opened by azide, bromide, and iodide in the presence of a catalytic amount of TMEDA to give the desired compounds in good yields (Table 4, entries 1−6).[10] Even in the absence of KCN, the stronger nucleophilicity of the azide ion, compared to that of cyanide led to the ring opening of bicyclic aziridines **1f**

(9) For *meso*-aziridines, see, for example, ref 4h.

(10) While Hou's method is successfully applicable to the ring opening of aziridines with TMSCl, ring opening of **1a** with the silyl chloride under the conditions did not proceed at all to recover the starting material.

Table 3. TMEDA-Catalyzed Ring Opening of 2,3-Disubstituted *N*-Tosylaziridines with TMSCN

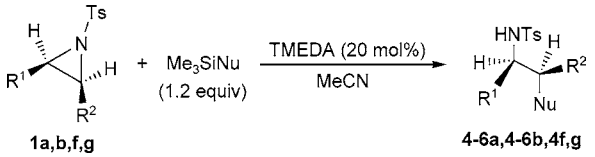


entry	aziridine	R^1	R^2	R^3	Me_3SiCN (equiv)	T (°C)	time (h)	yield (%)
1[a]	**1f**	H	$-(CH_2)_3-$		1.2	60	24	70 (**2f**)
2[a]	**1g**	H	$-(CH_2)_4-$		1.2	60	24	57[b] (**2g**)
3	**1g**	H	$-(CH_2)_4-$		1.2	60	72	97 (**2g**)
4[a]	**1h**	H	n-C_5H_{11}	Me	1.5	100	48	0
5	**1h**	H	n-C_5H_{11}	Me	1.5	80	100	90 (**2h**, **3h**)[c]
6	**1i**	n-C_5H_{11}	H	Me	1.5	80	100	80 (**2i**, **3i**)[c]

[a] Without KCN. [b] Recovery of **1g**: 41%. [c] Regioisomer ratio: **2h**/**3h** = 67/33; **2i**/**3i** = 80/20.

and **1g** to afford the corresponding products in quantitative yields (Table 4, entries 7 and 8). The reactions listed in Table 4 did not proceed in the absence of a Lewis base (TMEDA) at all.

Table 4. TMEDA-Catalyzed Ring Opening of *N*-Tosylaziridines with TMSNu



entry	aziridine	R^1	R^2	Nu	T (°C)	time (h)	yield (%)
1	**1a**	n-C_6H_{13}	H	N_3	rt	24	90 (**4a**)
2	**1a**	n-C_6H_{13}	H	Br	rt	48	88 (**5a**)
3	**1a**	n-C_6H_{13}	H	I	rt	24	97 (**6a**)
4	**1b**	CH_2Ph	H	N_3	rt	24	88 (**4b**)
5	**1b**	CH_2Ph	H	Br	rt	48	88 (**5b**)
6	**1b**	CH_2Ph	H	I	rt	48	99 (**6b**)
7	**1f**	$-(CH_2)_3-$		N_3	50	48	97 (**4f**)
8	**1g**	$-(CH_2)_4-$		N_3	50	48	98 (**4g**)

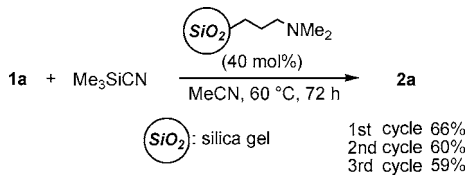
Heterogeneous catalysts immobilized on silica gel have been developed extensively. Among these, silica gel functionalized with amino groups has proved to be a useful insoluble catalyst for Knoevenagel condensations,[11] the oxidation of alkanes,[12] and Michael addition reactions.[13] The utility associated with the reusability and simple workup

(11) Angeletti, E.; Canepa, C.; Martinetti, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 105−107.

(12) Kurusu, Y.; Neckers, D. C. *J. Org. Chem.* **1991**, *56*, 1981−1983.

(13) Mdoe, J. E. G.; Clark, J. H.; Macquarrie, D. J. *Synlett* **1998**, 625−627.

Scheme 1. Application of a Lewis Base Catalyst Immobilized on Silica Gel to the Ring Opening and Its Reusability



procedures in cases where this catalyst is used prompted us to investigate its application to the present reaction. When aziridine **1a** was treated with TMSCN in the presence of 40 mol % of 3-(dimethylamino)propyl-functionalized silica gel in acetonitrile at 60 °C for 72 h, the desired ring opening proceeded, affording **2a** in 66% yield. The catalyst was found to be reusable after washing with an alkaline solution and **2a** was produced in 60% yield in the second cycle and 59% in the third cycle (Scheme 1).

In summary, the novel and efficient nonmetallic catalyzed regioselective ring-opening of aziridines with silylated nucleophiles is described herein. The reaction provides a facile route to the synthesis of β-amino acids and 1,2-diamines. Further investigations of the scope of the reaction are currently underway.

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Supporting Information Available: General experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Representative procedure for ring opening of an aziridine **1a**. To a solution of *N*-tosylaziridine **1a** (84.3 mg, 0.3 mmol) in acetonitrile (1.2 mL) were added trimethylsilyl cyanide (48 μL, 0.36 mmol) and TMEDA (9 μL, 0.06 mmol). The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After consumption of the starting material, removal of solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography using *n*-hexane−AcOEt as an eluent to give the ring-opening product **2a** (76.7 mg, 83%): colorless oil; IR (neat, cm^{-1}) 2251 (CN); ^1H NMR (270 MHz, $CDCl_3$) δ 0.84 (t, 3H, *n*-$C_5H_{10}CH_3$, J = 6.8 Hz), 1.07−1.60 (m, 10H, *n*-$C_5H_{10}CH_3$), 2.44 (s, 3H, Ar−CH_3), 2.50−2.68 (m, 2H, CH_2CN), 3.38−3.46 (m, 1H, N−C*H*), 4.75 (d, 1H, N*H*, J = 7.6 Hz, D_2O exchangeable), 7.32 (d, 2H, *m*-H, J = 8.2 Hz), 7.75 (d, 2H, *o*-H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.05, 21.60, 22.45, 25.13, 25.30, 28.50, 31.49, 33.90, 50.01, 116.74(CN), 126.96, 129.76, 136.93, 143.83; MS (CI, methane) *m*/*z* (relative intensity) 309 ($[M + 1]^+$, 61), 268 ($[M - CH_2CN]^+$, 100); HRMS (CI, methane) *m*/*z* calcd for $C_{16}H_{25}N_2O_2S$ (M + H) 309.1637, found 309.1646. Anal. Calcd for $C_{16}H_{24}N_2O_2S$: C, 62.30; H, 7.84; N, 9.08. Found: C, 61.89; H, 7.52; N, 8.92.