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Ring-opening reaction of aziridines with amines under the influence of dimethyl sulfoxide

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ABSTRACT

The ring-opening reaction of various aziridines with amines proceeded at room temperature to afford the corresponding 1,2-diamines in good to excellent yields using only 3–5 equiv dimethyl sulfoxide (DMSO) to aziridines in hexane. This reaction can be performed with easy handling and proceeds under mild reaction conditions. Also a variety of amines are available as a nucleophile.

To dedicated to late Tomoko Kakinuma, past member in our laboratory.

Aziridines are versatile intermediates in synthetic organic chemistry.[1] Many nucleophilic ring-opening reactions of aziridines were reported.[2] Using amines as a nucleophile in the ring-opening reactions of aziridines, 1,2-diamines can be obtained. Synthesizing 1,2-diamines efficiently is important because their building blocks are contained in many biologically and medicinally active compounds such as penicillins, oseltamivir, and other pharmaceuticals.[3] Conventional methods of inducing the ring-opening reactions of aziridines with amines require a metal reagent such as $Yb(OTf)_3$,[4a] $Sn(OTf)_2$ or $Cu(OTf)_2$,[4b] $LiClO_4$,[4c, h] $InBr_3$,[4d] $LiNTf_2$,[4e] $BiCl_3$,[4f] $TaCl_5$,[4g] SmI_2,[4i] or sulfated zirconia.[4j] Green chemical methods were also reported, but the examination of amines did not widely conducted in most of those methods.[5]

In recent years, dimethyl sulfoxide (DMSO) received renewed attention as a promoter,[6a, c, e] an oxidant,[6f, h] and a reactant[6b, d, g] of efficient organic reactions. We also developed many novel reactions using DMSO and molecular sieves (MS) 4A during the course of our intensive work.[7] For example, under the influence of DMSO and MS 4A, the Knoevenagel reaction of *N*-tosylimines with active methylene compounds,[7g] the double Michael addition of dithiols to acetylenic carbonyl compounds,[7h] and the aza-Henry reaction of *N*-tosylimines with nitroalkanes[7j] proceeded smoothly to produce the corresponding products without a metal catalyst or base. Based on these investigations, we undertook the ring-opening reaction of aziridines with amines using DMSO and MS 4A.

Wu *et al.* already reported the ring-opening reaction of aziridines with various nucleophiles in DMSO in 2006,[5i] but there were still some issues to be resolved: (1) a large amount of DMSO (2.0 mL to 0.25 mmol aziridines) is used; (2) heating (reactions are conducted at 60 °C) is needed; and (3) only aromatic amines can be applied to this reaction. Here, we describe that the ring-opening reaction of various aziridines with aromatic and aliphatic amines proceeding by using only 3–5 equiv DMSO to aziridines at room temperature to afford the corresponding 1,2-diamines in good to excellent yields.

Initially, we attempt the ring-opening reaction of aziridine **1a** (0.30 mmol), which is derived from cyclohexene[8] with 1.2 equiv benzylamine **2a** in DMSO (1 mL), in the presence of MS 4A (100 mg). As expected, the corresponding 1,2-diamine is obtained in 92% yield (Table 1, entry 1). We subsequently examine the effect of solvents (entries 2–8). Other aprotic polar solvents such as DMF and MeCN give the desired product in lower yields in comparison with DMSO (entries 2 and 3). Using MeOH as a solvent, we obtain the desired product in 45% yield (entry 4). CH_2Cl_2, THF, and toluene are found to be ineffective for this reaction (entries 5–7). To our surprise, in the case of a hexane solvent, the corresponding product is obtained in 75% yield (entry 8). The examination of the solvent reveals that DMSO is suitable for this reaction and hexane also gives comparatively good results.

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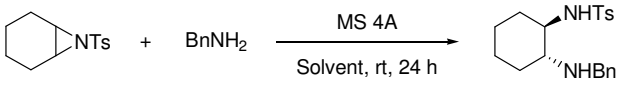
Table 1. Screening of solvents[a]



1a **2a** **3aa**

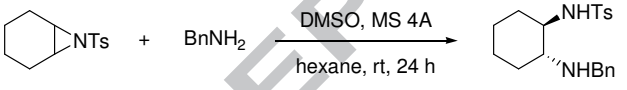
Entry	Solvent	Yield[b] (%)
1	DMSO	92
2	DMF	71
3	MeCN	54
4	MeOH	45
5	CH_2Cl_2	28
6	THF	22
7	toluene	6
8	hexane	75

[a]Reactions were carried out using an aziridine **1a** (0.30 mmol) and benzylamine **2a** (0.36 mmol) in solvent (1 mL) in the presence of MS 4A (100 mg).

[b]Isolated yield of purified product.

In our previous work on the double Michael addition of dithiols to acetylenic carbonyl compounds,[7h] we found that the reaction proceeded similarly by using only 5 equiv DMSO to substrates in hexane in place of using DMSO as a solvent (2 mL to 0.30 mmol substrates). Therefore, we expect that the amount of DMSO can be reduced by using hexane as a solvent. Thus, we investigate the equivalent of DMSO to aziridine in hexane (Table 2). Fortunately, when reducing DMSO from 1 mL to 107 µL (5 equiv to aziridine), the desired 1,2-diamine is obtained in 96% yield (entry 2). We obtain the same result by reducing DMSO down to 3 equiv (entry 3), whereas the yields decreases when we use less than 3 equiv DMSO (entries 4–8). From the above results, 3 equiv is considered the adequate amount of DMSO.

Table 2. Screening of the amount of DMSO[a]



1a **2a** **3aa**

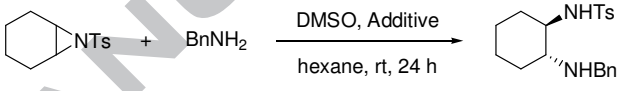
Entry	DMSO	Yield[b] (%)
1	47 equiv, 1 mL	92
2	5 equiv, 107 µL	96
3	3 equiv, 64 µL	96
4	2 equiv, 43 µL	94
5	1 equiv, 21 µL	86
6	0.5 equiv, 11 µL	84
7	0.1 equiv, 2 µL	75
8	0 equiv	75

[a]Reactions were carried out using an aziridine **1a** (0.30 mmol) and benzylamine **2a** (0.36 mmol) in hexane (1 mL) in the presence of MS 4A (100 mg).

[b]Isolated yield of purified product.

The effect of additives is subsequently investigated (Table 3). When the reaction is conducted without an additive, the corresponding 1,2-diamine is obtained in 94% yield (entry 1). Adding 100 µL H_2O, the yield decreases (entry 2). Adding 100 mg MS 4A gives a higher yield (entry 3). We speculate that MS remove a trace amount of water in the reaction mixture to prevent a loss of Lewis basicity of DMSO. Therefore, it is better to perform the reaction in absolute dehydrated conditions in the presence of a dehydrating reagent. Then, the reaction is performed testing various dehydrating reagents (entries 4–9). MS 4A, 5A, Drierite®, and Na_2SO_4 give the desired product in the same yield; however, we choose MS 4A as it gives the most reliable results in our many reported reactions.[7] An examination of the MS 4A amount added (entries 10–13) indicates that 50 mg MS 4A is the most suitable for the reaction as it gives the highest yield. Additionally, when the reaction is performed without hexane, the desired compound is also obtained in 96% yield (entry 14). According to this result, we believe that the higher substrate concentration in DMSO accelerates the reaction. Taking the experimental convenience into consideration, we use hexane as a solvent for further investigations.

Table 3. Screening of additives[a]



1a **2a** **3aa**

Entry	Additive	Yield[b] (%)
1	none	94
2	H_2O (100 µL)	77
3	MS 4A (100 mg)	96
4	MS 3A (100 mg)	94
5	MS 5A (100 mg)	96
6	MS 13X (100 mg)	92
7	Drierite® (100 mg)	96
8	$MgSO_4$ (100 mg)	91
9	Na_2SO_4 (100 mg)	96
10	MS 4A (70 mg)	95
11	MS 4A (50 mg)	98
12	MS 4A (30 mg)	95
13	MS 4A (10 mg)	91
14	MS 4A (50 mg)	96[c]

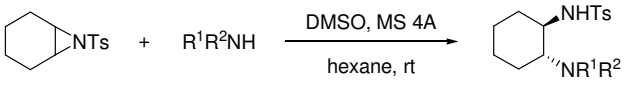
[a]Reactions were carried out using an aziridine **1a** (0.30 mmol) and benzylamine **2a** (0.36 mmol) in hexane (1 mL) in the presence of DMSO (0.90 mmol).

[b]Isolated yield of purified product.

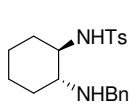
[c]Reaction was carried out without hexane.

The scope of the present study is to investigate this reaction using various amines, as shown in Scheme 1.[9] The reaction with various aliphatic and aromatic amines as nucleophiles is successful. Not only primary amines but also secondary cyclic amines are applicable nucleophiles among aliphatic amines (**3aa**–**3ao**), although the reaction with diethylamine or diisopropylamine gives no desired product. Using 5 equiv DMSO and extending the reaction time, the corresponding 1,2-diamines

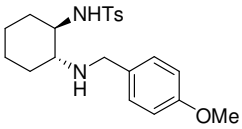
Scheme 1. Ring-opening reaction of aziridines with various amines[a]



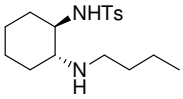
1a **2** **3**



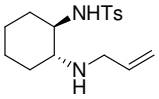
3aa, 98%



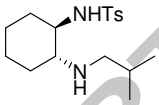
3ab, 94%



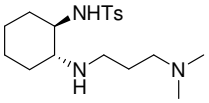
3ac, 79%



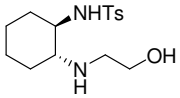
3ad, 65%



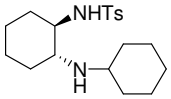
3ae, 69%



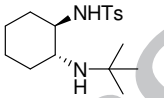
3af, 91%



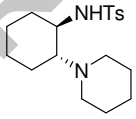
3ag, 73%



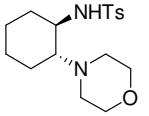
3ah, 75%



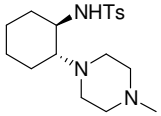
3ai, 35%



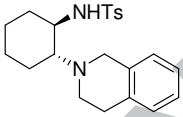
3aj, 86%



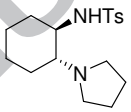
3ak, 91%



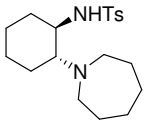
3al, 100%



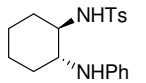
3am, 98%



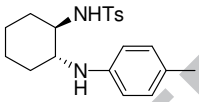
3an, 95%



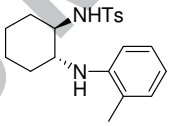
3ao, 94%



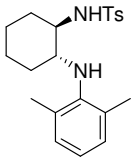
3ap, 59% (81%)[b]



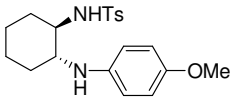
3aq, 91%[b]



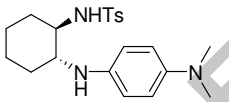
3ar, 54%[b]



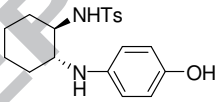
3as, 13%[b]



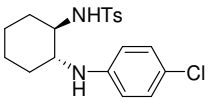
3at, 94%[b]



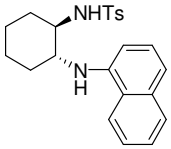
3au, 93%[b]



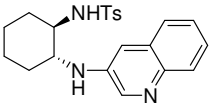
3av, 78%[b, c] (91%)[c, d]



3aw, 56%[b]



3ax, 46%[b]



3ay, 28%[b]

[a]Reactions were carried out using an aziridine **1a** (0.30 mmol) and an amine **2** (0.36 mmol) in hexane (1 mL) in the presence of DMSO (0.90 mmol) and MS 4A (50 mg) for 24 h. Yield of isolated product after chromatographic purification is shown.

[b]5 equiv DMSO were used and reaction was performed for 48 h.

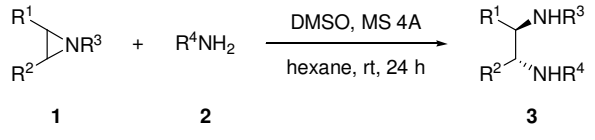
[c]Yield of isolated product after recrystallization.

[d]Reactions were carried out using an aziridine **1a** (5.0 mmol, 1.3 g) and an amine **2v** (5.0 mmol, 0.55 g) in hexane (10 mL) in the presence of DMSO (25 mmol, 1.8 mL) and MS 4A (800 mg) for 48 h.

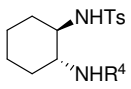
are obtained in practical yields when aromatic amines as employed as a nucleophile (**3ap**–**3ay**). The reaction of aziridine with steric-hindered or electron-deficient amines gives the corresponding 1,2-diamines in lower yields (**3ai**, **3ar**, **3as**, and **3aw**). 4-Nitroaniline and ethyl 4-aminobenzoate do not give the desired compounds. Aromatic secondary amines such as *N*-methylaniline, 1,2,3,4-tetrahydroquinoline, and carbazole are also checked in this reaction system, but the corresponding products are not obtained. A successful result is obtained from a gram-scale reaction using 1.0 equiv amine to aziridine (**3av**).

We further evaluate the ring-opening reaction of a variety of aziridines with benzylamine **2a** and aniline **2p**, as summarized in Scheme 2. Cyclopentene-derived aziridine is also suitable in

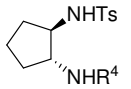
Scheme 2. Ring-opening reaction of various aziridines with amines[a]



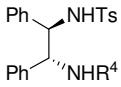
1 **2** **3**



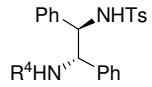
3aa, R^4 = Bn, 98%
3ap, R^4 = Ph, 59%



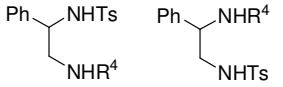
3ba, R^4 = Bn, 72%
3bp, R^4 = Ph, 25%



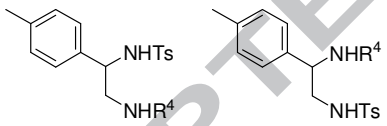
3ca, R^4 = Bn, 5%
3cp, R^4 = Ph, 0%



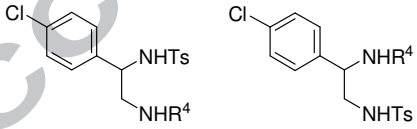
3da, R^4 = Bn, 96%
3dp, R^4 = Ph, 47%



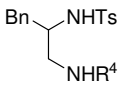
3ea + **3ea'**, R^4 = Bn, 97%, 36:64 dr[b]
3ep + **3ep'**, R^4 = Ph, 95%, 15:85 dr[c]



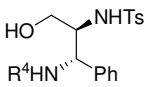
3fa + **3fa'**, R^4 = Bn, 87%, 25:75 dr[b]
3fp + **3fp'**, R^4 = Ph, 90%, 3:97 dr[c]



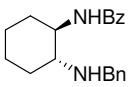
3ga + **3ga'**, R^4 = Bn, 90%, 46:54 dr[b]
3gp + **3gp'**, R^4 = Ph, 81%, 9:91 dr[c]



3ha, R^4 = Bn, 76%
3hp, R^4 = Ph, 50%



3ia, R^4 = Bn, 87%
3ip, R^4 = Ph, 76%[d]



3ja, 53%

[a]Reactions were carried out using an aziridine **1** (0.30 mmol) and an amine **2** (0.36 mmol) in hexane (1 mL) in the presence of DMSO (0.90 mmol) and MS 4A (50 mg). Yield of isolated product after chromatographic purification is shown.

[b]Ratio of regioisomers was determined by isolated yield of each product.

[c]Ratio of regioisomers was determined by ^{1}H NMR analysis of the mixture.

[d]Yield of isolated product after recrystallization.

these reaction conditions (**3ba** and **3bp**), but treatment of aziridines derived from cycloheptene and cyclooctene does not produce the corresponding compounds. The reaction of aziridines prepared from *trans*-stilbene is successful, whereas *cis*-stilbene-derived aziridine is not a suitable substrate (**3ca**, **3cp**, **3da**, and **3dp**). Using aziridines derived from styrenes, the ring-opening reactions occur in a regioselective manner with preferential attack at the benzylic carbon (**3ea**, **3ep**, **3fa**, **3fp**, **3ga**, and **3gp**). Only one regioisomer is obtained in 50%–87% yields when the reactions are conducted with aziridines prepared from allylbenzene and cinnamyl alcohol, which has a free hydroxy group (**3ha**, **3hp**, **3ia**, and **3ip**). When the reaction is performed with *N*-Bz aziridine, the desired compound is obtained in 53% yield (**3ja**). Cyclohexene-derived aziridines which have *N*-Boc, *N*-Ph, and *N*-Bn protecting groups are inert for this reaction with no product forming.

In conclusion, a simple and convenient method for the ring-opening reaction of aziridines with amines is developed. This reaction has the following synthetic advantages: (1) in contrast to conventional methods, the present reaction does not need a metal reagent or heating; (2) a wide range of aziridines can be employed; (3) not only aromatic amines but also aliphatic amines are available as a nucleophile; (4) the reaction can be performed with easy handling and proceeds smoothly under mild reaction conditions; and (5) only 3–5 equiv DMSO to aziridines are needed to complete the reaction. Mechanistic studies and the application of DMSO-promoted benign reactions in other efficient reactions are currently being assessed in our laboratory.

Acknowledgment

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Supplementary data

References and notes

1. For reviews, see: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194; (c) Callebaut, G.; Meiresonne, T.; Kimpe, N. D.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954.
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8. Aziridines were prepared according to the procedure reported in references: (a) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485; (b) Thakur, V. V.; Sudalai, A. *Tetrahedron* **2003**, *44*, 989.

9. Dehydrated DMSO was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. Typical experimental procedure is as follows: benzylamine **2a** (39 μL, 0.36 mmol) and DMSO (64 μL, 0.90 mmol) were added to a solution of 7-tosyl-7-aza-bicyclo[4.1.0]heptane **1a** (75.8 mg, 0.30 mmol) in hexane (1 mL) in the presence of MS 4A (50 mg) at room temperature under argon atmosphere. The resultant mixture was stirred for 24 h at room temperature, and the reaction was quenched with water. The organic materials were extracted with AcOEt, washed with brine, and dried over Na_2SO_4. *trans-N*-(2-(Benzylamino)cyclohexyl)-4-methylbenzenesulfonamide **3aa** (105.9 mg, 98%) was isolated by thin layer chromatography on silica gel.

Graphical Abstract

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Ring-opening reaction of aziridines with amines under the influence of dimethyl sulfoxide

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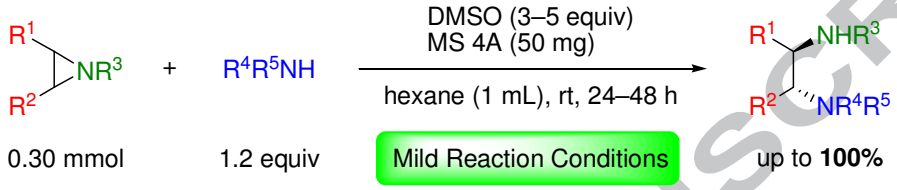
Toshihiro Isobe, Takeshi Oriyama*



Highlights

- Only 3–5 equiv DMSO to aziridines are needed to complete the reaction.
- The reaction can be performed with easy handling and proceeds at room temperature.
- A variety of amines are available as a nucleophile.