

Communications

Ring-opening of *cis*-3-Substituted-2-vinylaziridines with Heteroatom Nucleophiles[†]

Ga-Eun Lee, Mi-Ri Shin, and Han-Young Kang*

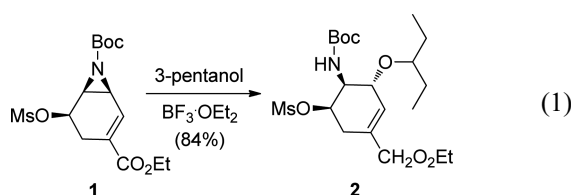
Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea

*E-mail: hykang@chungbuk.ac.kr

Received July 16, 2013, Accepted August 5, 2013

Key Words : Aziridine, Ring-opening, Heteroatom nucleophiles, Diaminocyclitol, Stereoselective synthesis

Aziridines have been used as key intermediates for the synthesis of many nitrogen-containing natural products and biologically active compounds. The chemical transformation caused by ring-opening with nucleophiles is the main synthetic utility of aziridines.¹ Vinylaziridines, classified as functionalized aziridines, have been considered to be increasingly attractive building blocks in organic synthesis.² Although unsubstituted 2-vinylaziridines have been targets for intense synthetic applications, 3-substituted-2-vinylaziridines as synthetic intermediates have relatively not been studied much. During the course of our synthetic studies on oseltamivir phosphate (Tamiflu), we utilized the ring-opening reaction of aziridines that contain the *cis*-3-substituted-2-vinylaziridine structure as a core step, which proceeded with excellent regio- and stereoselectivity (eq. 1).³ Aziridine **1**, containing an alkenyl aziridine moiety, was attacked by 3-pentanol in a regio- and stereoselective fashion to exclusively afford the desired product.



These excellent selectivities of activated vinylaziridines in the nucleophilic opening were also reported for the synthesis of Tamiflu by Kim and co-workers.⁴ The selective ring opening is a result of the favored nucleophilic attack at the position of the ring carbon adjacent to the vinyl group due to the stereoelectronic effect. However, no systematic studies on the ring-opening of *cis*-3-substituted-2-vinylaziridines especially under Lewis acidic conditions have yet been reported. Because of their potential in organic synthesis, we have investigated the nucleophilic ring-opening reactions of *cis*-3-substituted-2-vinylaziridines by heteroatom nucleophiles in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as was the choice of Lewis acid from the previous studies by Kim and co-workers.

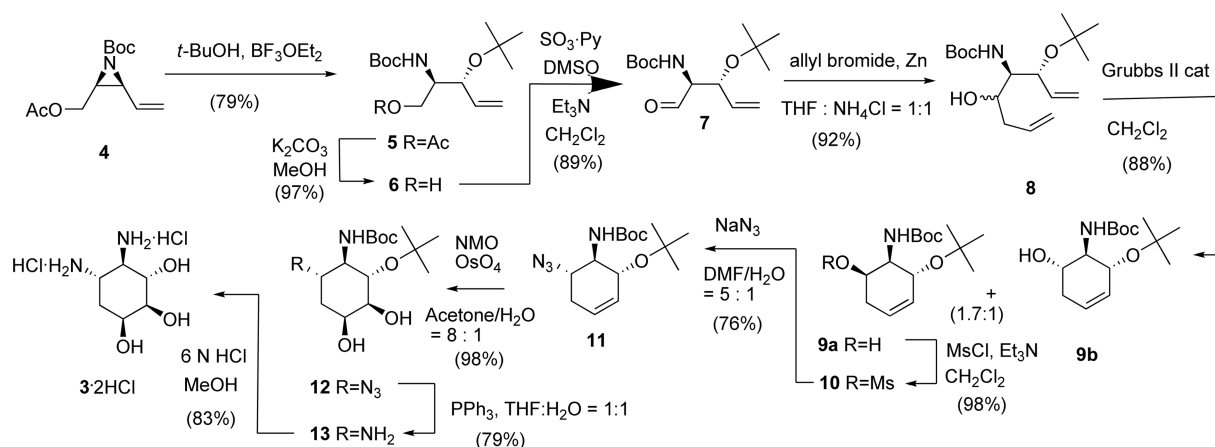
The results of the ring opening reaction of *N*-protected-*cis*-2-vinyl-3-(benzyloxymethyl)aziridines as model compounds for *cis*-3-substituted-2-vinylaziridines with various heteroatom nucleophiles are summarized in Table 1. Methanol is a good nucleophile to provide the desired 1,2-aminoalcohol derivative as a single product in excellent yield. We analyzed briefly the effect of solvents with methanol. Although other solvents such as DMF and THF also gave the product, CH_2Cl_2 was employed as a preferred solvent because of the high yield and ease of handling. All the reactions were, therefore, examined in CH_2Cl_2 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as a Lewis acid unless mentioned otherwise. All alcohols behaved as good nucleophiles to exclusively give the desired products (entry 1-7).

It is worthwhile to mention that even isopropyl alcohol (entry 3) and *tert*-butyl alcohol (entry 4) showed excellent regio- and stereoselectivity. When the aziridine ring was substituted with a benzyl group at the nitrogen atom (entries

Table 1. Nucleophilic opening of *cis*-2-vinylaziridines

Entry	NuH	R	Acid	Solvent	T (°C)	Reaction Time	Yield (%)
1	MeOH	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	-20	5 min	92
2	EtOH	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	-20	5 min	88
3	<i>i</i> -PrOH	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	-20	5 min	75
4	<i>t</i> -BuOH	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	neat	RT	5 min	67
5	MeOH	Bn	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	RT	4 h	67
6	<i>i</i> -PrOH	Bn	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	40	19 h	75
7	<i>t</i> -BuOH	Bn	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	RT	24 h	75
8	CH_3COOH	Boc	—	CH_2Cl_2	RT	30 min	88
9	PhCOOH	Boc	—	CH_2Cl_2	40	12 h	85
10	CH_3COOH	Bn	—	CH_3CN	RT	12 h	80
11	AllylNH_2	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_3CN	80	24 h	67
12	BenzylNH_2	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_3CN	80	19 h	92
13	Pyrrolidine	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_3CN	80	15 h	96
14	PhSH	Boc	$\text{BF}_3 \cdot \text{OEt}_2$	CH_2Cl_2	-78	15 h	78

[†]This paper is to commemorate Professor Myung Soo Kim's honourable retirement.



Scheme 1. Synthesis of 6-deoxycyclohexyldiamine **3**.

5-7), the alcohols also provided the corresponding ring-opened products with superior selectivity.

Ring-opening with carboxylic acids was also possible but with different reactivities (entries 8-10). In this case, addition of a Lewis acid was not required. *N*-Boc activated aziridines underwent the ring-opening relatively smoothly. With the substitution of the benzyl group, the aziridine was opened when CH₃CN was used as a solvent (entry 10). However, no desired opening was observed when CH₂Cl₂ was employed as a solvent. Introduction of a nitrogen functionality was also feasible (entries 11-13), that is, amines efficiently opened the aziridine rings to produce 1,2-diamino derivatives with excellent regio- and stereoselectivities. The ring openings proceeded efficiently at elevated temperature (80 °C) with reasonable yields. With *N*-activated aziridines with Boc groups, amines could be successfully used to obtain the desired 1,2-diamino derivatives with excellent selectivity (entries 11-13). We also briefly tested thiophenol as a sulfur nucleophile. In the case of an activated aziridine, introduction of the sulfur functionality is feasible (entry 14). All the cases displayed in Table 1 show excellent selectivities, and the desired products are obtained as a single isomer.

Because stereoselective synthesis of compounds with a 1,2-functional moiety was easily achieved by ring-opening reactions with nucleophiles, usually in the presence of a Lewis acid, we applied the ring-opening reactions to a biologically active target to explore the synthetic potential. Aminocyclitols belong to a diverse class of compounds with rich biological activities. In particular, vicinal *cis*-diamino inositol analogs have drawn attention because of their use in a broad range of medical treatments including viral infections. We were intrigued to the synthesis of the carba-sugar derivative, namely 6-deoxycyclohexyldiamine **3**.⁵ This *trans*-diaminocyclitol is a synthetic target in connection with developing sugar-based glycosidase inhibitors. We thought that 6-deoxycyclohexyldiamine **3** could be an ideal candidate for exploring the potential of the above ring opening reaction in organic synthesis. Our synthesis of (+)-**3** is shown

in Scheme 1. The ring opening of the known optically active vinyl aziridine **4**³ with *t*-BuOH in the presence of BF₃·OEt₂ afforded the corresponding acetate **5** as the sole product in good yield. Hydrolysis of the acetate **5** and oxidation of the resulting alcohol generated aldehyde **7**, which was subjected to allylation with an allylzinc reagent (allyl bromide, Zn) to give **8** as a mixture. The RCM reaction of the resulting mixture proceeded smoothly providing the mixture of cyclized products **9a** and **9b** (1.7:1). After separation, the major product **9a** was converted to azide **11** by a two-step sequence (mesylation followed by an S_N2 nucleophilic substitution). Dihydroxylation of **11** followed by the Staudinger reaction provided **13**. The double deprotection of Boc and *t*-Bu groups under acidic conditions completed the synthesis of the desired diaminocyclitol (+)-**3** as a hydrogen chloride salt. The spectral data were in complete agreement with those reported previously.⁵

Acknowledgments. This work was supported by the research grant of the Chungbuk National University in 2011.

References

- For some recent leading references and reviews on the ring-opening of aziridines, see: (a) Gorai, M. K.; Tiwari, D. P.; Jain, N. *J. Org. Chem.* **2013**, *78*, 7121. (b) Stancović, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Speybroeck, V. V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643. (c) Lu, P. *Tetrahedron* **2010**, *66*, 2549. (d) Ghorai, M. K.; Kumur, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137. (e) Schneider, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2082. (f) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979. (g) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
- Ohno, H. in *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 2.
- Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 8792.
- Kim, C. U.; Lew, W.; Williams, M. A.; Hongtao, L.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.
- Cong, X.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2004**, *69*, 5314.