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Communications

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

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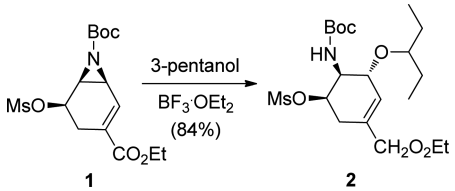
Aziridines have been used as key intermediates for the synthesis of many nitrogen-containing natural products and biologically active compounds. The chemical transformation caused by ring-opening with nucleophiles is the main synthetic utility of aziridines.[1] Vinylaziridines, classified as functionalized 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-substututed-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.



1 **2** (1)

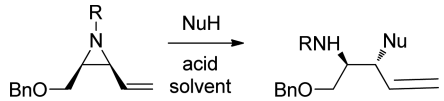
These excellent selectivities of activated vinylaziridines in the nucleophilic opening were also reported for the synthesis of Tamiflu by Kim and co-workers.[4] The selective ring opening is a result of the favored nucleophilic attack at the position of the ring carbon adjacent to the vinyl group due 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 $BF_3{\cdot}OEt_2$ as was the choice of Lewis acid from the previous studies by Kim and co-workers.

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

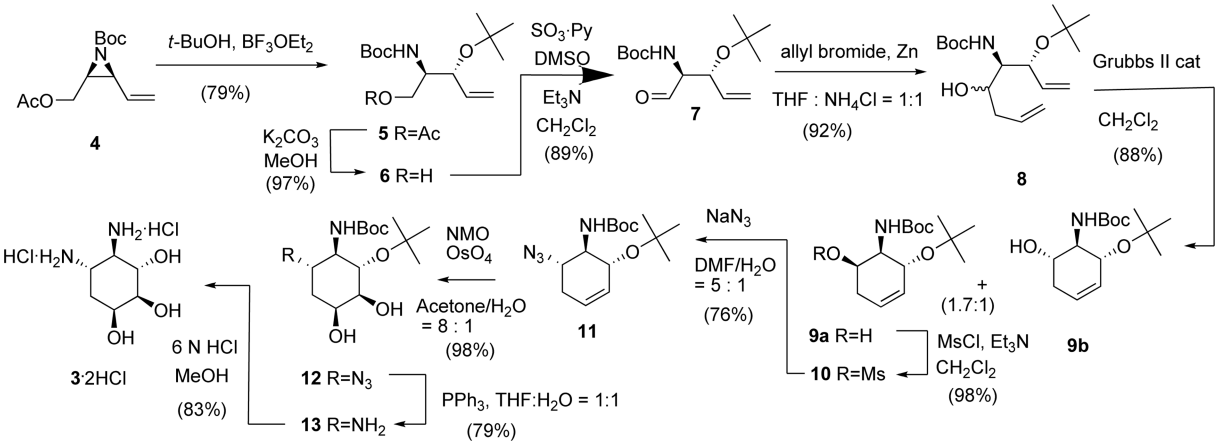
The results of the ring opening reaction of *N*-protected-*cis*-2-vinyl-3-(benzyloxymethyl)aziridines as model compounds for *cis*-3-substituted-2-vinylaziridines with various heteroatom nucleophiles are summarized in Table 1. Methanol is a good nucleophile to provide the desired 1,2-amino-alcohol derivative 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 $BF_3{\cdot}OEt_2$ 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	$BF_3{\cdot}OEt_2$	CH_2Cl_2	–20	5 min	92
2	EtOH	Boc	$BF_3{\cdot}OEt_2$	CH_2Cl_2	–20	5 min	88
3	*i*-PrOH	Boc	$BF_3{\cdot}OEt_2$	CH_2Cl_2	–20	5 min	75
4	*t*-BuOH	Boc	$BF_3{\cdot}OEt_2$	neat	RT	5 min	67
5	MeOH	Bn	$BF_3{\cdot}OEt_2$	CH_2Cl_2	RT	4 h	67
6	*i*-PrOH	Bn	$BF_3{\cdot}OEt_2$	CH_2Cl_2	40	19 h	75
7	*t*-BuOH	Bn	$BF_3{\cdot}OEt_2$	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	$BF_3{\cdot}OEt_2$	CH_3CN	80	24 h	67
12	$BenzylNH_2$	Boc	$BF_3{\cdot}OEt_2$	CH_3CN	80	19 h	92
13	Pyrrolidine	Boc	$BF_3{\cdot}OEt_2$	CH_3CN	80	15 h	96
14	PhSH	Boc	$BF_3{\cdot}OEt_2$	CH_2Cl_2	–78	15 h	78



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 CH_3CN was used as a solvent (entry 10). However, no desired opening was observed when CH_2Cl_2 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 $BF_3{\cdot}OEt_2$ 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]

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