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Regiochemical Pathway in the Ring Opening of 2-Acylaziridines†

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The synthetic utility of nitrogen containing three-membered ring, aziridine[1], stems from the ring-opening reaction toward acyclic α- or β-amines or ring expanded heterocycles.[2] The regioselectivity of this reaction is one of the most essential elements of their synthetic values. The origin of ring openings or ring expansion reactions of aziridines is the ring strain which is quite similar to cyclopropane and oxirane when the ring nitrogen has hydrogen.[1] However, the characteristics and the ring strain of aziridine depend on the substituents at the aziridine-ring nitrogen.[3] The aziridine ring bearing electron withdrawing substituent, so called activated aziridine, is quite labile to the incoming nucleophiles. Unactivated aziridine is stabilized by the electron-donating substituent at the ring nitrogen with the resistance to the reaction with nucleophiles for the ring-opening reactions. Thereby, proper activation is needed to carry out the reaction of unactivated aziridines, and often made through chelation with Lewis acid or bond formation with acyl, trimethylsilyl, protonyl or alkyl group toward aziridinium ion.

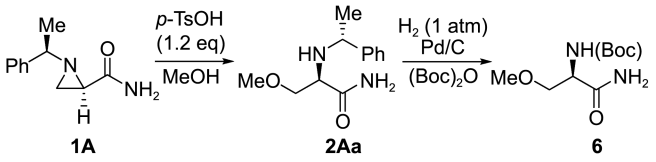
An extensive study on the regiochemical pathways has been carried out with unactivated aziridine since we prepared enantiomerically pure 2-substituted aziridine bearing *N*-(α-methyl)benzyl group.[4] What we have found was the reaction is dependent on all three factors including the structure of starting substrate, reagent for the activation and the reacting nucleophiles.[5,6] Among them one decisive element of the reaction pathway is the starting substrate. When the substituent at C2 is alkenyl or phenyl the reaction proceeds with the breakage of the bond between C2 and N of the aziridine ring due to the allylic or benzylic activation.[6] Other substituents direct the incoming nucleophiles to C3 with some exceptions of large size nucleophiles including bromine and iodine.[5c,6] However, the regiochemical pathway of unactivated 2-acylaziridine with nucleophiles, i.e. the specific site of 2-acylaziridine reacting with the incoming nucleophiles, has not been identified yet. Herein, we would like to report on the regiochemical pathways in the ring-opening reactions of 1-(α-methyl)benzyl-2-acylaziridines with oxygen nucleophiles throughout various activation. These reactions yield synthetically valuable 1,2-alkoxyamine or hydroxyamines.[7]

At first ethyl [1'(*R*)-α-methylbenzyl]aziridine-2(*R*)-carboxamide (**1A**) was reacted in methanol with 1.2 equivalent of *p*-toluenesulfonic acid (*p*-TsOH) for the protonation of the ring nitrogen. The reaction yielded one single isomer (**2Aa**) in 82% yield whose structure was identified by the comparison with the known compound (entry 1).

The initially formed ring-opening reaction product was then subjected into catalytic hydrogenation reaction in the presence of $(Boc)_2O$ and Pd/C to afford 1,2-alkoxyamine (**6**). The physical and spectral data showed the reaction product is (2*R*)-2-*t*-butoxycarbonylamino-3-methoxypropionamide (**6**).[8] Evidently, the ring-opening reaction occured at the less hindered C3 with complete retention of the configuration at C2.

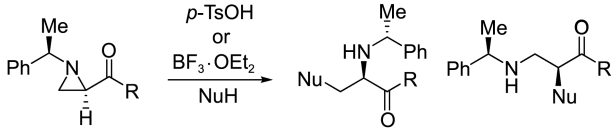
The same reaction with *i*-PrOH instead of MeOH also works well to give the expected product (**2Ab**) as a single isomer in 61% yield (entry 2). Then we carried out the reactions with different activating reagent other than proton. Lewis acid $BF_3{\cdot}OEt_2$ works well to activate the ring toward *i*-PrOH nucleophile which was used as solvent to yield the product in 78% (entry 3). Reducing the amount of nucleophiles (MeOH and H_2O in CH_3CN) did not affect the reactions, affording the expected products **2Aa** and **2Ac** in 72 and 81% yield, respectively (entries 4 and 5).

Since we knew the reaction worked well with the substrate [1'(*R*)-α-methylbenzyl]aziridine-2(*R*)-carboxamide we carried

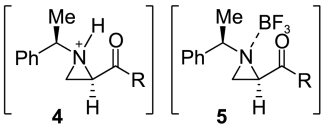


1A **2Aa** **6**

Scheme 1



1A (R=NH_2)
1B (R=OEt)
1C (R=CH_3)



Scheme 2

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

the same reaction with the ester. The reaction of ethyl [1'(*R*)-α-methylbenzyl]aziridine-2(*R*)-carboxylate (**1B**) in MeOH with 1.2 equivalent of *p*-TsOH also yielded a single isomer α-amino-β-methoxypropanoate (**2Ba**) in 73% yield (entry 6). Changing the activator from proton to $BF_3{\cdot}OEt_2$ did not alter the reaction at all to provide the same product **2Ba** in 60% yield in MeOH (entry 7). We have found 10 mol equivalent of MeOH in CH_3CN is enough for the reaction being completed in 72% yield under the same reaction condition with $BF_3{\cdot}OEt_2$ (entry 8). The same reaction with H_2O as the nucleophile instead of MeOH afforded α-amino-β-hydroxypropanoate (**2Bc**) in 87% yield (entry 9).

Then we extended the reaction to 2-acetyl-[1'(*R*)-α-methylbenzyl]aziridine (**1C**). As we expected the ring-opening reaction of this substrate was complicated due to the formation of an acetal with MeOH in the presence of protic or Lewis acid. In most cases the initial reaction product was identified as dimethylacetal which was further reacted with acid and alcohol to yield the ring-opened product. This acetal could be isolated when we carried the reaction of 2-acetyl-[1'(*R*)-α-methylbenzyl]aziridine in MeOH as the solvent in the presence of 1.2 equivalent of *p*-TsOH at room temperature. The same reaction under reflux without isolation of the acetal gave the ring-opening products in 64% yield which was identified as 4-amino-3-methoxybutan-2-one (**2Ca**) and 3-amino-4-methoxybutan-2-one (**3Ca**) with the ratio of 3:5 (entry 10). This result implies the ring-opening reaction occurs not at the stage of 2-acylaziridine but at 2-acetalaziridine without any electronic involvement of the carbonyl group. Changing the nucleophile which cannot form acetal may give an opportunity to study the effect of carbonyl in the aziridine-ring opening. The reactions with H_2O as the nucleophile in CH_3CN with proton or $BF_3{\cdot}OEt_2$ to yield the reaction product in 63 and 91% yield as a single regioisomer which was identified as 3-amino-4-hydroxy-2-one (**2Cc**) (entries 11 and 12). This showed us the regiochemical pathway of the 2-acylaziridine case is the same as aziridine-2-carboxylate or carboxamide.

Table 1. The ring opening of 2-acylaziridine **1** with oxygen nucleophiles in the presence of either *p*-TsOH or $BF_3{\cdot}OEt_2$

Entry	R	Activator	NuH	Solvent	Products (%)
1	NH_2	H^+ (1.2 Eq.)	MeOH	MeOH	**2Aa** (82)
2	NH_2	H^+ (1.2 Eq.)	*i*-PrOH	*i*-PrOH	**2Ab** (61)
3	NH_2	$BF_3{\cdot}OEt_2$ (1.5 Eq.)	*i*-PrOH	*i*-PrOH	**2Ab** (78)
4	NH_2	$BF_3{\cdot}OEt_2$ (1.2 Eq.)	MeOH (10 Eq.)	CH_3CN	**2Aa** (72)
5	NH_2	$BF_3{\cdot}OEt_2$ (1.5 Eq.)	H_2O (10 Eq.)	CH_3CN	**2Ac** (81)
6	OEt	H^+ (1.2 Eq.)	MeOH	MeOH	**2Ba** (73)
7	OEt	$BF_3{\cdot}OEt_2$ (1.2 Eq.)	MeOH	MeOH	**2Ba** (60)
8	OEt	$BF_3{\cdot}OEt_2$ (1.2 Eq.)	MeOH (10 Eq.)	CH_3CN	**2Ba** (72)
9	OEt	$BF_3{\cdot}OEt_2$ (1.5 Eq.)	H_2O (10 Eq.)	CH_3CN	**2Bc** (87)
10	Me	H^+ (1.2 Eq.)	MeOH	MeOH	**2Ca**, **3Ca** (64)
11	Me	H^+ (1.2 Eq.)	H_2O (10 Eq.)	CH_3CN	**2Cc** (63)
12	Me	$BF_3{\cdot}OEt_2$ (1.5 Eq.)	H_2O (10 Eq.)	CH_3CN	**2Cc** (91)

From this study we were able to draw a conclusion that the ring-opening reactions of aziridines bearing carbonyl at C2 take place at C3 to yield α-amino compound when proton or $BF_3{\cdot}OEt_2$ was used to activate the unactivated aziridines as **4** or **5** in scheme 2. The regiochemical pathway of ring-opening reactions is completely opposite to the reactions of 2-acyl-1-methyl-1-benzylaziridinium ions with various nucleophiles.[5] When 2-acyl-1-benzylaziridine is activated by alkylation as 1-methyl-1-benzylaziridinium ions, the ring-opening reaction by the nucleophilic attack takes place at C2.[6] The same reaction occurs at C3 for the same aziridine when proton or Lewis acid instead of alkyl group was used for the activation as demonstrated in this study.

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