

## Regiospecific Reductive Ring Cleavage of *N*-Substituted Aziridine-2-carboxylates and An Aziridine-2-methanol via Catalytic Hydrogenation Using Pd as a Catalyst

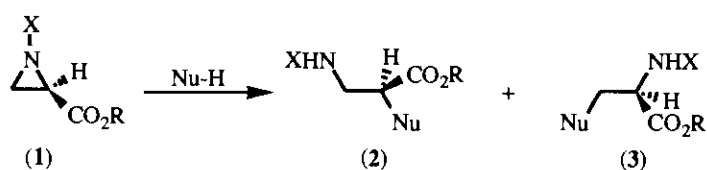
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**Abstract:** Regiospecific reductive ring cleavage was accomplished in the reaction of *N*- $\alpha$ -methylbenzyl substituted aziridine-2-carboxylate and aziridine-2-methanol under a catalytic hydrogenation condition. The regiospecificity was determined by the substituent at C-2.

The chemistry and the preparation of enantiomerically pure aziridine-2-carboxylates have been the target of many synthetic efforts for the synthesis of both  $\alpha$ - and  $\beta$ -amino acids which can be building blocks for biologically important compounds.<sup>1,2</sup> The presence of the ring strain in the aziridines has provided a characteristic feature in their ring-opening reactions. The control of the stereochemistry as well as regiochemistry in the ring-opening reactions becomes very important to make those reactions synthetically useful. Most ring-opening reactions have been studied on activated aziridines which contain a *N*-substituent that can conjugatively stabilize the nitrogen lone pair electrons in the transition state of ring-opening reactions.

Regiospecific ring opening of aziridine-2-carboxylates would yield either  $\alpha$ - or  $\beta$ -amino acids and considerable efforts have been made to address the problem (Scheme 1). Heteroatom nucleophiles such as nitrogen<sup>3</sup>, oxygen<sup>4</sup>, sulfur<sup>5</sup>, and chloride<sup>5(a),(c)</sup> attack C-3 regioselectively to provide  $\alpha$ -amino acid derivatives (2). However, a mixture of products has been obtained from the reaction of the aziridine-2-carboxylate with carbon nucleophiles and azide.<sup>6</sup>

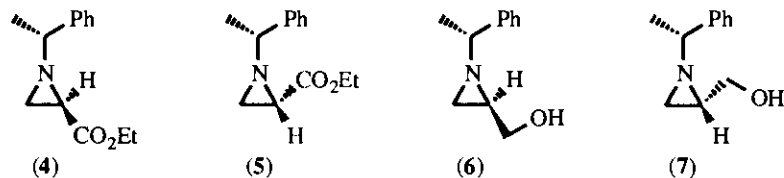


Scheme 1

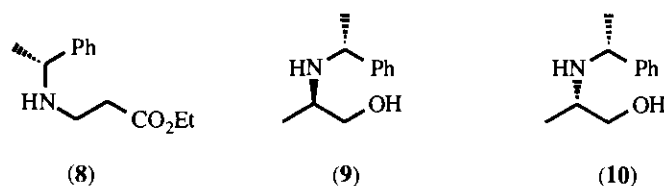
Recently, regiospecific ring cleavages of *N*-substituted aziridine-2-carboxylic acid derivatives with carbon nucleophiles were reported.<sup>7</sup> A few publications have been made on the ring-opening reactions of activated aziridino alcohols by hydride reagents and those of activated aziridine-2-carboxylates by transfer hydrogenation.<sup>2</sup>

However, no publication has been made on the reductive ring-opening reaction of *N*-alkyl substituted enantiomerically pure aziridino alcohols and aziridine-2-carboxylates by catalytic hydrogenation process.

Being interested in the reduction characteristics of the *N*-alkyl substituted aziridines, optically active aziridine-2-carboxylates (4) and (5) were prepared from the reaction of (*R*)-(+)- $\alpha$ -methylbenzylamine and ethyl-2,3-dibromopropionate in 95% yield. Both diastereomers (4) and (5) were easily separable by flash column chromatography and  $\text{LiAlH}_4$  reduction of the each diastereomers provided corresponding alcohols (6) and (7)<sup>8</sup> in



quantitative yield. Catalytic hydrogenation of (4) and (5) in AcOH with 20 w% of  $\text{Pd}(\text{OH})_2$  proceeded with C(2)-N bond cleavage in 3 hours at room temperature to provide exclusively one product, a  $\beta$ -amino ester (8), but the isolation yield was 80%. However, catalytic hydrogenation of (6) and (7) in EtOH with 20 w% of  $\text{Pd}(\text{OH})_2$  provided C(3)-N bond cleavage products (9) and (10) in >95% isolated yields. The absolute configurations at the amino bearing carbons of (9) and (10) were established after treating each of the compounds with carbonyl diimidazole followed by cleaving the ( $\alpha$ )-methylbenzyl group with  $\text{Na}/\text{NH}_3(l)$  to obtain cyclic carbamates. The optical rotations and NMR spectrum data of the cyclic carbamates were compared with those of cyclic carbamates derived from optically active (L)- and (D)-alaninols.

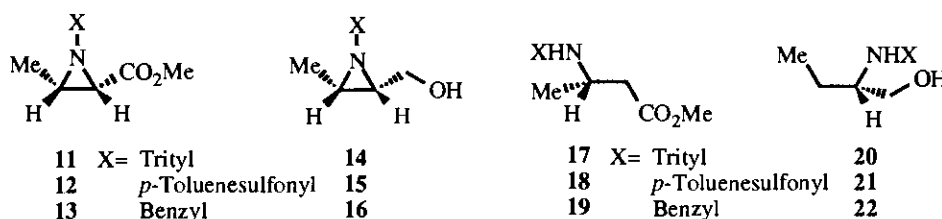


Recently, Evans and Davis showed that *N*-paratoluenesulfonyl-3(*S*)-phenyl substituted aziridine-2-carboxylate can be regioselectively reduced by transfer hydrogenation to give C(3)-N bond cleaved product.<sup>9</sup> The above results indicate that the C-N bond of suitably substituted aziridines can be regioselectively reduced by catalytic hydrogenation with the right choice of a catalyst and a solvent.

We also prepared variously *N*-substituted aziridine-2 carboxylates and aziridino alcohols (11 ~ 16) from (L)-threonine following the literature procedure<sup>10</sup> and studied their reduction characteristics under the above catalytic hydrogenation condition.

The catalytic hydrogenation of both the *N*-Trityl aziridine-2-carboxylate (11) and aziridino alcohol(14) in EtOH did not proceed at all. However, *N*-paratoluenesulfonyl aziridine-2-carboxylate (12) consistently provided C(2)-N bond cleaved product (18) in 80% yield after 2 day's stirring at room temperature in EtOH. The catalytic hydrogenation of the corresponding alcohol (15) did not proceed in EtOH and a mixture of products was obtained in AcOH. The catalytic hydrogenation of the *N*-benzyl aziridine-2-carboxylate (13) in AcOH provided two

products which were treated with (Boc)<sub>2</sub>O to give a (9:1) mixture of N-Boc derivative of the starting material and the N-Boc derivative of the C(2)-N bond reduction product **19** in 70 % yield. This result indicates that the debenzoylation is occurring faster than the reductive ring cleavage and the cleavage occurs between C(2)-N bond which is consistent with the previous results.



The above results show that the C(2)-N bond of 3-methyl N-paratoluenesulfonyl aziridine-2-carboxylate can be regiospecifically cleaved to provide both 3(R)- and 3(S)-amino butanoic acid derivatives depending on the starting amino acid and those compounds can be used for the synthesis of biologically important compounds as enantiomerically pure form. The N-benzyl derivative also seemed to follow the same pathway but the removal of the N-benzyl group proceeded faster than the reductive ring-opening. Contrary to the result we obtained from the reductive ring-opening of N-( $\alpha$ )-methylbenzyl substituted aziridino alcohols (**6**) and (**7**), we could not obtain ring reduction product from the aziridino alcohol derivatives **14**–**16**. It seems that the presence of the  $\alpha$ -methyl-benzyl group on the nitrogen of the aziridine ring is very important to keep the benzyl group during the reductive ring cleavage. We are currently investigating controlling factors of the above reactions and the possibilities of extending the scope of this process to other synthetically useful systems.

**Acknowledgment:** The authors are grateful to OCRC and MOE(BSRI-95-3412) for the financial support.

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8. (6):  $^1\text{H}$  NMR(200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.24 (m, 5H), 3.88(dd, 1H,  $J=11.6, 3.5$  Hz), 3.46(dd, 1H,  $J=11.6, 5.8$  Hz), 3.10-2.95(br, 1H), 2.54(q, 1H,  $J=6.6$  Hz), 1.84-1.78(m, 1H), 1.70(d, 1H,  $J=3.5$  Hz), 1.46(d, 3H,  $J=6.6$  Hz), 1.37(d, 1H,  $J=6.4$  Hz).  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ )  $\delta$  144.5, 128.5, 127.2, 126.8, 69.1, 62.7, 40.4, 30.7, 23.1.  $[\alpha]_{\text{D}}^{20}=+71.8$ ( $c=1.0$ ,  $\text{CHCl}_3$ ). (7):  $^1\text{H}$  NMR(200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.26(m, 5H), 3.61(dd, 1H,  $J=11.5, 3.6$  Hz), 3.33(dd, 1H,  $J=11.5, 5.2$  Hz), 2.54(q, 1H,  $J=6.6$  Hz), 1.93(d, 1H,  $J=3.5$  Hz), 1.74-1.66(m, 1H), 1.50(d, 1H,  $J=6.5$  Hz), 1.43(d, 3H,  $J=6.6$  Hz).  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ )  $\delta$  144.8, 128.7, 127.4, 126.7, 69.4, 62.4, 39.0, 31.1, 22.7.  $[\alpha]_{\text{D}}^{20}=+53.3$  ( $c=10.1$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{15}\text{NO}$ : C, 74.54; H, 8.53; N, 7.90. Found: C, 74.39; H, 8.86; N, 7.92.
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(Received in Japan 20 June 1995; revised 18 September 1995; accepted 22 September 1995)