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Preparation of 2,3-diaminopropionate from ring opening of aziridine-2-carboxylate

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Abstract—Ring opening reaction of an enantiomerically pure aziridine-2-carboxylate with an azide nucleophile under aqueous acidic media proceeded efficiently and stereoselectively to give 3-amino-2-azidopropionate which is converted to orthogonally protected 2,3-diaminopropionate.

The importance of enantiopure 2,3-diaminopropionate can be found as a fragment of various biologically important molecules such as roxifiban,[1] cyclotheonamide[2] and many potential drug candidates.[3] An easy access of 2,3-diaminopropionate or its synthetic precursor would therefore promote the drug discovery program. Additional utility of 2,3-diaminopropionate was found recently as a probe to investigate the structure of peptide and proteins.[4] Thereby its large scale preparation is absolutely necessary to carry out the solid phase peptide synthesis cooperating 2,3-diaminopropionate as one of unnatural amino acids. Up to now only one synthetic method is available starting from aspartic acid via Curtius rearrangement as the core reaction including many tedious protection and deprotection steps.[2,5] Herein we would like to report a simple and efficient method for the synthesis of enantiopure 2,3-diaminopropionate from the regioselective ring opening reaction of a commercially available chiral aziridine-2-carboxylate in high yield.

Since we reported the production of aziridine-2-carboxylic acid (−)-menthol ester in industrial scale, we have been interested in the preparation of diverse nitrogen containing chiral molecules.[6] Methods we developed include manipulation of carboxylate group, ring expansion and ring opening reaction with many different nucleophiles such as oxygen, nitrogen, sulfur and halides.[6] Even though many examples of ring opening reaction of activated aziridine by azide nucleophiles were reported,[7] it was not possible to produce 2,3-diaminopropionate by direct ring opening reaction of aziridine-2-carboxylate with benzyl substituent on the nitrogen due to its inertness towards external nucleophiles. In this report we would like to describe the first direct ring opening reaction of *N*-benzylaziridine-2-carboxylate with azide as a nitrogen nucleophile under acidic aqueous media to give 3-amino-2-azidopropionate.

Chiral [1′(*R*)-α-methylbenzyl]aziridine-2(*R*)-carboxylate (−)-menthol ester **1a** was reacted in 50% aqueous ethanol at pH 4.0, adjusted by addition of sulfuric acid, with sodium azide in the presence of 10 mol% of $AlCl_3 \cdot 6H_2O$ as a catalyst to yield the ring opening product 2-azido-3-[1′(*R*)-α-methylbenzylamino]-propionate **2a** in 95% yield (Scheme 1).

The ring opening product **2a** was then reacted with methyl oxalyl chloride followed by catalytic hydrogenation

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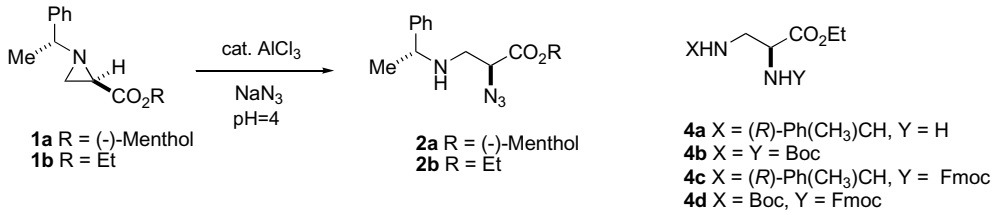
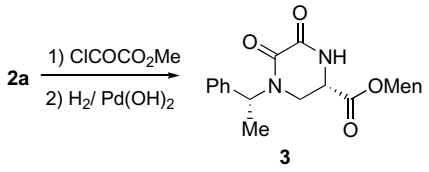


1a R = (-)-Menthol
1b R = Et

2a R = (-)-Menthol
2b R = Et

4a X = (*R*)-Ph(CH$_3$)CH, Y = H
4b X = Y = Boc
4c X = (*R*)-Ph(CH$_3$)CH, Y = Fmoc
4d X = Boc, Y = Fmoc

Scheme 1.



3

Scheme 2.

with $Pd(OH)_2$ to yield 2,3-dioxopiperidine-5-carboxylate **3** in 74% yield (Scheme 2). The absolute configuration of C-5 of the piperazine bearing the newly formed carbon–nitrogen bond was identified as *R* in the X-ray crystalline structure shown in Figure 1.[8] This outcome shows that the ring opening reaction proceeds with complete inversion at the reaction centre as expected. This reaction was applicable to several hundred gram scale without any difficulties in isolation and purification. The same reaction was possible with ethyl aziridine-2-carboxylate **1b** in 86% yield.

Ethyl 2-azido-3-(1-α-methylbenzylamino)-propionate **2b** was served as the starting substrate towards many different diamine derivatives. Catalytic hydrogenation with 2 equiv of Boc_2O in the presence of Pd/C provided diaminopropionate **4b** with Boc protections on the nitrogens of both amines. The azido group was reduced with Ph_3P and H_2O to yield 2-amino-3-[1′(*R*)-α-methylbenzylamino]-propionate **4a** in 71% yield. Subsequent protection of the free amine with *N*-(9-fluorenylmethoxycarbonyloxy)succinamide[9] yielded compound **4c** which was further hydrogenated with Boc_2O to give

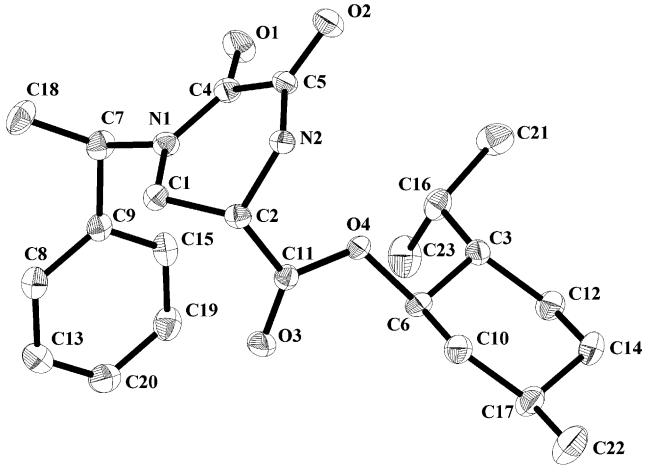
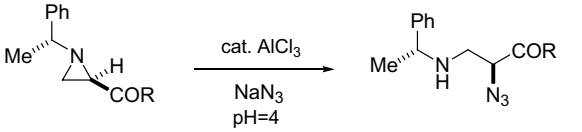


Figure 1.



1c R = CH(CH$_3$)$_2$
1d R = Ph
1e R = 4-F-Ph
1f R = 4-Cl-Ph
1g R = Pyrene

2c R = CH(CH$_3$)$_2$, 75%
2d R = Ph, 64%
2e R = 4-F-Ph, 82%
2f R = 4-Cl-Ph, 71%
2g R = Pyrene, 78%

Scheme 3.

orthogonally protected diaminopropionate **4d** in 48% overall yield.

This ring opening reactions of aziridine with azide in the presence of $AlCl_3$ were also applicable to 2-acylaziridines[10] such as **1c**–**f** and **1d** to afford the corresponding vicinal azido amino products **2c**–**f** and **2d** in quite good yields (Scheme 3).

In summary, ring opening reaction of enantiomerically pure aziridine-2-carboxylate with azide under aqueous acidic media proceeded efficiently and stereoselectively to give 3-amino-2-azidopropionate that was served as the starting substrate for orthogonally protected 2,3-diaminopropionate.

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8. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 263351. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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