Conjugate addition of amines to chiral 3-aziridin-2-yl-acrylates

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A R T I C L E   I N F O

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A B S T R A C T

Conjugate addition of benzylamine to chiral methyl cis-3-aziridin-2-yl-acrylates was successfully proceeded to yield 3-aziridin-2-yl-3-benzylaminopropionates in high yield with high stereoselectivity. The addition products were used for the asymmetric synthesis of vicinal diamine derivatives including 4-amino-5-methylpyrrolidin-2-one, 3,4-diaminopentanoate, and 5-chloromethyl-4-alkoxy carbonylmethylimidazolidin-2-one.

Synthesis of stereoisomerically well-defined 1,2-diamines is still a great challenge to many organic chemists due to their vast utilities as catalysts, metal-ligands, and sub-unit of some natural products. Especially β,γ-diamino acids and their cyclic forms like 4-aminopyrrolidin-2-one and imidazolidin-2-one have unique properties as peptidomimetics and as constituents of biologically active molecules including renin-inhibitory statin analogs, anti-fungal and cytotoxic microsclerodermins, and antipsychotic nemonapride. Furthermore, the reduced form of 4-aminopyrrolidin-2-one provides an entry into the 3-amino-pyrolidinone family of alkaloids.

Considering the vast utilities of these compounds, limited methods are available and most of which is based on α-amine acids as starting material through homologations followed by introducing one more amine functionality. These methods were suffered from the limited sources of starting substrates and the multi-reaction steps including low yield. In this Letter is described a general and facile synthetic method to access enantiomERICALLY pure anti β,γ-diamino acids and their cyclic forms using chiral aziridine.

During last several years we have shown that enantiomERICALLY pure aziridine-2-carboxylate is a configurationally stable surrogate of α- or β-amino acids. Homologation and proper functionalization of carboxylate followed by aziridine ring opening provided many valuable compounds such as unnatural amino acids, sphinganine, phytosphingosine,12 ceramide analogs, and terminal 1,2-diamines. Homologation by two carbons and introduction of one more amino group adjacent to the aziridine-ring will be able to provide a good synthetic intermediate toward the targeted β,γ-diamino acids and their cyclic forms.

At first trans- and cis-3-[(1′R)-phenylethylaziridinyl]-2R- and (25′)-2-acrylates were selectively prepared from aziridine-2-carboxaldehyde. The reaction of [(1′R)-phenylethylaziridinyl]-2R-carboxaldehyde with (EtO)2POCH2CO2R yielded trans-3-[(1′R)-phenylethylaziridinyl]-3-carboxylate in more than 95% yield with the ratio of 98:2 regardless of R (methyl and ethyl). The same reaction with Ph2PCH2CO2R leading to alkyl cis-3-[(1′R)-phenylethylaziridinyl]-2R- and (25′)-2-acrylate, 1 and 2, was also successfully provided in more than 93% yield with the ratio of 88:12 (R = Me) and 86:14 (R = Et). Interestingly, only the cis and trans isomers bearing methyl ester were chromatographically...
Addition of benzylamines to methyl cis-3-[(1'R)-phenylethylaziridin]-2(5)-yl]-acrylate (1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RNH2</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio (3A:3B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH2NH2 (a)</td>
<td>rt</td>
<td>14</td>
<td>95</td>
<td>2.9:1</td>
</tr>
<tr>
<td>2</td>
<td>PhCH2NH2 (a)</td>
<td>0</td>
<td>24</td>
<td>91</td>
<td>2.9:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCH2NH2 (a)</td>
<td>-40</td>
<td>20</td>
<td>98</td>
<td>4.0:1</td>
</tr>
<tr>
<td>4</td>
<td>(R)-PhCH2CHNH2 (b)</td>
<td>50</td>
<td>7</td>
<td>95</td>
<td>3.3:1</td>
</tr>
<tr>
<td>5</td>
<td>(S)-PhCH2CHNH2 (c)</td>
<td>50</td>
<td>7</td>
<td>97</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

*The reaction was carried out with amine in MeOH.

The inseparable diastereomeric mixture of 3AA and 3BA obtained from entry 2 in Table 1 was further reacted with triphosgene and NaH to yield 4-chloromethyl-5-methoxycarbonylmethylimidazolin-2-ones 5 (major) and 6 (Scheme 1).14

The coupling constants of two vicinal hydrogens at C4 and C5 of compounds 5 (major) and 6 (minor) were 7.5 and 3.0 Hz, respectively. On the basis of these values we could determine the stereochemistry of 3AA and 3BA as erythro and threo, respectively.14,15

A similar selectivity was observed with methyl cis-3-[(1'R)-phenylethylaziridin]-2(5)-yl]-acrylate (2) as the starting substrate and benzylamine (a) to give a erythro (4AA) and threo (4BA) mixture with the ratio as 2.3:1 and 2.6:1 (entries 1–3 of Table 2). Both the chiral nucleophiles (R)-α-methylbenzylamine (b) and (S)-α-methylbenzylamine (c) with 2 yielded addition products with poor selectivities as 1.2:1 and 2.1:1, respectively (entries 4 and 5 of Table 2).

The drastic difference in the stereoselectivity was observed during the addition reaction of the chiral nucleophiles (R)-α-methylbenzylamine (b) and (S)-α-methylbenzylamine (c) to either 1 or 2 (entries 4 and 5 in Table 1 and Table 2). This implies the participation of the α-methylbenzyl group at the ring nitrogen and the coming nucleophile resulted the ‘matched’ (entry 5 in Table 1 and ‘mismatched’ cases (entry 4 in Table 1, and entries 4 and 5 in Table 2) in the transition state during the course of the reaction.16

The possible transition state stems from the most stable conformer of 2-substituted aziridine with two substituents X and Y.

Table 2
Addition of benzylamines to methyl cis-3-[(1'R)-phenylethylaziridin]-2(5)-yl]-acrylate (2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RNH2</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio (4A:4B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH2NH2 (a)</td>
<td>rt</td>
<td>14</td>
<td>96</td>
<td>2.3:1</td>
</tr>
<tr>
<td>2</td>
<td>PhCH2NH2 (a)</td>
<td>0</td>
<td>24</td>
<td>91</td>
<td>2.3:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCH2NH2 (a)</td>
<td>-40</td>
<td>30</td>
<td>95</td>
<td>2.6:1</td>
</tr>
<tr>
<td>4</td>
<td>(R)-PhCH2CHNH2 (b)</td>
<td>50</td>
<td>8</td>
<td>82</td>
<td>1.2:1</td>
</tr>
<tr>
<td>5</td>
<td>(S)-PhCH2CHNH2 (c)</td>
<td>50</td>
<td>8</td>
<td>95</td>
<td>2.1:1</td>
</tr>
</tbody>
</table>

*The reaction was carried out with amine in MeOH.

Yields, not optimized.

Roll ratios, determined by 1H NMR.

Scheme 1. Reagents and conditions: (i) 1 NaH, Cl3COCOCl, -10 °C, THF, 3 h.

Separable (Rf values, 0.75 and 0.70 for cis and trans, hexane/EtOAc, 1:1 (v/v)).
Figure 2. (a), (b) Front and side views of the aziridine with two substituents X and Y at N1 and C2. (c) View of methyl cis-3-[[[(1R)-phenylethyl]aziridin]-2(R)-yl]-acrylate (I) and the possible approaching faces of the amine nucleophile in the transition state model.

Scheme 2. Reagents and conditions: (i) (1) H2 (1 atm), Pd(OH)2, rt. 4 h, (2) (Boc)2O, MeOH, rt, two steps 89%. (ii) LiOH, EtOH/H2O = 5:1 (v/v) C176C, 8 h, rt, ion-exchange column, 82%.

situated in trans-relationships as shown in Figure 2 (a) and (b). This trans-relationship was also observed in many crystalline structures of aziridines.17 Putting both substituents of phenylethyl (X) and methoxycarbonylphenyl (Y) groups generates the structure (c) in Figure 2 with possible two faces, re and si, for the nucleophile to come.

Among two possible directions re face attack is more favorable rather than si face away from the steric hindrance, which is the controlling factor to yield the erythro adduct as the major product along with the additional stereodifferentiation by (R)-α-methylbenzylamine. This stereochemical pathway is opposite to the reaction with chelation-controlled transition state to yield the three product.14

The addition product 3Ac was further treated with an atmospheric pressure of hydrogen in the presence of Pd(OH)2 catalyst followed by reaction with (Boc)2O to yield (2R,5S)-4-tert-butyloxycarbonylamo-5-methylpyrrolidin-2-one (7) in a 89% yield. Hydrolysis of 7 followed by anion exchange column afforded the known (3R,4S)-4-amino-3-tert-butyloxycarbonylamino-2-pentanoic acid (8) in a 82% yield (Scheme 2).18 The addition product 3Ac will be served as a synthetic intermediate for the preparation of various chiral diamines through aziridine ring opening with various nucleophiles.8

In conclusion, the conjugate addition of benzylamine to chiral methyl cis-3-[[[(1R)-phenylethyl]aziridin]-2(R)- and (2S)-yl]-acylates provides the erythro adduct, 3-(aziridin-2-yl)-3-benzylaminopropanoic as the major product. Additional stereodifferentiation by (S)-α-methylbenzylamine to the substrate (2R)-acylates yielded a single enantiomeric adduct in high yield which was used as the precursor for the substituted nitrogen-containing heterocycles and enantiomerically pure β,γ-diaminocids.

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Supplementary data
Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.087.

References and notes
14. In our early work we observed that the configuration of (α)-methylbenzyl group at N1 of aziridine affected drastically the reactivity on the substitution reaction of 2-sulfonyloxymethylaziridines. Han, S.-M.; Ma, S.-h.; Ha, H.-J.; Lee, W. K. Tetrahedron. 2008, 64, 11110.

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