Synthesis of Functionalized Bicyclic Triazoles from Chiral Aziridines

Min Sung Kim,a Hyo Jae Yoon,a Baeck Kyong Lee,a Ji Hyun Kwon,a Won Koo Lee,*a Yongeun Kim,b Hyun-Joon Haab

a Department of Chemistry and Interdisciplinary Program of Integrated Biotechnology, Sogang University, Seoul 121-742, Korea
Fax +82(2)7010967; E-mail: wonkoo@sogang.ac.kr
b Department of Chemistry, Hankuk University of Foreign Studies, Yongin, Kyunggi-Do 449-719, Korea
Fax +82(31)3304566; E-mail: hjha@hufs.ac.kr

Received 9 June 2005

Abstract: Enantiomerically pure 3-substituted-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazoles were synthesized efficiently from the sequential reactions including a regioselective ring-opening of 1-aziridine-2-yl-propargylic alcohols by azidotrimethylsilane and the subsequent intramolecular 1,3-dipolar cycloaddition between alkynyl and azide.

Key words: aziridine, triazole, cycloaddition, alkyne, azide

The importance of triazoles found in many biologically active products has been emphasized in organic chemistry. They consist of essential structural backbone of various pharmaceuticals with anti-HIV, antimicrobial, β-lactamase inhibitory, antiviral and antiepileptic activities. Therefore, methodologies for the preparations of triazoles have attracted much attention from both academia and industry. However, there are only a few preparative methods available from azidoallenes, hexofuranose, 2-carboxy-4-chlorophenylazide and polystyrene-sulfonyl hydrazide. The requirement for a more efficient preparative method toward enantiomerically pure functionalized bicyclic triazoles prompted us to develop a new facile synthetic route. Herein we report a new strategy for the efficient preparation of multi-functionalized bicyclic triazoles from the sequential reactions including a regioselective ring-opening of 1-aziridine-2-yl-propargylic alcohols by azidotrimethylsilane and the subsequent intramolecular 1,3-dipolar cycloaddition between alkynyl and azide.

We recently reported the preparation of the Weinreb amide from the commercially available chiral aziridine-(2S)-carboxylic acid menthol ester10 in one step with Weinreb’s amine hydrochloride and AlMe3 in CH2Cl2 in high yield.11 The amide 1 was reacted with various lithium acetylides to provide the corresponding alkynyl ketones 2 in high yields. We also reported the chelation-controlled stereoselective reduction of 2-acylaziridines toward erythro isomer in the presence of ZnCl2 and NaBH4 in MeOH in high yields.11 This methods afforded various (1S,2R)-1-aziridine-2-yl-propargylic alcohols 3 in good yield.12 The other three isomers, (1S,2S)-1-aziridine-2-yl-propargylic alcohols 4 were prepared by the reported reduction method with L-Selectride® in good yield (Scheme 1).13 Both of 1-aziridin-2-yl-propargylic alcohols 3 and 4 were utilized for the preparation of cis- and trans-3-substituted-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole.

Scheme 1 Preparation of 1-aziridin-2-yl-propargylic alcohols

Since the aziridine nitrogen is quite basic and also nucleophilic, ring-opening reactions are initiated by the formation of the azirinium ion intermediate.10 When 1-aziridine-2-yl-propargylic alcohols were reacted with azidotrimethylsilane an activated aziridinium species I would be produced by the silylation of the aziridine nitrogen. Then, regioselective ring-opening reaction with the cleavage of C(3)–N bond proceeded by an azide that was liberated from azidotrimethylsilane.14 Treatment of ring-opening product with 6 N aqueous HCl solution afforded azido amino alcohol II. This crude reaction mixture was concentrated, dissolved in DMF and heated to 130 °C (Scheme 2).15 Consequently, the intramolecular 1,3-dipolar cycloaddition16 efficiently converted the azido alkynes II to the corresponding bicyclic triazoles 5. We applied the same reaction condition toward various amino hydroxyl substituted bicyclic triazoles starting from 1-aziridine-2-yl-propargylic alcohols 3 bearing phenyl (5A), substituted phenyl (5B–E), pyridyl (5F), pyrenyl (5G), linear alkyl (5H)
Pd(OH)$_2$ as a catalyst. Hydrogenation at room temperature in the presence of bicyclic triazoles (Scheme 2) established the substitution patterns of the coupling constants of the two vicinal protons at C-4 and C-5. The measurement of two sets of the coupling constants (5a and 6a, 5i and 6i) clearly established the substitution patterns of cis- and trans-4,5-difunctionalized bicyclic triazoles (Table 3) by the difference of 1.3 Hz and 2.2 Hz, respectively.

The absolute configuration at C-4 of the 3-substituted-4,5-disubstituted bicyclic triazoles was indirectly established by measuring the coupling constants of the two vicinal protons at C-4 and C-5. The measurement of two sets of the coupling constants (5a and 6a, 5i and 6i) clearly established the substitution patterns of cis- and trans-4,5-difunctionalized bicyclic triazoles (Table 3) by the difference of 1.3 Hz and 2.2 Hz, respectively.

The removal of $\alpha$-methylbenzyl nitrogen protecting group from bicyclic triazoles (5 or 6) was achieved at ease by hydrogenation at room temperature in the presence of Pd(OH)$_2$ as a catalyst. $N$-$\alpha$-Methylbenzyl-protected amino bicyclic triazoles are also convertible to the corresponding cyclic carbamate (Scheme 3), at which stage the $\alpha$-methylbenzyl nitrogen protecting group can also be removed. This procedure was exemplified with the compound 5a. Hydrogenation of 5a in the presence of Pd(OH)$_2$ as a catalyst produced free amino alcohol 9a in 84% yield. The removal of $\alpha$-methylbenzyl nitrogen protecting group from 5a also could be achieved by the sequential reactions. At first bicyclic triazole 5a was converted to the corresponding cyclic carbamate 7a in 84% yield by treatment of triphosgene and NaH. The subsequent removal of the $\alpha$-methylbenzyl group was accomplished by treating with anisole and MeSO$_3$H to give 8a in 93% yield. Then the cyclic carbamate 8a was hydrolyzed in aqueous EtOH using LiOH to provide the corresponding free amino bicyclic triazole 9a in 82% yield (Scheme 3). This procedure was applicable to the compounds bearing hydrogenation-sensitive functional group like olefin on 5i and 6i.

Table 1: Synthesis of cis-3-Substituted-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole

<table>
<thead>
<tr>
<th>Products</th>
<th>R</th>
<th>Yield (%)$^{ab}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>$\text{Ph}$</td>
<td>83</td>
</tr>
<tr>
<td>5b</td>
<td>$\text{Ph}$</td>
<td>85</td>
</tr>
<tr>
<td>5c</td>
<td>$\text{CF}_3$</td>
<td>84</td>
</tr>
<tr>
<td>5d</td>
<td>$\text{F}$</td>
<td>81</td>
</tr>
<tr>
<td>5e</td>
<td>$\text{Me}$</td>
<td>86</td>
</tr>
<tr>
<td>5f</td>
<td>$\text{NH}$</td>
<td>74</td>
</tr>
<tr>
<td>5g</td>
<td>$\text{H}$</td>
<td>78</td>
</tr>
<tr>
<td>5h</td>
<td>$\text{Me}$</td>
<td>75</td>
</tr>
<tr>
<td>5i</td>
<td>$\text{Ph}$</td>
<td>89</td>
</tr>
</tbody>
</table>

$^a$ All products characterized by $^1$H NMR, IR spectroscopy, and mass spectrometry.

$^b$ Isolated yields after purification.

In conclusion, we developed a new method for the preparation of enantiomerically pure cis- and trans-3-substituted-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole from the sequential reactions including a regioselective ring-opening of 1-aziridine-2-yl-propargylic alcohols by azidotrimethylsilane and intramolecular 1,3-dipolar cycloaddition between alkyne and azide.

Acknowledgment

We gratefully acknowledge the financial support of the following institutions: The Korea Science and Engineering Foundation (R01-2005-000-10032-0 and the Center for Bioactive Molecular Hybrides to HJH), Korea Research Foundation (KRF-2002-070-C00060 to WKL) and Imagen for providing enantiomerically pure chiral aziridines. WKL acknowledges the special fund from Sogang University in 2004.
Table 2  Synthesis of trans-3-Substituted-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole

![Image of chemical reaction]

<table>
<thead>
<tr>
<th>Products</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>6i</td>
<td></td>
<td>89</td>
</tr>
</tbody>
</table>

* All products characterized by 1H NMR, IR spectroscopy, and mass spectrometry.
* Isolated yields after purification.

Table 3 Coupling Constants of cis- and trans-3-Substituted-4-hydroxy-5-amino Bicyclic Triazoles

![Image of chemical structure]

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>(J_{s,5}) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Ph</td>
<td>OH</td>
<td>H</td>
<td>5.6</td>
</tr>
<tr>
<td>5i</td>
<td>1-Cyclohexenyl</td>
<td>OH</td>
<td>H</td>
<td>5.5</td>
</tr>
<tr>
<td>6a</td>
<td>Ph</td>
<td>H</td>
<td>OH</td>
<td>4.3</td>
</tr>
<tr>
<td>6i</td>
<td>1-Cyclohexenyl</td>
<td>H</td>
<td>OH</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Scheme 3 Formation of carbamate and removal of the nitrogen protecting group

![Image of chemical reaction]

References

12. The same product, (1S,2R)-1-aziridine-2-yl-propargylic alcohol (3), could be obtained from addition reactions of the aziridine-(2S)-carboxaldehyde with the corresponding organolithium reagents to afford aziridine-(2S)-propargylic alcohols. The chelation controlled reduction of the carbonyl group of 2-aziridine as shown in Scheme 1 provided better stereoselectivity than the addition of organolithium reagents to the aziridine-(2S)-carboxaldehyde. See: Park, C. S.; Choi, H. G.; Lee, H. J.; Lee, W. K.; Ha, H.-J. Tetrahedron: Asymmetry 2000, 11, 3283.
15. Preparation of (4S,5S)-4-Hydroxy-3-phenyl-5-[(1R)-1-phenylhthalamino]-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (5a).

To a solution of aziridine-(2S)-propargylic alcohol (3a, 110 mg, 0.40 mmol) in 2.00 mL of CH2Cl2 under nitrogen atmosphere was added TMSCl, at r.t. The mixture was stirred for 3 h at r.t. then quenched with 6 N HCl. The aqueous layer was extracted with CH2Cl2. The combined extracts were dried over MgSO4, and the solvent was evaporated to give product as yellow oil. The crude product was stirred in 2.10 mL of DMF at r.t. The mixture was stirred under a nitrogen atmosphere for 16 h at 130 °C. The solvent was evaporated to give the crude product as yellow oil which was purified by silica gel flash chromatography with 50% EtOAc–hexane to give 106 mg of 5a as a white solid in 83% yield; mp 128–129 °C; \([\alpha]_D^{25} = +38.2 (c 1.0, CHCl_3)\).

1H NMR (500 MHz, CDCl3): \(\delta = 7.82\) (d, \(J = 7.4\) Hz, 2 H), 7.37–7.25 (m, 8 H), 4.78 (d, \(J = 5.6\) Hz, 1 H), 4.51 (dd, \(J = 11.6, 6.9\) Hz, 1 H), 4.10 (dd, \(J = 11.5, 6.8\) Hz, 1 H), 4.01 (q, \(J = 6.4\) Hz, 1 H), 3.92 (td, \(J = 6.9, 5.6\) Hz, 1 H), 1.46 (d, \(J = 6.4\) Hz, 3 H).

13C NMR (125 MHz, CDCl3): \(\delta = 144.0, 142.3, 138.1, 130.4, 129.1, 128.9, 128.2, 128.0, 126.9, 126.2, 64.5, 62.9, 57.2, 51.1, 24.3\). Anal. Calcd for C_{19}H_{20}N_{4}O: C, 71.2; H, 6.29; N, 17.5. Found: C, 71.3; H, 6.30; N, 17.2.


(18) **Removal of α-Methylbenzyl Nitrogen Protecting Group from 5a.**

To a solution of phenylethylamino bicyclic triazole (5a, 110 mg, 0.34 mmol) in 1.90 mL of MeOH was added Pd(OH)$_2$ at r.t. The mixture was stirred for 30 h under 120 psi of H$_2$ (g) at r.t. then the catalyst was filtered and washed with MeOH. The solvent was evaporated to give product as yellow oil which was purified by recrystallization from CH$_2$Cl$_2$ to give 61 mg (84%) of 3-phenyl-5-amino-4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (9a) as a white solid: mp 197–198 °C; [α]$_D$ = +106.5 (c 0.7, CH$_3$OH). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.82 (d, $J$ = 8.0 Hz, 2 H), 7.38 (t, $J$ = 7.3 Hz, 2 H), 7.28 (t, $J$ = 7.5 Hz, 1 H), 5.03 (d, $J$ = 5.5 Hz, 1 H), 4.55 (dd, $J$ = 11.1, 7.4 Hz, 1 H), 4.14 (td, $J$ = 7.4, 5.6 Hz, 1 H), 3.96 (dd, $J$ = 11.1, 7.3 Hz, 1 H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 141.6, 139.3, 130.6, 128.8, 128.2, 125.9, 65.4, 58.6, 51.7. Anal. Calcd for C$_{11}$H$_{12}$N$_4$O: C, 61.1; H, 5.59; N, 25.9. Found: C, 61.2; H, 5.53; N, 26.0.