Synthetic Utilization of 2,6-Dioxa-3-azabicycloalkenes toward Cyclic Ethers

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The nitrosoalkenes are very useful synthetic intermediates because of double bond in conjugation with nitroso group. The [4+2] cycloaddition reaction of vinylnitroso compounds with electron-rich alkenes furnishes 5,6-dihydro-4H-1,2-oxazines (1). The N-O bond of 1,2-oxazines can be reductively cleaved to obtain hydroxyketones, while C-O bond of 1,2-oxazines can be cleaved under acidic or thermal conditions. These reactions have been utilized to prepare pyrroles, pyridines, γ-lactones, and so on. Herein we would like to report the expansion of [4+2] cycloaddition reaction of vinylnitroso compounds derived from α-halooximes or α,α-dihalooximes toward the preparation of cyclic ethers via 2,6-dioxa-3-azabicycloalkenes.

It has been reported that the hetero Diels-Alder reaction of nitrosoalkenes, generated in situ from α-halooximes, with allylic alcohols provides dihydro-4H-oxazinylmethanols. In our synthetic route, the introduction of a halogen atom at the 4-position of oxazine ring 4a derived from halooximes 2 leads to 2,6-dioxa-3-azabicycloalkenes 5 via intramolecular nucleophilic substitution of a halogen atom by a hydroxy group (Scheme 1). The reductive cleavage at N-O bond of the oxazine ring yields cyclic ether 6.

As a starting material, α,α-dihalooximes 2a were chosen to provide halo-substituted oxazine derivatives 4a. Thus, dihaloketones were treated with hydroxylamine in MeOH at room temperature for 2-4 days to furnish compounds 2a. Halovinylnitroso compounds generated in situ by the reaction of 2a with Na₂CO₃ or Cs₂CO₃, underwent [4+2] cycloaddition with allylic alcohols 3 to give isomeric mixtures of 5,6-dihydro-4-halo-1,2-oxazines 4a in 35-94% yield. Alternatively, slight modification of reaction pathway was adopted as follows. Bromo compounds 4a were prepared from the bromination of compounds 4b, which was derived from monobromooximes 2b, with NBS. When these oxazines 4a were treated with a base such as NaH or KH, 1,4-disubstituted 2,6-dioxa-3-azabicyclo[3.n+1.1]3-alkene 5 were obtained as only trans isomers in 73-92% yield.

The reductive cleavage of N-O bond of bicyclic oxazines 5 with Raney nickel (methanol : H₂O = 5 : 1) gave stereoselectively acylated cyclic ethers 6 in good yield. The results were shown in Table 1. In the case of entries 2 and 6,

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Table 1. Reductive Cleavage of Bicyclic Oxazines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxazine</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>62%</td>
</tr>
<tr>
<td>4</td>
<td></td>
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<td>71%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>73%</td>
</tr>
</tbody>
</table>

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Scheme 1
where R is t-butyl, we could not directly prepare 4a. Thus, bromination of 4b was utilized.

As an effort to expand the synthetic application of this reaction, pyranyl product 7 from entry 3 was subjected to Baeyer-Villiger oxidation to obtain compound 8 in 82% yield. Subsequent hydrolysis of ester group and oxidation of lactol yielded mevalonolactone 9. Currently we are investigating our method for the synthesis of other heterocycles 10 with heteroatoms such as nitrogen and sulfur atoms.

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**References**

1. (a) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutoul-Argyrou-


