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

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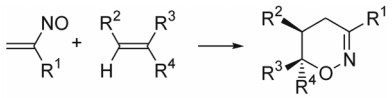
The nitrosoalkenes are very useful synthetic intermediates because of double bond in conjugation with nitroso group.[1] The [4+2] cycloaddition reaction of vinylnitroso compounds with electron-rich alkenes furnishes 5,6-dihydro-4*H*-1,2-oxazines (**1**).[1j] The N-O bond of 1,2-oxazines can be reductively cleaved to obtain hydroxyketones, while C-O bond of 1,2-oxazines can be cleaved under the acidic or thermal conditions. These reactions have been utilized to prepare pyrroles,[2] pyrrolidine,[3] pyridines,[4] γ-lactones,[5] 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.



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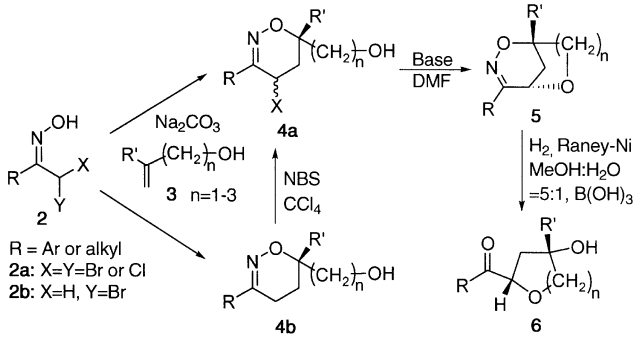
It has been reported that the hetero Diels-Alder reaction of nitrosoalkenes, generated *in situ* from α-halooximes, with allylic alcohols provides dihydro-4*H*-oxazinylmethanols.[6] In our synthetic route, the introduction of a halogen atom at the 4-position of oxazine ring **4a** derived from halooximes **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**.

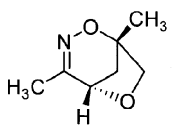
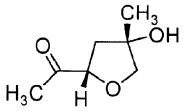
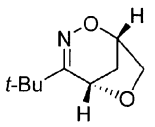
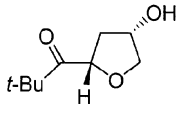
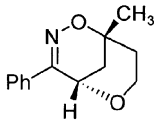
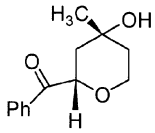
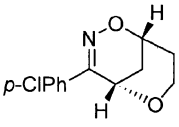
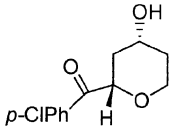
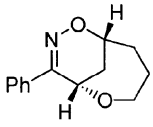
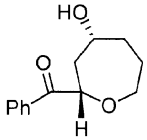
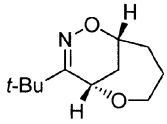
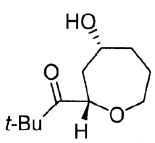
As a starting material, α,α-dihalooximes **2a** were chosen to provide halo-substituted oxazine derivatives **4a**. Thus, dihaloketones were treated with hydroxylamine in MeOH at room temperature for 2-4 days to furnish compounds **2a**. Halovinylnitroso compounds generated *in situ* by the reaction of **2a** with Na_2CO_3 or Cs_2CO_3, 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.



Scheme 1

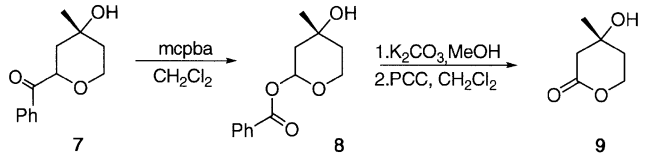
The reductive cleavage of N-O bond of bicyclic oxazines **5** with Raney nickel (methanol : H_2O = 5 : 1) gave stereoselectively acylated cyclic ethers **6** in good yield.[7] The results were shown in Table 1. In the case of entries 2 and 6,

Table 1. Reductive Cleavage of Bicyclic Oxazines

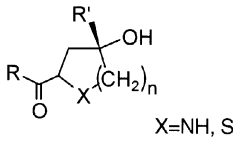
Entry	Oxazine	Product	Yield
1			91%
2			78%
3			62%
4			71%
5			81%
6			73%

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**.[8]



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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