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

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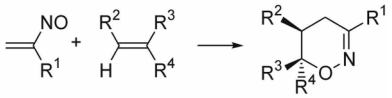
The nitrosoalkenes are very useful synthetic intermediates because of double bond in conjugation with nitroso group.[1] The [4−2] cycloaddition reaction of vinylnitroso compounds with electron-rich alkenes furnishes 5,6-dihydro-4*H*-1,2-oxazines (**1**).[1j] The N-O bond of 1,2-oxazines can be reductively 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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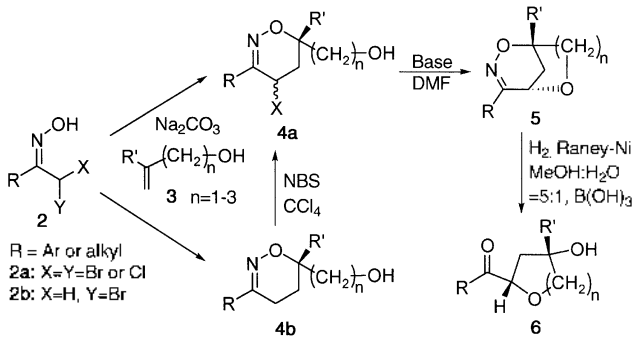
It has been reported that the hetero Diels-Alder reaction of nitrosoalkenes, generated *in situ* from α-halooximes, with allylic alcohols provides dihydro-4*H*-oxazinylmethanols.[6] In our synthetic route, the introduction of a halogen atom at the 4-position of oxazine ring **4a** derived from halooximes **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**.

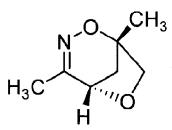
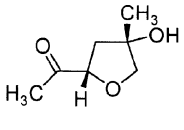
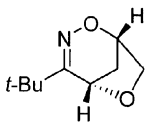
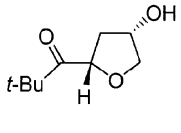
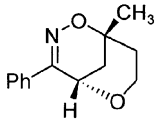
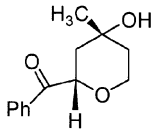
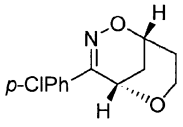
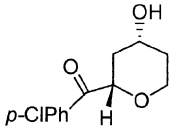
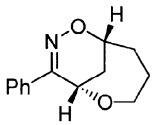
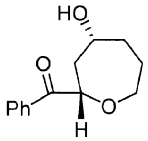
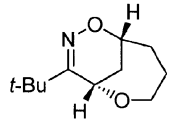
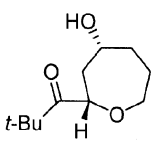
As a starting material, α,α-dihalooximes **2a** were chosen to provide halo-substituted oxazine derivatives **4a**. Thus, dihaloketones were treated with hydroxylamine in MeOH at room temperature for 2-4 days to furnish compounds **2a**. Halovinylnitroso compounds generated *in situ* by the reaction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

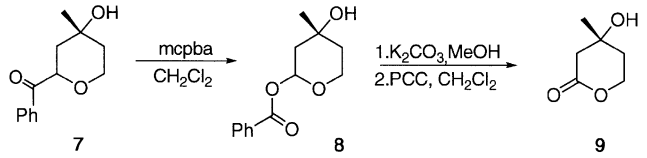
The reductive cleavage of N-O bond of bicyclic oxazines **5** with Raney nickel (methanol : H_2O = 5 : 1) gave stereoselectively acylated cyclic ethers **6** in good yield.[7] The results were shown in Table 1. In the case of entries 2 and 6,

Table 1. Reductive Cleavage of Bicyclic Oxazines

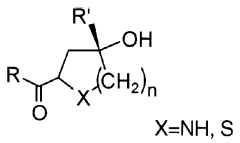
Entry	Oxazine	Product	Yield
1			91%
2			78%
3			62%
4			71%
5			81%
6			73%

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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References

1. (a) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. *Tetrahedron Lett.* **2000**, *41*, 4819-4822. (b) Tahdi, A.; Titouani, S. L.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 65-70. (c) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1-120. (d) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107-1117. (e) Zimmer, R.; Collas, M.; Roth, M.; Reissig, H. U. *Liebigs Ann. Chem.* **1992**, 709-714. (f) Arnold, T.; Orschel, B.; Reissig, H.-U. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1033-1035. (g) Hippeli, C.; Reissig, H. U. *Liebigs Ann. Chem.* **1990**, 217-226. (h) Arnold, T.; Reissig, H. U. *Synlett* **1990**, 514-516. (i) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; pp 71-93. (j) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53-73. (k) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007-4016. (l) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. 1* **1979**, 249-257.
2. (a) Oppolzer, W.; Bättig, K.; Hudlicky, K. *Tetrahedron* **1981**, *37*, 4359-4364. (b) Nakanishi, S.; Shirai, Y.; Takahashi, K.; Otsuji, Y. *Chem. Lett.* **1981**, 869-872.
3. Angermann, J.; Homann, K.; Reissig, H.-U.; Zimmer, R. *Synlett* **1995**, 1014-1016.
4. Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 258-262.
5. Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089-1090.
6. Stevensen, T. M.; Patel, K. M.; Crouse, B. A.; Folgar, M. P.; Hutchison, C. D.; Pine, K. K. *Synthesis and Chemistry of Agrochemicals*; Baker, D. R., Fenyes, J. G., Basarab, G. S., Eds.; ACS Symposium Series 584; American Chemical Society: Washington DC, 1995; vol. IV, pp 197-205.
7. Fisera, L.; Goljer, I.; Jaroskora, L. *Collect. Czech. Chem. Commun.* **1988**, *53*, 1753-1760.
8. (a) Takano, S.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1984**, 8283. (b) Bolitt, V.; Mioskowski, C. *J. Org. Chem.* **1991**, *56*, 4238-4240.