

## Bromocycloetherification Using NBS-Acetonitrile

Chae-ho Cook, Youn-sang Cho, Sang-sup Jew, and Young-Hoon Jung

College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151, Korea

(Received, 21 March 1985)

**Abstract** □ Bromocycloetherification of a series of 3- and 4-olefinic alcohols using NBS-acetonitrile gave corresponding bromo-tetrahydrofuran with high regio- and stereoselectivity.

**Keywords** □ Bromocycloetherification, Bromolactonization, NBS, Acetonitrile, Bromo-oxetane, Bromo-tetrahydrofuran, Baldwin's rule, heterolytic cleavage.

In order to synthesize the tetrahydrofuran- or tetrahydropyran containing compounds of biological interest such as Nonactin<sup>1</sup> and Monensin<sup>2</sup>, a few cycloetherification reactions have been used.<sup>3</sup> Among them haloetherification reaction<sup>4</sup> appears to be the most useful method because it is expected that it will show high regio- and stereoselectivity like halolactonization.

In connection with studies on the behavior of mild N-X bond of N-haloimide compounds in aprotic polar solvent, we had developed an effective bromolactonization method using N-bromosuccinimide (NBS) in N, N-dimethyl formamide (DMF).<sup>5</sup> From this success, it was felt that if this method is applied to olefinic alcohols instead of olefinic acids, an efficient bromocycloetherification method could be developed. Under the same reaction condition as the bromolactonization, the bromocycloetherification was investigated. We found that DMF was not appropriate solvent for the bromocycloetherification. But by using acetonitrile instead of DMF, the reaction was very mildly effected. However, the reason is not yet clear.

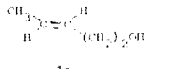

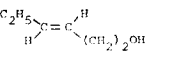

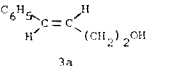
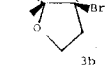
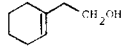

Although a few bromocycloetherification

reactions of synthetic intermediates for total syntheses of biologically important organic compounds, using NBS-acetonitrile, were quite recently reported,<sup>6</sup> these reactions, especially their limitations, had not been investigated systematically.

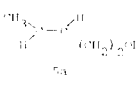
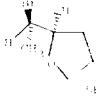
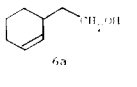

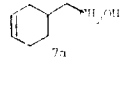

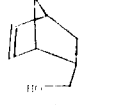

The typical procedure was as follows;

To a stirred solution of 7.9 mmol of an 4-olefinic alcohol **6a** in 6 ml of dry acetonitrile at room temperature under nitrogen, was added a solution of 10.3 mmol of NBS in 14 ml of dry acetonitrile dropwise. After 0.5 hrs, the reaction mixture was diluted with ethyl ether, washed with sat. NaHCO<sub>3</sub> sol'n, H<sub>2</sub>O and sat. NaCl sol'n, dried over MgSO<sub>4</sub> and evaporated in vacuo to give crude products. These products were purified by the Slica-gel Column Chromatography to give the bromocycloether. The results are summarized in Table I and II.

**Table I: Bromocyclization of 3-olefinic alcohol.**

3-olefinic alcohol	product	reaction time (hrs)	Yield (%)
 1a	 1b	20	20
 2a	 2b	20	31
 3a	 3b	2	56
 4a	 4b	2	38

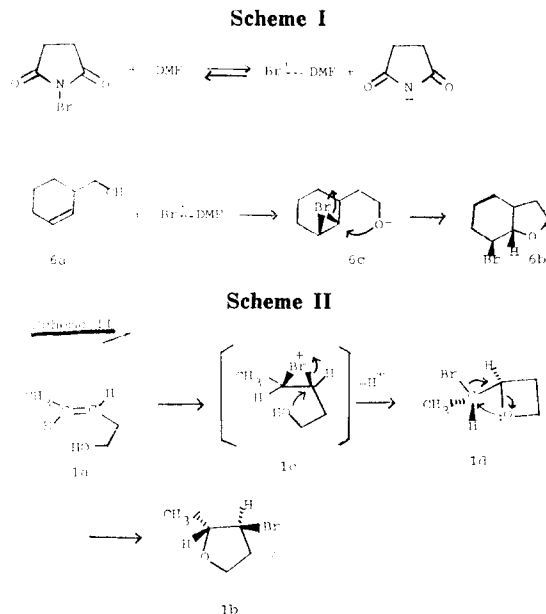
**Table II: Bromocyclization of 4-olefinic alcohol.**

4-olefinic alcohol	Product	Reaction temperature (°C)	Yield (%)
		0	69
		0, 5	93
		10	56
		1, 5	63

In case of 3-olefinic alcohols, 20~50% yields of bromo-tetrahydrofurans were obtained, whereas the bromoetherification of 4-olefinic alcohols gave good to excellent yields of bromo-tetrahydrofuran (56~93%). However, the yields were not optimised.

This reaction is suggested to be performed such as Schem I. That is, the initiating reagent for the bromocycloetherification,  $\text{Br}^+$  or its closely related equivalent was thought to be generated from the heterolytic cleavage of the mild N-Br bond of the NBS by the aprotic polar solvent, acetonitrile. The bromonium ion **6c** resulted from the reaction of an olefinic group of the olefinic alcohol **6a** with the  $\text{Br}^+$  or its closely related equivalent appears to be intramolecularly attacked by a hydroxy group of the alcohol.

In case of 3-olefinic alcohols **1a**, bromo-oxetane **1d** or bromotetrahydrofuran **1b** seems to be obtained according to the position attacked by intramolecular nucleophile. By Baldwin's rule<sup>7</sup>, 4-Exo-Tet and 4-Exo-Trig is favorable to 5-Exo-Tet and 5-Exo-Trig respectively. Th-



erefore, it was thought that bromo-oxetane **1d** is kinetically favorable product but because of its unstability, it was converted to more stable bromo-tetrahydrofuran **1b** such as Scheme II.

From the bromocycloetherification of a series of 4-olefinic alcohols, bromo-tetrahydrofuran is exclusively formed because of the stability of bromo-tetrahydrofuran and Baldwin's rule that 5-Exo-Tet and 5-Exo-Trig take precedence of 5-Endo-Tet and 5-Endo-Trig respectively.

The attack of intramolecular nucleophile to bromonium ion is thought to be proceeded in trans fashion similarly to bromolactonization. On the basis of the above trans fashion and the suggested mechanism on the conversion of the bromo-oxetane to bromo-tetrahydrofuran, the stereochemistry of the products was tentatively assigned.

#### ACKNOWLEDGEMENT

This work is supported by the grants from Research Institute of Pharmaceutical Sciences

attached to College of Pharmacy, Seoul National University (1984)

## LITERATURE CITED

- 1) Ireland, R.E., and Vevert, J.P.: A chiral total synthesis of (-)- and (+)-Nonactic acid from carbohydrate precursors and the Definition of the transition for the Enolate Claisen Rearrangement in Heterocyclic Systems. *J. Org. Chem.*, **45**, 4260 (1980)
- 2) Collum, D.B., McDonald, J.H., and Still, O.C.: Synthesis of the Polyether Antibiotic Monensin. I. Strategy and Degradations. *J. Am. Chem. Soc.*, **102**, 2117 (1980)
- 3) a) Pougny, J.R., Nassr, M.A.M., and Sinay, P.: Mercuricyclisation in Carbohydrate Chemistry: A highly stereoselective route to -D-C- glucopyranosyl derivatives. *J. Chem. Soc. Chem. Commun.*, 375 (1981)
- b) Nicolaou, K.C., Magold, R.L., Sipio, W.J., Barnette, W.E., Lysenko, Z., and Joullie, M. M.: Phenylselenoetherification. A highly efficient cyclization process for the synthesis of O- and S-Heterocycles. *J. Am. Chem. Soc.*, **102**, 3784 (1980)
- c) Walba, D.M., and Stoudt, G.S.: Oxidative cyclization of 5, 6-Dihydroxyalkenes promoted by Cr(VI) Oxo species; A novel cis-2, 5-Disubstituted Tetrahydrofuran Synthesis. *Tetra. Lett.*, **23**, 727 (1982)
- 4) a) Wong, H., Chapuis, J., and Monkovic, I.: Stereochemical course of Bromocyclizations of -unsaturated alcohols. II. Approaches to various Oxaazabicyclooctane and-nonane systems. *J. Org. Chem.*, **39**, 1042 (1974)
- b) Hoyer, T.R., and Caruso, A.J.: Total synthesis of dl-Ancistrofuran: A study of cyclic ether formation. *ibid.*, **46**, 1198 (1981)
- c) Rychnovsky, S., and Bartlett, P.A.: Stereoccontrolled synthesis of cis-2, 5-Disubstituted Tetrahydrofurans and cis- and trans-Linalyl Oxides. *J. Am. Chem. Soc.*, **103**, 3963 (1983)
- 5) a) Cook, C., Cho, Y., Jew, S., and Suh, Y.: Studies on the novel halolactonization using N-haloimides under non-aqueous media (I). Bromolactonization reaction. *Seoul Uni. J. Pharm. Sci.*, **4**, 109 (1979)
- b) Cook, C., and Kang, E.: Novel bromolactonization using N-bromophthalimide. *Arch. Pharm. Res.*, **4**, 137 (1981)
- c) Jew, S.: Novel aspects of bromolactonization reaction using N-haloimides in an aprotic polar solvent. *ibid.*, **5**, 97 (1982)
- d) Cook, C., Cho, Y., Jew, S., Suh, Y., and Kang, E.: Halolactonization reaction using N-haloimides. *ibid.*, **6**, 45 (1983)
- 6) a) Feldman, K.S., Mechem, C.C., and Nader, L.: Total synthesis of ( $\pm$ )-Panacene. *J. Am. Chem. Soc.*, **104**, 4011 (1982)
- b) Fukuyama, T., Wang, C.L.T., and Kishi, Y.: Total synthesis of Monensin. 2. Stereocontrolled synthesis of the right half of Monensin. *ibid.*, **101**, 260 (1979)
- 7) Baldwin, J.E.: Rules for Ring Closure. *J. Chem. Soc. Chem. Commun.*, 734 (1976)