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# 3-Halohydantoins as Halolactonization Reagents

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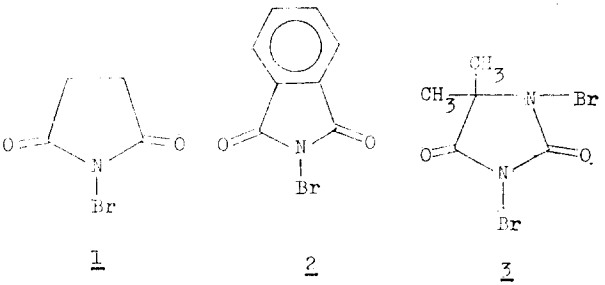
**Abstracts** □ By the reaction of **15** with 3-halohydantoins(**4**—**14**) in N,N-dimethylformamide, which were prepared from corresponding hydantoins, 3-bromo-5,5-dimethylhydantoin was found to be the most convenient reagent for halolactonization reaction.

**Keywords** □ 3-Halohydantoins, N,N-dimethylformamide, 3-Bromo-5,5-dimethylhydantoin, Halolactonization, (2-Cyclohexenyl)-2-acetic acid.

Halolactonization is the cyclization reaction between halonium ion intermediate, which results from the reaction of olefinic group of olefinic acid with $X^+$ generated from halolactonization reagent, and an intramolecular nucleophile, carboxyl group of olefinic acid.[1] This reaction, a very efficient method for regio-and steroselective introduction of functional groups on the double bond has been prominently applied to the synthetic organic chemistry.[2]

The iodolactonization, which has been the most frequently used, is usually carried out in aqueous sodium bicarbonate solution of an olefinic acid with a solution of iodine in aqueous potassium iodide.[3] Such a requirement of aqueous basic media for iodolactonization has rendered severe limitations to the scope of this reaction. Thus, new procedures employing organic solvents as reaction media under neutral conditions have been investigated.[4] The new cyclization reactions *i.e.*, phenylselenolactonization and phenylsulfurlactonization, appearing to have the value equivalent to halolactonization in synthetic organic chemistry, were recently reported.[5]

In connection with the studies on the N-haloimides in aprotic polar solvents, mild procedures for halolactonization utilizing N-haloimides have been investigated by us. Here we recently succeeded in exploitation of the greatly mild methods for bromolactonization using N-bromosuccinimide(**1**)[6] and N-bromophthalimide(**2**).[7]

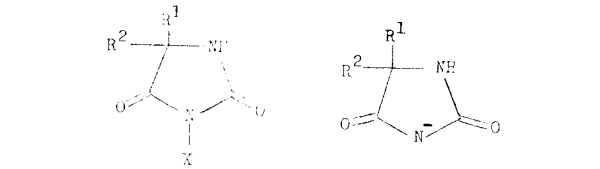


**1** **2** **3**

**Fig. 1**:

Having an eye to the following two facts (1) the successful exploitation of **1** and **2** as mild bromolactonization reagents (2) the reactivity of 1,3-dibromo-5,5-dimethylhydantoin (3) similar to **1** in allylic bromination[8a] and oxidation,[8b] we set about investigating a new procedure for halolactonization employing 3-halohydantoins (**4**—**14**).

In an aprotic polar solvent such as N,N-dimethylformamide(DMF), a $X^+$ and a hydantoin anion(**4′**—**14′**) or closely related equivalents were expected to be generated from a heterolytic

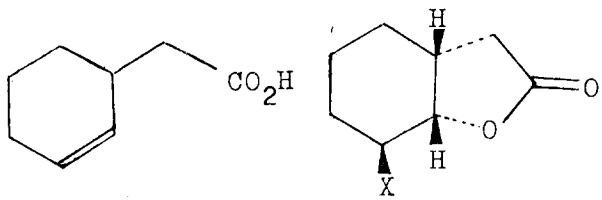


4 $R^1$=H, $R^2$=H, X=Br
5 $R^1$=$CH_3$, $R^2$=$CH_3$, X=Cl
6 $R^1$=$CH_3$, $R^2$=$CH_3$, X=Br
7 $R^1$=$CH_3$, $R^2$=$CH_3$, X=I
8 $R^1$=$C_2H_5$, $R^2$=$C_2H_5$, X=Br
9 $R^1$, $R^2$=$-(CH_2)_5-$, X=Br
10 $R^1$=H, $R^2$=$C_6H_5$, X=Cl
11 $R^1$=H, $R^2$=$C_6H_5$, X=Br
12 $R^1$=H, $R^2$=$C_6H_5$, X=I
13 $R^1$=$C_6H_5$, $R^2$=$C_6H_5$, X=Br
14 $R^1$=$CH_3$, $R^2$=$(CH_3)_2CH$, X=Br

**Fig. 2:**

cleavage of the nitrogen-halogen bond of 3-halohydantoins(**4**—**14**) expected to generate as illustrated in the above equation. It was thought that the former was more strongly solved with DMF than the latter.[9] The former would be able to behave as mild initiator on halonium ion formed from the double bond of olefinic acid and the latter would sufficiently transform the carboxyl group to the carboxylate ion so that the reactivity of intramolecular nucleophile was able to be increased.

3-Halohydantoins(**4**—**14**) were prepared from corresponding hydantoins, easily synthesized according to literatures, with chlorine, bromine, iodine in aqueous sodium hydroxide(1 mole equivalent) solution.[10] In order to find the most efficient 3-halohydantoin as the halolactonization reagent, by utilizing (2-cyclohexenyl)-2-acetic acid(**15**) as a substrate for halolactonization reaction, which is very reactive under general halolactonization,[11] the halolactonization reactions with the use of **4**—**14** were carried out as follows; To a stirred solution of **15**(3.6 mmole) in dry DMF(5ml) under nitrogen at 20~25°C was added a solution of **4**—**14**(4.3 mmole) in dry DMF(5ml). After being stirred for 20 hours, the reaction mixture was diluted with ethyl acetate and the organic solution was successively washed with 5% $NaHCO_3$, $H_2O$ ant sat. NaCl. Filtration and evaporation in vacuo gave crude halolactone(**16**) which was then column-chromatogrammed on a silica gel (benzene : ethyl acetate=10 : 1).



**15**

**16a** X=Cl
**16b** X=Br
**16c** X=I

**Fig. 3:**

For the purpose of elucidating the effect of alkyl-substituents of C-5 position of 3-halohydantoins by using 3-bromohydantoins such as **4**,[12] **6**,[13b] **8**,[13d] **9**,[13a] **11**,[12] **13**,[13d] and **14**,[13e] in the first place, the bromolactonization reactions were carried out. The obtained bromolactone(**16b**[12]) was as follows respectively, **4**(81%), **6**(82%), **8**(81%), **9**(65%), **11**(77%), **13**(66%) and **14**(89%). It was seen that when both substituents at C-5 position were two hydrogens or alkyl groups such as **4**, **6**, **8** and **14**, 81~89% yields of **16b** were obtained, respectively.

In the next place for the purpose of the elucidation of the effect of halogen-3 substituents, using 3-chloro-(**5**)[13a] and 3-iodohydantoin (**7**)[13c] instead of 3-bromohydantoin(**6**), where both substituents at C-5 were methyl groups, halolactonization were effected to afford chlorolactone(**16a**)[12] and iodolacton(**16c**)[14] in 18% and 91% yields, respectively. The reactivity of

**5**, **6**, and **7** as halolactonization reagent in aprotic polar solvent DMF was thought to follow the order: **7**≥**6**>**5**, *i.e.*, I≥Br>Cl. In the case of **11**, where $R^1$ is hydrogen and $R^2$ is phenyl group, the tendency that 3-bromohydantoin(**11**) was much more reactive than 3-chlorohydantoin(**10**)[12]; that is 77%(**16b**) and 3%(**16a**) yields were obtained. This result agreed with the case of **5** and **6** but 3-iodohydantoin(**12**),[12] beyond our expectation, showed very low reactivity in contrast with **7**. Why such a large difference in the reactivity between 3-iodohydantoin **7** and **12** has been seen, was so far ambiguous.

From the afore-mentioned results and the ready availability, we chose 3-bromo-5,5-dimethylhydantoin(**6**) the most convenient reagent for halolactonization reaction.

## ACKNOWLEDGMENT

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## LITERATURE CITED

1) House, H.O., *Modern Synthetic Reactions* 2nd ed., W.A. Benjamin Inc., Meleno Park, California, 441 pp. (1972).

2) Dowle, M.D. and Davies, D.I., Synthesis and Synthetic Utility of Halolactones. *Chem. Soc. Rev.*, **8**, 171(1979) and references cited therein.

3) a) Bougault, M.J., Action De L'acide Hypoiodeux Naissant Sur Les Acides Non Satures. Lactones iodees. *Ann. Chim. Phys.* **14**, 145(1908) and references cited therein. b) *idem*, Action De L'acide Hypoiodeux Naissant Sur Les Acides Non Satures. *ibid.*, **15**, 296(1908).

4) a) Corey, E.J. and Hase, T., Studies on the Total Synthesis of Rifamycin. Highly Stereoselective Synthesis of Intermediates for Construction of the C(15) to C(29) chain. *Tetra. Lett.*, **1979**, 335. b) Terashima, S. and Jew, S., Asymmetric Halolactonization Reaction: A Highly Efficient Synthesis of Optically Active $\alpha$-Hydroxy Acids from $\alpha,\beta$-Unsaturated acids. *Tetra. Lett.*, **1977**, 1005. c) Jew, S., Terashima, S., and Koga, K., Asymmetric Halolactonization-Asymmetric Synthesis of Optically active $\alpha,\alpha$-I' Disubstituted-$\alpha$-Hydroxy Acids from $\alpha,\beta$-Un saturated Acids by the use of Halolactonization Reaction I. *Tetrahedron*, **35**, 2337(1979). d) Cambie, R.C., Hayward, R.C., Roberts, J.L., Rutledge, P.S., Iodolactonizations using Thallium (I) Carboxylates. *J. Chem. Soc.* Perkin I, **1974**, 1864. e) Bartlett, P.A. and Myerson, J., Highly Stereoselective Synthesis (+)-$\alpha$-Multistriatin. *J. Org. Chem.*, **44**, 1625(1979).

5) Nicolaou, K.C., Seitz, S.P., Sipio, W.J., and Blount, J.F., Phenylseleno-and Phenylsulfenolactonizations. Two Highly Efficient and Syntheti Useful Cyclization Procedures. *J. Am. Chem. Soc.*, **101**, 3884(1979) and references cited therein.

6) Cook, C., Cho, Y., Jew, S., and Suh, Y., Studies on Novel Haloactonization Using N-Haloimides under Non-aqueous Media(1). *Seoul Uni. J. Pharm. Sci.*, **4**, 109(1979).

7) Cook, C., and Kang, E., Novel Bromolactonization Using N-Bromophthalimide. *Arch. Pharm. Res.*, **4**, 137(1981).

8) a) Oakes, V., Rydon, H.N., and Undheim, K., Polyazanaphthalenes. part VII. Some Derivative of Quinazoline and 1,3,5-Triazanaphthalene. *J. Chem. Soc.*, **1962**, 4678. b) Corral, R.A., and Orazi, O.O., Oxidation of Secondary Aromatic Alcohols with N-Bromoamides. *Chem. Comm.*, **1965**, 5.

9) Pizey, S.S., *Synthetic Reagents*, vol I. John Wiely and Sons Inc., New York, 4pp. (1974) and references cited therein.

10) Vogel, A.I., *Practical Organic Chemistry*, 3rd ed., Longmans, Green and Co. Ltd., London,

926pp. (1956).

11) van Tamelen, E.E., and Shamma, M., Assignment of the Olefinic Position in Unsaturated Acids by Means of the Iodolactonization Reaction. *J. Am. Chem. Soc.*, **76**, 2315(1954).

12) All new compounds give IR, NMR, and/or mass spectral in complete accord with the desired structures.

13) a) Ishii, Y., Ito, Y., and Kato, S., Synthesis of Hydantoin Derivatives and Halogenation of N-Halohydantoin. *Kogyo Kagaku Zasshi.*, **61**, 1254 (1958). b) Orazi, O.O., and Meseri, J., Halogenation with 3-Bromo-5, 5-Dimethylhydantoin. *Anales. Assoc. Quim.Argen.*, **37**, 192(1949). c) Corral, R.A. and Orazi, O.O., N-Iodohydantoins. *ibid.*, **44**, 11(1956). d) Orazi, O.O., Fondovila, M.E., and Corral, R.A., Bromoderivatives of 5, 5-Disubstituted Hydantoins. *ibid.*, **40**, 109(1952). e) Waugh, T.D., and Waugh, R.C., N-Brominated Imides and Hydantoins. U.S. pat. 2,971,960(1961).