

Novel Aspects of Bromolactonization Reaction Using N-Haloimides in an Aprotic Polar Solvent

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Abstracts □ Depending upon the results obtained by the bromolactonization of olefinic acids (9~11) by means of N-bromosaccharin (4), the influence of the stabilities of the imidic anions resulted from heterolytic cleavage of N-haloimides, such as N-bromosuccinimide (1), N-bromophthalimide (2), and N-bromosaccharin (3) in dry N,N-dimethylformamide on the reactivity is elucidated.

Keywords: □ Bromolactonization reaction, Heterolytic cleavage, N-haloimides, N-Bromosaccharin, imidic anion, N,N-Dimethylformamide.

The reaction of an halonium ion intermediate, resulted from the electrophilic attack of halolactonization initiator on the double bond group of olefinic acid with carboxyl group or carboxylate anion is called halolactonization reaction.¹⁾ The cleavage of the halonium ion, which is believed to be performed by intramolecular S_N-like reaction, i.e., the intramolecular attack of the carboxyl group or carboxylate anion on the halonium ion, furnishes the completely stereoselective halolactone.¹⁾ Thus, this reaction has been valuably applied to modern synthetic organic chemistry because biologically very important natural and unnatural compounds with lactone skeleton exist in great abundance and variety²⁾ and lactones are very effectively employed as synthons.³⁻⁵⁾

When it is applied for the purpose of usual synthetic utility, iodolactonization reaction has

been considered to be most effective,⁶⁾ although a few successful applications of bromolactonization reaction was recently reported.^{4b,4c,5)} It has also been known that in the case of separating mixtures of isomeric olefinic acids or determining the structure and stereochemistry of many other Diels-Alder adducts of olefinic acids with cyclopentadiene, iodolactonization, in particular, was more discriminating.⁶⁾

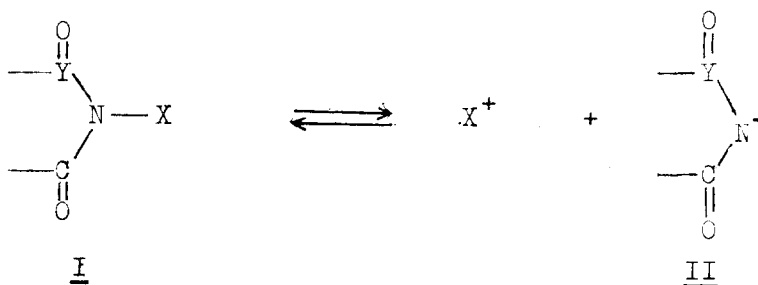
However, since the usual requirement for iodolactonization reaction is aqueous basic media, severe limitations, is rendered, in particular, to its application of the total synthesis i.e., the iodolactonization of the olefinic acid with a rather large number of important functional and protecting groups.

Thus, new procedures involving organic solvents as reaction media under neutral conditions instead of basic aqueous media, have been developed.⁸⁾ We have recently reported very convenient procedure for bromolactonization reaction using N-bromosuccinimide (1),^{7a)} N-bromophthalimide (2),^{7b)} and 3-bromo-5,5-dimethylhydantoin (3)^{7c)} in connection with studies on the novel reaction of N-haloimides in an aprotic polar solvent and new reactions phenylselenolactonization and phenylsulfurlactonization, which were equivalent to halolactonization reaction in synthetic organic chemistry were developed by K.C. Nicolaou.⁹⁾

For the purpose of elucidating the mechanism

of halolactonization employing N-haloimides in an aprotic polar solvent and developing a new procedure for halolactonization reaction, I chose N-bromosaccharin (4)¹⁰ because of the slightly low dissociation constant^{11a)} of saccharin (7) in comparison with succinimide (5)^{11b)} and phthalimide (6)^{11b)} and ready availability of 7.

In an aprotic polar solvent, *i.e.*, N,N-dimethylformamide (DMF), acetonitrile, or hexamethylphosphoric triamide, the formation of a X⁺ ion and an imidic anion (**II**) or closely related equivalents from heterolytic cleavage of the N-X bond of N-haloimide (**I**) is expected as illustrated below.

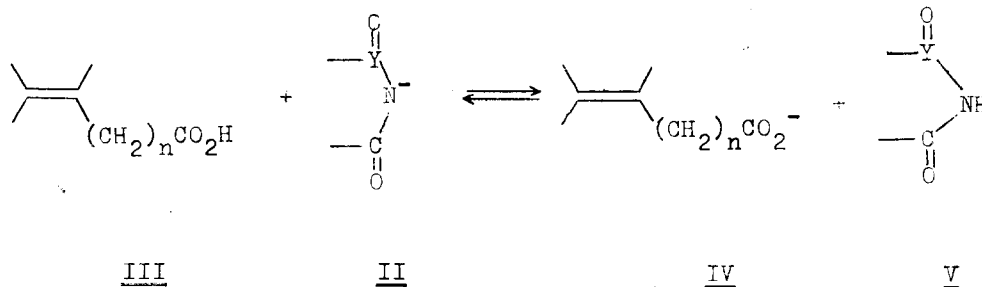


X=Cl, Br and I; Y=C and S

Equation 1

It is thought that the former will be more strongly solvated than the latter¹²⁾ Thus, the former will be able to react with the olefinic acid (**III**) very mildly to lead to the formation of halonium ion and the latter will sufficiently

convert the carboxyl group of **III** to the carboxylate ion (**IV**) so that the activity of intramolecular nucleophile can be increased as following equation 2.



n=1 and 2

Equation 2

In order to elucidate this halolactonization, here are two problems concerned with. One is the generation of X⁺ by heterolytic cleavage and the other is the regioselectivity which was thoroughly rationalized in terms of weak bridged carbonium ion intermediate as the fine character

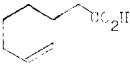
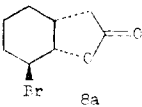
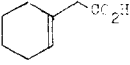
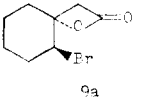
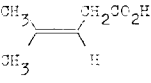
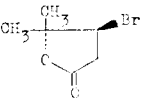
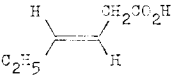
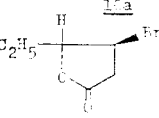
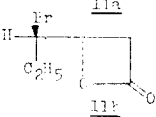
of halonium ion intermediate.¹³⁾ We are in the not touched problem, the generation of X⁺ ion. Assuming that the generation of X⁺ ion is occurred such as equation 1, the more acidic the conjugate acid of **II** is the more X⁺ ion exist so that the rate of this reaction will be

increased.

The bromolactonization using **4** as cyclization reagent in dry DMF, which was prepared from commercially available soluble saccharin according to the literature, was carried out as follows: To a solution of olefinic acid (**3** mmole) in 5 ml of dry DMF, a solution of **4** (**3.9** mmole) in 5 ml of dry DMF was added by means of syringe at room temperature under nitrogen

during 30 minutes. After the resulting solution was stirred for 24 hours, ethyl acetate was added to dilute and the organic solution was successively washed with 5% NaHCO₃, H₂O and sat. NaCl, dried over anhyd. MgSO₄, and evaporated in vacuo to afford crude bromolactone. This was then purified with silica gel column chromatography to give following results (Table I)

Table I: Bromolactonization of olefinic acids using NBSC under N₂ at rt for 20 hrs.

Run No	Olefinic acid	Bromolactone ¹⁵⁾	Yields(%)		
			NBS ^{7a)}	NBP ^{b)}	NBSC
1	 8-14a)	 8a	83	90	35
2	 9-14b)	 9a	88	79	11
3	 10-14c)	 10a	41	31	7
4	 11-14d)	 11a	49	20	8
		 11b	30	20	5

The dissociation constant of saccharin (**7**), succinimide (**5**), and phthalimide (**6**) is 2.1×10^{-12} , 3.2×10^{-10} , and 5×10^{-9} respectively. Therefore it is anticipated that relative reactivities of N-bromoimides follow approximately the order of N-bromophthalimide (**2**) N-bromosuccinimide (**1**) N-bromosaccharin(**4**).

In the bromolactonization of **8** (run number 1), which is considered to be the most appro-

priate substrate of bromolactonization in comparing the reactivity of reagent, the obtained result completely agrees with the fact anticipated. In the bromolactonization of **9**, **10**, and **11** (run numbers 2, 3, and 4) this reagent showed much lower reactivity than N-bromosuccinimide (**1**) and N-bromophthalimide (**2**), however, a slight preponderance of reactivity of **2** over **1**, expected from the meager difference of dissoci-

ation constant, is not seen.

Thus, from afore mentioned results, the conclusion that the generation of X^+ and imidic anion was really performed in this reaction was for the first time obtained. We can also conclude that the reactivity of N-haloimide (I) is related to the stability of imide anion (II) by heterolytic cleavage of N-X bond in an aprotic polar solvent, i.e., the acidity of conjugated acid of imidic anion (V), if being roughly said. N-bromosaccharin (4), regardless of much easier availability of soluble saccharin which is the precursor of 4, can not be a convenient bromolactonization reagent, but the possibility that this reagent may be the very convenient reagent for radical-type reaction aroused by homolytic cleavage is perceived.

In connection with the elucidation of the reaction of N-haloimides (I) in aprotic polar solvent, I am currently engaged in applying this reagent to the radical-type reaction, allylic bromination and oxidation.

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