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Novel Bromolactonization Using N-Bromophthalimide

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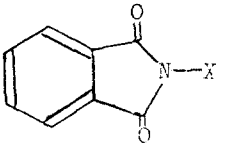
Abstract□Reaction of olefinic acids with N-bromophthalimide in dry N,N-dimethylformamide at room temperature gives bromolactones in good yields.

Keywords□ Bromolactonization, N-Bromophthalimide, N,N-Dimethylformamide, γ-Bromo-β-lactone

Intramolecular cyclization of an incipient bromonium ion intermediate with carboxyl group(CO_2H) is known as bromolactonization[1]. This reaction which is a completely excellent method for regio- and stereoselective functionalization of olefinic bonds is nicely applied to the synthesis of biologically important compounds[2] and to the asymmetric synthesis of α-hydroxy acids[3]. It can be effected with the use of Br_2[4], sodium hypobromite[5], acetylhypobromite[6], or N-bromosuccinimide[7] as cyclization reagents, however the scope and the yield are very limited.

As an extension to our previous work on the elucidation of new ionic reaction of N-haloimides in aprotic polar solvent, we investigate a new method for bromolactonization which can be carried out under a milder reaction condition, especially in non-aqueous and non-basic medium. A recent report[8] on the phenylselenolactonization which is equivalent to the halolactonization in synthetic organic chemistry and where N-phenylselenophthalimide(**1**) is used as a cyclization initiator, suggests a new method for bromolactonization employing N-bromophthalimide (NBP) (**2**).



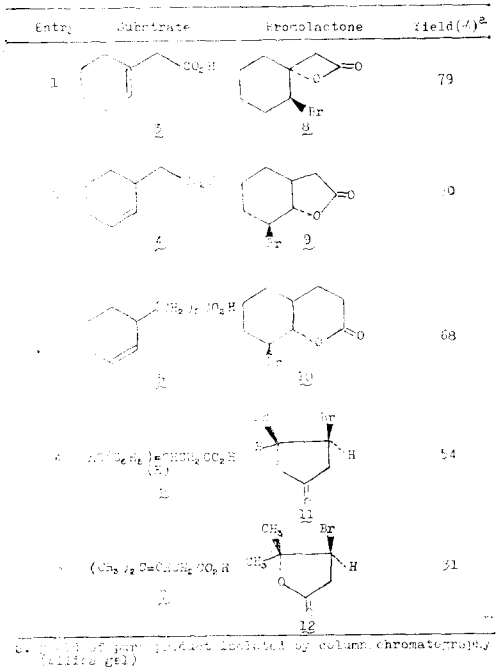
1: X=SePh
2: X=Br

We wish to describe here a novel method for bromolactonization employing NBP(**2**) as a cyclization initiator under aprotic polar solvent, dry N,N-dimethylformamide (DMF), at room temperature.

A typical example is given as follows. To a solution of olefinic acid(3.0 mmole) in 5ml of dry DMF, a solution of NBP(**2**) (3.9 mmole) in 5ml of dry DMF is added at room temperature under nitrogen. After the reaction mixture is stirred for 20 hrs, it is diluted with ethyl acetate and the organic solution is washed successively with 5% $NaHCO_3$, H_2O, and satd. NaCl. Filtration and concentration *in vacuo* give bromolactones which are then purified with silica-gel column chromatography to afford following results. (Table I)

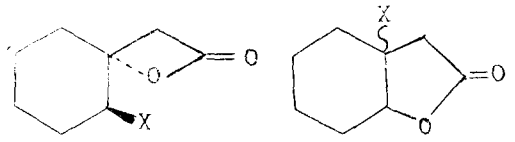
A polar intermediate bromonium ion or a closely related equivalent is formed by

Table I: Bromolactonization of unsaturated acids.



electrophilic attack of Br^+ on the double bond of olefinic acids and then attacked by intramolecular nucleophile CO_2H to afford bromolactone, however it is not unambigous that the reaction entity Br^+ is generated by the heterolytic cleavage of N-Br bond of (**2**) in aprotic polar solvent, DMF.

As can be seen in Table 1, for β-, γ-, and δ-cyclohexenylalkanoic acids (**3**[9a], **4**[9b], and **5**[9c]) corresponding bromolactones, γ-bromo-β-lactone(**8**)[10], δ-bromo-γ-lactone (**9**)[10], and ϵ-bromo-δ-lactone(**10**)[10] are obtained in good yields, however straight-chained β-alkenoic acids **6**[9c] and **7**[9d] afford the respective γ-bromo-β-lactones **11**[10] and **12**[10] in relatively low yields. In case of the lactonization of β-cyclohexenylalkanoic acid (**3**) using I_2[11], PhSeCl[12], and PhSCl[13], thermodynamically stable β-iodo-(**14a**), β-phenylseleno-(**14b**), and β-phenylsulfenyl-γ-lactone (**14c**)



13 14

a: X=I a: X=I
b: X=SePh b: X=SePh
c: X=SPh c: X=SPh

have been regioselectively obtained. The reason for this is the fact that initially formed γ-iodo-(**13a**), γ-phenylseleno-(**13b**), and γ-phenylsulfenyl-β-lactone(**13c**) are rearranged to the thermodynamically stable γ-lactones. It is of particular interest that bromolactonization of **3** give only γ-bromo-β-lactone(**8**) in high yield regardless of usual work-up and silica-gel column chromatography.

In connection with studies on the new reaction using N-haloimides, further investigation on the scope and mechanism of this novel bromolactonization is in progress.

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