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3-Bromo-5, 5-dimethylhydantoin Induced Ring Closure(I)
Bromolactonization

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Abstract□ Reaction of unsaturated acids with 3-bromo-5,5-dimethylhydantoin in dry DMF at room temperature gives bromolactones in 58 ~91% yields.

Keywords□ Bromolactonization, 3-Bromo-5,5-dimethylhydantoin, N,N-Dimethylformamide, γ-Bromo-β-lactone

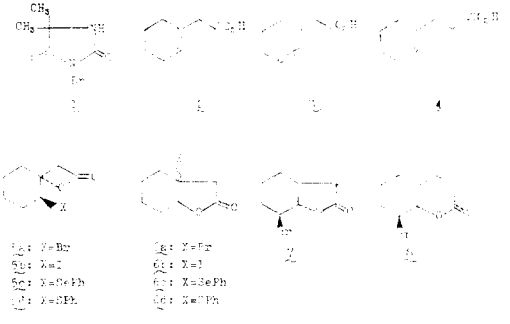
The bromolactonization, intramolecular reaction which involves trapping of the intermediate bromonium ion by internal nucleophile CO_2H, has usually required drastic reaction conditions employing Br_2[1], sodium hypobromite[2], acetyl hypobromite[3], and N-bromosuccinimide[4].

The recent successful application of N-bromosuccinimide to mild bromolactonization[5] suggests the use of N-bromohydantoins which are comparable with N-bromosuccinimide in allylic bromination[6] and oxidation[7].

Here we wish to describe a new method of the milder bromolactonization employing 3-bromo-5,5-dimethylhydantoin (1), which is carried out in dry N,N-dimethylformamide (DMF) at room temperature.

By an electrophilic attack of Br^+, which is presumably generated by heterolytic cleavage of N-Br bond of **1** in aprotic polar solvent DMF, on the double bond of unsaturated acids, a polar intermediate bromonium ion or a closely related equivalent is formed and then attacked by intramolecular nucleophile CO_2H to produce the bromolactone. Stereochemistry is tentatively assigned on mechanistic grounds.

The experimental procedure is as follows: To a solution of unsaturated acid (3.6 mmole) in 5 ml of dry DMF, a solution of 1(4.3 mmole) in 5 ml of dry DMF is added at room temperature under nitrogen over 5 minutes. 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. After drying of the ethyl acetate solution with $MgSO_4$ and concentration *in vacuo*, the crude reaction mixture is purified with silica-gel column chromatography to afford bromolactone; the unsaturated acids **2**[8a],



3[8b], and **4**[8c] give bromolactones **5**[9] (91%), mp 67°C, **7**[9] (82%), mp 59°C, and **8**[9] (58%), caramel respectively.

This mild procedure, using easily available cyclization initiator **1**, gives regio- and stereo-controlled bromolactones. Cyclization of **2** with I_2[10a], PhSeCl[10b], or PhSCl[10c] gives the more thermodynamically stable γ-lactones **6b**, **6c**, or **6d** which are converted through rearrangement of kinetically controlled β-lactones **5b**, **5c**, or **5d** respectively. However, by our mild bromolactonization method initially formed spiro-β-lactone **5a**, which is not rearranged to the more stable corresponding lactone **6a**, can completely be isolated in spite of usual work-up and silica-gel column chromatography.

In connection with studies on the reaction using N-haloimides in aprotic polar solvent, we are currently engaged in examining the limitation and mechanism of this bromolactonization. We are also exploring the possibility of applying optically active N-bromohydantoin, which is prepared from optically active α-amino acid, to asymmetric bromolactonization.

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