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A Novel Bromolactonization Reaction Using Racemic 3-Bromo-5-isobutyl-5-methylhydantoin

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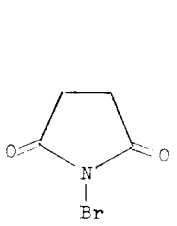
Abstracts ☐ By using racemic 3-bromo-5-isobutyl-5-methylhydantoin (**3a'**) in dry N, N-dimethylformamide which is a model reagent for asymmetric bromolactonization, bromolactonization of a series of olefinic acids was carried out to furnish corresponding bromolactones in moderate yields.

Keywords ☐ Bromolactonization, 3-Bromo-5-isobutyl-5-methylhydantoin, N, N-Dimethylformamide, Bromolactone, A model reagent for asymmetric bromolactonization.

Halolactonization, a very efficient method for regio-and stereoselective introduction of functional groups on the double bond of olefinic acid, has been prominently applied to the synthesis of biologically very important products.[1~3] In connection with the importance of halolactonization in synthetic organic chemistry, we have developed mild procedures for it by employing N-haloimides i.e., N-bromosuccinimide (**1**),[4a] N-bromophthalimide (**2**),[4b] and 3-halo-5, 5-disubstituted hydantoins (**3**),[4c,5] in aprotic polar solvent, N,N-dimethylformamide.

The methods by which optically active lactone, a very important intermediate in synthetic organic chemistry can be obtained, are (1) transformation of optically active olefinic acid obtained by chemical resolution to optically



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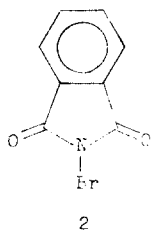

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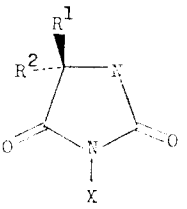

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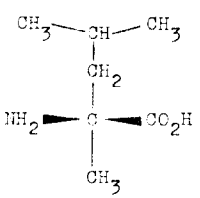

4

3a R^1=CH_3, R^2=$(CH_3)_2CH_2CH$, X=Br

3b R^1=CH_3, R^2=$(CH_3)_2CH_2CH$, X=H

3c R^1,R^2=CH_3, X=Br

Fig 1:

active lactone (2) asymmetric synthesis of lactone. Recently the optically active lactones obtained by halolactonization of optically active olefinic acids were successfully applied to the synthesis of erythromycin[2b] and rifamycin.[2c] However, the latter is thought to be more effective than the former since it is theoretically possible to obtain optically active lactone from achiral starting compound in 100% optical yield. We especially have taken much interest in **3**, since optically active **3a** which is thought to be easily available via optically active hydantoin (**3b**) starting from L-amino acid (**4**), can be used as a reagent for asymmetric synthesis of lactone. There is the sole report[6] on the asymmetric synthesis of lactone, which was the reaction of dimethylsulfoxonium methylide with optically active oxazepinedione derivatives.

We recently found that among 3-halo-5, 5-disubstituted hydantoins (**3**), 3-bromo-5, 5-dialkylsubstituted hydantoin was the most convenient halolactonization reagent and from this limitation on **3** as the reagent for halolactonization, we chose optically active 3-bromo-5-isobutyl-5-methylhydantoin (**3a**) as the model reagent for asymmetric synthesis of lactone, which was thought to be easily obtained via optically active 5-isobutyl-5-methylhydantoin (**3b**) starting from α-methyl-L-isoleucine (**4**). We thought that when bromolactonization of olefinic acids was performed under appropriate reaction condition, **3a** could differentiate the enantioface of the double bond of olefinic acids because of the introduction of chirality in 5-C position orginating from **4**.

In the first place for the purpose of investigating the chemical reactivity of optically active 3-bromo-5, 5-dialkylhydantoin (**3**) as the reagent for asymmetric bromolactonization reaction, by employing racemic 3-bromo-5-isobutyl-5-methylhydantoin (**3b'**) which show chemical reactivity identical to optically active **3b**, the bromolactonization of a series of olefinic acids (**5**—**8**) was performed.

According to the usual method,[7] the preparation of racemic **3b**, obtained from methyl ketone, with bromine (1 mol eq) in 18% aqueous NaOH (1 mol eq) furnish racemic **3b'** as white crystals (mp 145°C) in 86% yields: IR (nujol) cm^{-1} 3450, 3050-3160, 1700. The bromolactonization was performed as follows: To a stirred solution of a series of olefinic acids (3.6 mmole) in dry DMF (5ml) under nitrogen at 20~25°C was added a solution of racemic **3b'** (4.3 mmole) in dry DMF (5ml). After being stirred for 20 hours, the reaction mixture was diluted with ethyl acetate and organic solution was successively washed with 5% $NaHCO_3$, H_2O, and sat. NaCl. Filtration and evaporation in vacuo led to the formation of neutral components which was then purified with silica-gel column chromatography to give pure bromolactones: the olefinic acids **5**,[8a] **6**,[8b] **7**,[8c] and **8**[8d] gave bromolactones **9**(65%), **10**(14%), **11**(56%), and **12** (89%) respectively.

9: colorless crystalline solid, mp 67°C (EtOAc-Benzene=1: 10); Rf 0.42 (Hexane: Benzene=1:10); IR (nujol) ν_{max} 1825 (β-lactone); NMR (CCl_4) 1.30~2.50 (m, 8H, CH_2 ×4), 3.04 (1H, d, J=16.0 Hz, one of CH_2CO_2), 3.30 (1H, d, J=16.0 Hz, one of CH_2CO_2); Anal. Calcd. for $C_8H_{11}O_2Br$, C, 43.82; H, 5.06 Found C, 43.70; H, 5.09.

10: colorless crystalline solid, mp 57°C (EtOAc:); IR (**nu**jol) ν_{max} 1775(γ-lactone), NMR (CCl_4) 1.53 (3H, s, CH_3), 1.56 (3H, s, CH_3), 2.83 (1H, dd, J=15.0 and 8.0 Hz, one of CH_2CO_2), 3.17 (1H, dd, J=15.0 and 7.6 Hz, one of CH_2CO_2), 4.37 (1H, dd, J=8.0 and 7.6 Hz, CHBr); Anal. Calcd. for $C_6H_9O_2$

Br; C, 37.33; H, 4.70; Found C, 37.13; H, 4.81.

11: colorless crystalline solid, mp 55°C (EtOAc: Bezene=1:10); Rf 0.74 (Benzene: EtOAc: EtOH=20:2:3), IR (nujol) ν_{max} 1780 (γ-lactone); NMR (CCl_4) 2.85 (1H, dd, J=18.0 and 7.2 Hz, one of CH_2CO_2), 3.12 (1H, dd, J=18.0 and 6.6 Hz, one of CH_2CO_2), 4.10~4.45 (1H, m, CHBr), 5.55 (1H, d, J=6.0Hz, CHO), 7.37 (5H, s, aromatics); Anal. Calcd. for $C_{10}H_9O_2Br$: C, 49.86; H, 3.77; Found C, 50.00; H, 3.77.

12: colorless crystalline solid, mp 59°C (EtOAc:Benzene=1:10); Rf 0.5 (Benzene:EtOAc =10:1); IR (nujol) ν_{max} 1770 (γ-lactone); NMR ($CDCl_3$) 1.12~3.02 (7H, m, $CH_2\times3$ and CH), 2.18 (1H, dd, J=22.0 and 3.2 Hz, one of CH_2CO_2), 2.55 (1H, dd, J=22.0 and 6.0 Hz, one of CH_2CO_2), 4.32~4.60 (2H, m, CHBr and CHO); Anal. Calcd. for $C_8H_{11}O_2Br$; C, 43.86; H, 5.06; Found C, 43.74; H, 5.10.

In the case of cyclic-3-olefinic (5) and cyclic-4-olefinic acid (8), the corresponding bromolactones **9** and **12** were completely regio-and stereoselectively in good yields, 89% and 65% respectively. It was so sufficiently to attract our interest that the complete isolation of unstable kinetically controlled α-bromo-β-spirolactone (**9**) was similary achieved as in the case of other N-haloimides.[4a,4b,4c] The bromolactonization of acyclic-2-olefinic acids **6** and **7** furnished corresponding bromolactones **10** and **11** regio-and stereoselectively. The yield of the former (56 %) is moderate, but that of the latter (14%) is not sufficient. Although racemic **3a′** satisfied the requirement for convenient reagent of halolactonization, **3a′** is not so efficient as 3-bromo-5, 5-dimethylhydantoin. The reason was rationalized on the fact that the alkyl substituents of 5-C, methyl and iso-butyl group of **3a′** more congested than two methyl groups of 5-C of **3c**. In conclusion, the chemical reactivity of racemic **3a′** as a model reagent for asymmetric bromolactonization is sufficient, only if we chose appropriate olefinic acid for a substrate.

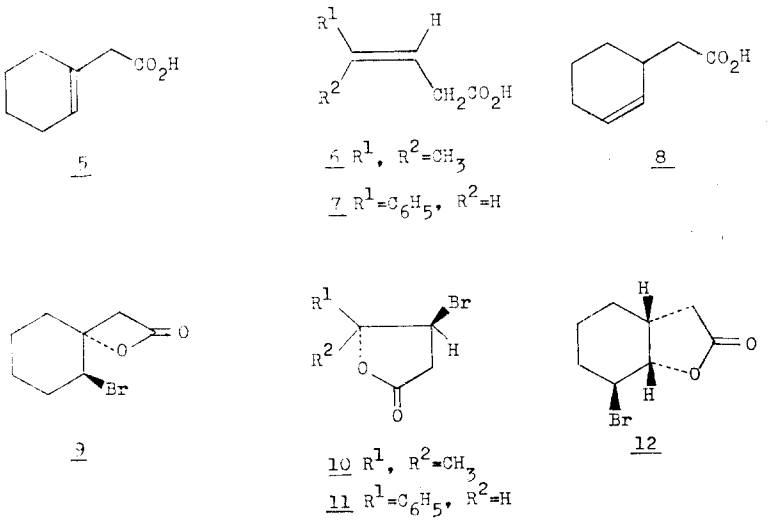

Fig. 2

Now we have being engaged in asymmetric bromolactonization using chiral 3-bromo-5, 5-dialkyl substituted hydantoins prepared from

natural and unnatural α-amino acids.

ACKNOWLEDGMENT

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