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A Regioselective Synthesis of β-Lactones; Bromolactonization of 2-Substituted-1-cyclohexenyl-1-acetic acid

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Bromolactonization of 2-substituted-1-cyclohexenyl-1-acetic acids with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and potassium tertiary butoxide (*t*-BuOK) in anhydrous DMF was found to proceed in a highly regioselective manner. The reaction predominantly resulted in the formation of β-lactones (greater than 96%).

Key words: Bromolactonization, β-Lactone

INTRODUCTION

β-Lactones have been detected as central structural unit in physiologically active natural products like obafloriη (Tymiak *et al.*, 1985) and lipstatin (Barbier, P. *et al.*, 1988). There have been wide applications of β-lactones in synthesis such as the stereospecific CO_2 elimination to form di- and tri-substituted alkenes or Grignard addition to the carbonyl group (Mulzer, 1991). Various synthetic approaches for β-lactones include cycloalkylation from β-halo acids, cycloacylation from β-hydroxy acids and C-C connections using metal catalysts (Mulzer, 1991).

Lactonization, effected with a variety of electrophiles, has been widely used in organic synthesis as an efficient synthetic tool for constructing various lactone target molecules and selective introduction of a hydroxy group onto the original ring by cleavage of the lactone cyclization product (Terashima *et al.*, 1977; Harding *et al.*, 1991). We, herein, wish to report a regioselective synthesis of β-lactones *via* bromolactonization of 2-substituted-1-cyclohexenyl-1-acetic acids.

MATERIALS AND METHODS

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Beckmann IR 20 A Infrared Spectrometer and reported in cm^{-1}. ^{1}H-NMR spectra were recorded on Perkin-Elmer R32 NMR Spectrometer using TMS as an internal standard and chemical shifts are reported as ppm units. Thin-layer chromatography was performed on E. Merck silica gel GF-254 precoated plates and the identification was done with UV light and colorization with spray of concentrated sulfuric acid followed by heating. Column chromatography was carried out on silica gel (Wakogel Q-20). 1,3-Dibromo-5,5-dimethylhydantoin (DBH) was prepared according to literature (Orazi *et al.*, 1952). β,γ-Unsaturated acid substrates for bromolactonization were prepared according to literature (Newman *et al.*, 1944; Cook *et al.*, 1936).

2-Benzyl-1-cyclohexenyl-1-acetic Acid

2-Benzylcyclohexanone (Stork *et al.*, 1963) (12 g, 0.064 mole) was treated with KOH (4.203 g, 0.064 mole) and acetonitrile (77 ml) acording to literature (Dibiase *et al.*, 1979). The reaction afforded a mixture of α,β- and β,γ-unsaturated nitrile (9 g, 0.043 mole). The product was then treated with KOH (11.2 g, 0.215 mole) in aqueous methanol (1 : 1, 38 ml). The mixture was heated at reflux for 18 hr. After cool to room temperature the mixture was acidified and the solvent was removed *in vacuo*. The residue was diluted with water (500 ml) and extracted with dichloromethane (3×100 ml). The organic layer was dried over magnesium sulfate and concentrated to give a crude unsaturated acid. The mixture of crude unsaturated acid was directly treated with diazomethane in ether. The solvent was removed in vacuo to afford a crude product (4 g, 35%). After separation by column chromatography (ether, hexane=1 : 9) of the crude product, methyl (2-benzyl-1-cyclohexenyl)-1-acetate (2 g, 0.008 mole) was

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treated with KOH (2.16 g, 0.032 mole) in aqueous methanol (1 : 1, 20 ml). The mixture was heated at reflux for 4 hr and methanol was removed in vacuo. The residue was diluted with water (300 ml) and extracted with dichloromethane (3×50 ml). The aqueous layer was acidified with conc-HCl and extracted with dichloromethane (3×50 ml). The organic layer was washed with water (30 ml) and brine (30 ml), and dried over magnesium sulfate. The solvent was removed in vacuo to give the product (1.72 g, 90%) as a white solid; m.p. 59.5-60.5℃ (crystal from hexane), IR (KBr) 2500-3300, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4-2.4 (8H, m, 4CH_2), 3.24 (2H, s, phCH_2), 3.5 (2H, s, -CH_2CO-), 7.45 (5H, s, ArH), 11 (1H, s, -COOH).

Bromolactonization

General procedure: To a solution of t-BuOK in anhydrous DMF was added slowly a solution of β,γ-unsaturated acid in anhydrous DMF. The mixture was stirred for 30 min and a solution of 1,3-dibromo-5,5-dimethyl hydantoin (DBH) in DMF was added dropwise. The resulting mixture was stirred for 20 hr at a given temperature. The reaction mixture was diluted with ethyl acetate (300-400 ml) and washed with saturated sodium bicarbonate solution (3×50 ml), water (5×30 ml) and brine (2×30 ml). The organic layer was then dried over magnesium sulfate and concentrated in vacuo to give a crude product. The crude product was purified by column chromatography.

a) Bromolactonization of 2-methyl-1-cyclohexenyl-1-acetic acid

i) The reaction of 2-methyl-1-cyclohexenyl-1-acetic acid **8** (217 mg, 1.407 mmole) with *t*-BuOK (173 mg, 1.1 eq) and dibromohydantoin (443 mg, 1.1 eq) in anhydrous DMF (15 ml) at room temperature afforded β-lactone **9** (194 mg, 78%); m.p. 48-49℃ (crystal from hexane); IR (nujol) 1840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10-2.50 (8 H, m, CH_2×4), 1.82 (3H, s, CH_3), 2.96 (1H, d, J=18 Hz, CH_2CO), 3.58 (1H, d, J=18 Hz, CH_2CO) and γ-lactone **10** (7 mg, 2%); m.p. 80-81℃ (crystal from hexane); IR (nujol) 1775 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30-2.50 (8H, m, CH_2×4), 1.57 (3H, s, CH_3), 2.97 (1H, d, J=18 Hz, CH_2CO), 3.21 (1H, d, J=18 Hz, CH_2CO).

ii) The reaction with 2-methyl-1-cyclohexenyl-1-acetic acid 8 (337 mg, 2.185 mmole) with *t*-BuOK (269 mg, 1.1 eq) and DBH (687 mg, 1.1 eq) in anhydrous CH_3CN (15 ml) at room temperature afforded β-lactone **9** (384 mg, 76%) and γ-lactone **10** (14 mg, 3%).

iii) The reaction with 2-methyl-1-cyclohexenyl-1-acetic acid **8** (321 mg, 2.080 mmole) with *t*-BuOK (240 mg, 1 eq) and DBH (1.189 g, 2 eq) in anhydrous DMF (25 ml) at 4℃ afforded β-lactone **9** (289 mg, 82%) and γ-lactone **10** (trace).

iv) The reaction with 2-methyl-1-cyclohexenyl-1-acetic acid **8** (254 mg, 1.647 mmole) with t-BuOK (190 mg, 1 eq) and DBH (942 mg, 2 eq) in anhydrous DMF (20 ml) at −15℃ afforded β-lactone **9** (172 mg, 72%) and γ-lactone **10** (trace).

b) Bromolactonization of 2-ethyl-1-cyclohexenyl-1-acetic acid

The reaction of 2-ethyl-1-cyclohexenyl-1-acetic acid **11** (574 mg, 3.410 mmole) with *t*-BuOK (458 mg, 1.1 eq) and DBH (4.950 g, 1.1 eq) in anhydrous DMF (15 ml) at room temperature afforded β-lactone **12** (427 mg, 79%) as an oil; IR (nujol) 1835 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.08 (3H, t, J=7 Hz, CH_2CH_3), 1.30-2.60 (10 H, m, CH_2×5), 3.00 (1H, d, J=17 Hz, CH_2CO), 3.68 (1H, d, J=17 Hz, CH_2CO) and γ-lacone **13** (13 mg, 1%) as an oil; IR (nujol) 1780 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10 (3H, t, J=7 Hz, CH_2CH_3), 1.30-2.70 (10H, m, CH_2×5), 3.12 (1H, d, J=17 Hz, CH_2CO), 3.58 (1H, d, J=18 Hz, CH_2CO).

c) Bromolactonization of 2-phenyl-1-cyclohexenyl-1-acetic acid

i) The reaction of 2-phenyl-1-cyclohexenyl-1-acetic acid **11** (200 mg, 0.926 mmole) with *t*-BuOK (114 mg, 1.1 eq) and DBH (291 mg, 1.1 eq) in anhydrous DMF (15 ml) at room temperature afforded β-lactone **12** (177 mg, 75%) as a white solid; m.p. 84℃ (crystal from hexane); IR (nujol) 1830 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20-2.80 (8H, m, CH_2×4), 3.06 (1H, d, J=17 Hz, CH_2CO), 3.53 (1H, d, J=18 Hz, CH_2CO), 7.20-7.70 (3H, m, Ar-H), 7.70-8.10 (2H, m, Ar-H).

ii) The reaction of 2-phenyl-1-cyclohexenyl-1-acetic acid **11** (236 mg, 1.092 mmole) with *t*-BuOK (126 mg, 1 eq) and DBH (625 mg, 2 eq) in anhydrous DMF (15 ml) at room temperature afforded β-lactone **12** (245℃ mg, 82%) as a white solid.

d) Bromolactonization of 2-benzyl-1-cyclohexenyl-1-acetic acidi)

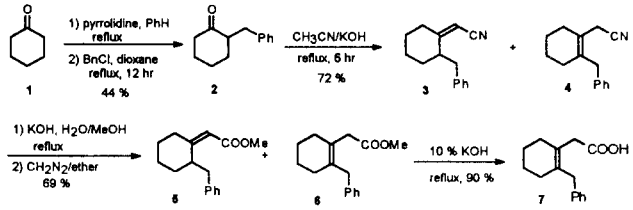
The reaction of 2-benzyl-1-cyclohexenyl-1-acetic acid **11** (200 mg, 0.913 mmole) with *t*-BuOK (106 mg, 1 eq) and DBH (260 mg, 1 eq) in anhydrous DMF (13 ml) at room temperature afforded β-lactone **12** (187 mg, 74%) as a white solid; m.p. (needle from hexane) 83-84℃; IR (nujol) 1805 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30-2.50 (8H, m, CH_2×4), 3.07 (1H, d, J=17 Hz, CH_2CO), 3.80 (1H, d, J=18 Hz, CH_2CO), 7.30 (5H, s, Ar-H).

ii) The reaction of 2-benzyl-1-cyclohexenyl-1-acetic acid **11** (59 mg, 0.259 mmole) with *t*-BuOK (30 mg, 1 eq) and DBH (74 mg, 1 eq) in anhydrous DMF (5 ml) at −15℃ afforded β-lactone **12** (51 mg, 73%) as a white solid.

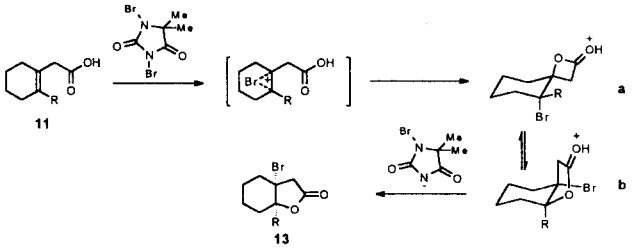
RESULTS AND DISCUSSION

Synthesis of Substrates for Bromolactonization

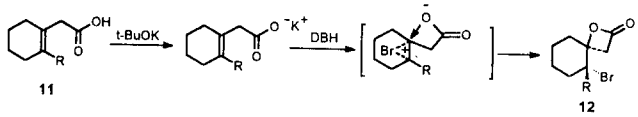
Substrates 2-methyl-, 2-ethyl- and 2-phenyl-1-cyclo-



Scheme 1. Synthesis of 2-benzyl-1-cyclohexenyl-1-acetic acid.



Scheme 2. Proposed rearrangement process of β-lactone to γ-lactone during bromolactonization without base.



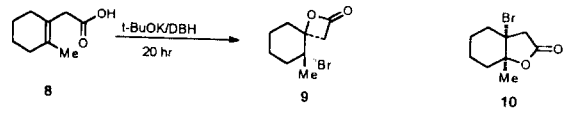
Scheme 3. Bromolactonization with *t*-BuOK as a base.

hexenyl-1-aceic acids were prepared by the known method (Cook *et al.*, 1936; Koo, 1985; Newman *et al.*, 1944). 2-Benzyl-1-cyclohexenyl-1-acetic acid was prepared as shown in scheme **1**. The treatment of cyclohexanone with pyrrolidine at reflux afforded enamine intermediate and the subsequent treatment with benzyl chloride provided 2-benzylcyclohexanone **2** in 44% yield (Stork *et al.*, 1963). Condensation of **2** with acetonitrile in the presence of KOH afforded a 1 : 1 mixture of **3** and **4** in 72% yield. The direct hydrolysis of the mixture by methanolic KOH followed by the treatment with diazomethane afforded a mixture of ester **5** and **6** in 69% yield. After chromatographic separation, ester **6** was hydrolyzed by 10% KOH in H_2O-MeOH (1 : 1) to give the desired substrate **7** in 90% yield.

Bromolactonization

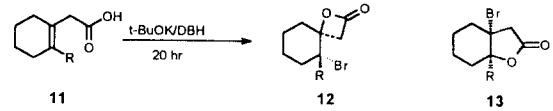
Since Jew *et al.* reported bromolactonization using NBS-DMF system (Jew *et al.*, 1979), the reaction of 1-cyclohexenyl-1-acetic acid with N-bromosuccinimide (NBS), N-bromophthalimide (NBP) and N-bromohydanoin (NBH) was examined (Cook *et al.*, 1979). The reaction afforded β-lactone as a sole product. The result was ascribed to the substitution pattern of the electrophilic site (β-position was less substituted than γ-position). This brought our attention to the reactivity of the 2-substituted-1-cyclohexenyl-1-acetic acids that

Table I.



Reaction Condition			Yield (%)		Total Yield
t-BuOK	DBH	Temp (℃)	**9**	**10**	
	1.1 eq	r.t.	49	43	92
1.1 eq	1.1 eq	r.t.	78	2	80
1.1 eq	2 eq	4	82	trace	82
1 eq	2 eq	−15	72	trace	72

Table II.



	Reaction Condition			Yield (%)		Total Yield
R-	*t*-BuOK	DBH	Temp. (℃)	**12**	**13**	
Et-	1.1 eq	2 eq	r.t.	79	1	80
Ph-	1.1 eq	1.1 eq	r.t.	76		76
	1.1 eq	2 eq	4	82		82
PHCH2-	1 eq	1 eq	r.t.	74	trace	74
	1 eq	1 eq	−15	73	trace	73

contained the similar substitution pattern at double bond. Initially bromolactonization was carried out with 2-methyl-1-cyclohexenyl-1-acetic acid by varying the amount of brominating agent (DBH) or temperature to find an optimum condition. The results are summarized in Table I. No regioselectivity was observed in the reaction without *t*-BuOK. It is believed that kinetically favored β-lactone is rearranged to thermodynamically favored γ-lactone via oxonium intermediate **a** and **b** as shown in scheme 2. This type of rearrangement was also observed by other groups (Barnett, *et al.*, 1975; Nicolaou, *et al.*, 1979).

However, excellent regioselectivity was obtained in all reactions using t-BuOK as a base. Having obtained an excellent selectivity, the bromolactonization was further examined with 2-ethyl-, 2-phenyl- and 2-benzyl-1-cyclohexenyl-1-acetic acid. The results are summarized in Table II. All the reactions afforded β-spirolactones in highly regioselective manner. The regioselectivity was greater than 96%. The reaction may proceed through a formation of potassium carboxylate salt followed by cyclization in 4-exo mode to give a β-spirolactone as shown in Scheme 3. The formation of potassium salt of carboxylic acid would eliminate the possibility of forming oxonium intermediates a and b as shown in Scheme 1 so that prevent the rearrangement of β-spirolactone to γ-lactone.

Bromolactonization of 2-substituted-1-cyclohexenyl-1-acetic acid using DBH and *t*-BuOK was examined and the reaction proceeded in highly regioselective manner. The methodology would give ample applica-

tions in organic synthesis especially in constructing β-lactone skeletons.

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