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Unusual Iodine Catalyzed Lactonization of γ-Methyl-γ,δ-pentenoic Acids: A Facile Synthesis of γ,γ-Dimethyl-γ-butyrolactones

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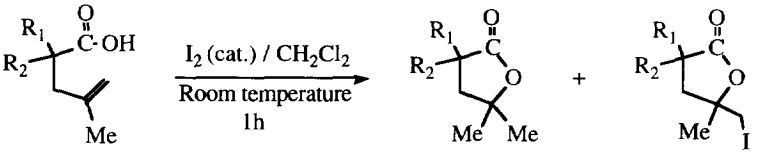
Abstract : γ,γ-Dimethyl-γ-butyrolactones were exclusively obtained from γ-methyl-γ,δ-pentenoic acids with a catalytic amount of iodine in good yields in methylene chloride.

The formation of halolactones from olefinic carboxylic acids, so-called "halolactonization", has been well recognized as one of the most useful construction process in organic synthesis, and the detailed understanding of the reaction mechanism and the procedures in most common use for halolactonization have been well recognized.[1] In connnection with our recent studies on the iodine-catalyzed cyclization reaction of 2-(β-methylallyl)phenols and 2-isobutenyl phenols to the corresponding 2,2-dimethyl-2,3-dihydrobenzofurans,[2] we describe herein a novel γ-lactonization of γ-methyl-γ,δ-pentenoic acids **1** in the presence of a catalytic amount of iodine to the corresponding γ,γ-dimethyl-γ-butyrolactones **2**.

Various α-carboxy-γ,γ-dimethyl-γ-butyrolactones[3] (entry 1~6 in Table 1) and γ,γ-dimethyl-γ-butyrolactones (entry 7~8 in Table 1) were obtained in excellent yields through the iodine-catalyzed lactonization of the corresponding β-methallyl malonic acids and their monodecarboxylated acids **1**[4] at room temperature in dichloromethane for 1 h, but trace amounts of iodinated products were detected in NMR analysis (Scheme 1 and Table 1).

We examined the lactonization reactions of α,α-diphenyl-γ-methyl-γ-pentenoic acids (**1i**)[6] with various halogens in dichloromethane without presence of base (Table 2), whereas treatment of **1i** in conc. H_2SO_4



1a~i → **2a~i** 85 ~ 99 % + **3a~i** trace

Scheme 1

Table 1. Iodine-catalyzed lactonization of γ-methyl-γ,δ-pentenoic acid derivatives.[a]

Entry	Acid	R_1	R_2	Catalyst (equiv.)	Product ratio[b] (**2** : **3**)	Isolated yield of **2** (%)
1	**1a**	H	COOH	I_2 (0.2)	98 : 2	85
2	**1b**	CH_3	COOH	I_2 (0.2)	100 : 0	95
3	**1c**	CH_2CH_3	COOH	I_2 (0.2)	97 : 3	88
4	**1d**	$CH_2CH_2CH_2CH_3$	COOH	I_2 (0.2)	99 : 1	95
5	**1e**	$CH_2CH{=}CH_2$	COOH	I_2 (0.2)	97 : 3	93
6	**1f**	Benzyl	COOH	I_2 (0.2)	100 : 0	93
7	**1g**	$CH_2CH_2CH_2CH_3$	H	I_2 (0.2)	97 : 3	85
8	**1h**	Benzyl	H	I_2 (0.2)	98 : 2	89

[a] Reaction condition : I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 1 h. [b] Determined by ^{1}H NMR (200 MHz) and gave the satisfactory spectral data (see ref. 3a, and 5).

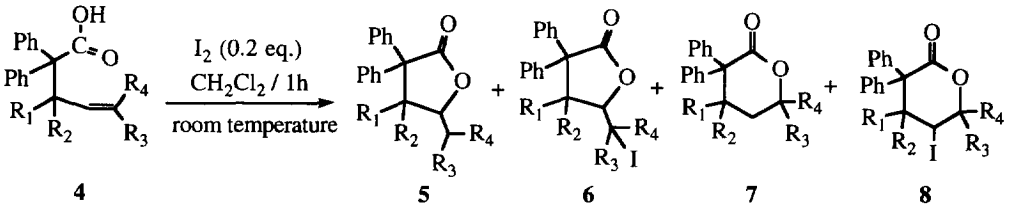
according to the literature[6(b)] gave **2i** in 75 % yield. Also the lactonization of α,α-diphenyl-γ,δ-pentenoic acid, β-methyl-γ,δ-pentenoic acid, β,β-dimethyl-γ,δ-pentenoic acid, δ,δ-dimethyl-γ,δ-pentenoic acid, and δ-methyl-γ,δ-pentenoic acid under the same conditions as above were examined (Scheme 2, and Table 3). The results in **Table 2** and **Table 3** indicated that a catalytic amount of iodine is highly effective to produce γ,γ-dimethyl-γ-butyrolactones **2**.

Although the reaction was conducted in a dry aprotic neutral solvent such as methylene chloride to avoid the external proton source which may generate HI with iodine,[4(a)] it was assumed that the reaction of γ-methyl-γ,δ-pentenoic acid (**1**) with iodine should generate HI. To prove the effect of free carboxyl group, the treatment of α,α-diphenyl-γ-methyl-γ,δ-pentenoic acid (**1i**) by the literature method[1] (aq. $NaHCO_3$,

Table 2. Lactonizations of α,α-diphenyl-γ-methyl-γ,δ-pentenoic acid (**1i**) in the presence of various halogens.

Entry	Halogen (equiv.)	Solvent	Reaction condition	Product ratio[a]		Total yield (%)
				2i	**3i**[b]	
1	I_2 (0.2)	CH_2Cl_2	room temperature / 1 hr	99	1	99
2	I_2 (3.0)	CH_2Cl_2	room temperature / 1 hr	94	6	99
3	ICl (0.2)	CH_2Cl_2	room temperature / 1 hr	75	25 (X = I)	75
4	IBr (0.2)	CH_2Cl_2	room temperature / 1 hr	67	33 (X = I)	82
5	Br_2 (0.2)	CH_2Cl_2	room temperature / 1 hr	73	27 (X = Br)	90
6	Br_2 (3.0)	CH_2Cl_2	room temperature / 1 hr	9	91 (X = Br)	92
7	Cl_2 (0.2)[c]	CH_2Cl_2	room temperature / 1 hr	100	0	43

[a] Determined by ^{1}H NMR (200 MHz) analysis of the reaction mixture after column chromatography.
[b] Typical halogenated product. [c] 2 Mol solution in DMF.



4 5 6 7 8

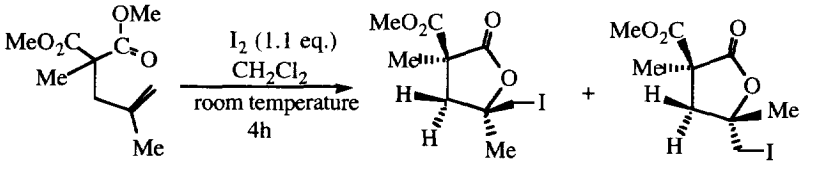
Scheme 2

Table 3. Lactonizations of substituded α,α-diphenyl-γ-methyl-γ,δ-pentenoic acids.

Entry	Substituents				Product composition (% yield)			
	R_1	R_2	R_3	R_4	**5**	**6**	**7**	**8**
1	H	H	H	H	86[a]	10[a]	-	-
2	Me	H	H	H	94[b] (cis /trans = 1)[a]	-	-	6[b] (trans)[a]
3	Me	Me	H	H	26[a]	-	42[b]	15[a]
4	H	H	Me	H	13[a]	18 (trans)[a]	-	-
5	H	H	Me	Me	-	-	49[b]	10[b]

[a] Determined by ^{1}H NMR (200 MHz) analysis of the mixture after column chromatography. [b] Isolated yield.

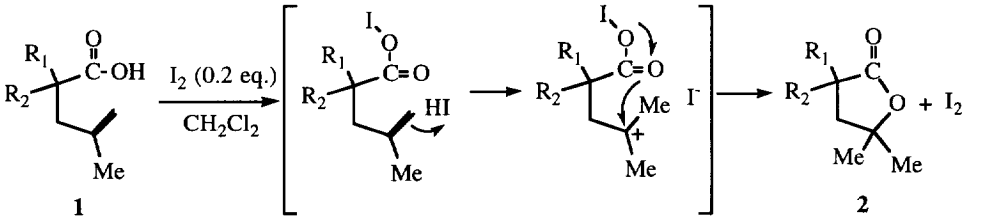
2 eq. / MeCN / I_2, 1.1eq. / 24 h) resulted in formation of the ioinated product, α,α-diphenyl-γ-iodomethyl-γ-methyl-γ-butyrolactone (**3i**)[7] in 97.7 % yield. The reaction of dimethyl methyl (β-methallyl)malonate (**8**) with iodine (1 equiv./ CH_2Cl_2 / room temperature, 4 h) gave the usual iodolactones **9** (92 %) as a diastereomeric mixture (syn/anti = 1/2) proved by ^{1}H NMR (300 MG) and NOE (Scheme 3). These results show that free carboxylic acid which should generate HI with iodine without presence of base was crucial to the iodine-catalyzed lactonization of γ-methyl-γ,δ-pentenoic acids for γ,γ-dimethyl-γ-butyrolactones.



8 **9**

Scheme 3

A plausible mechanism of γ-methyl-γ,δ-pentenoic acid **1** with iodine is illustrated in **Scheme 4**. The key feature of the mechanism may involve the reaction of HI, which is initially formed by the interaction of iodine with free carboxylic acid, to the double bond generating carbocation, and the steric hindrance of γ-substituted methyl group may be effective to prohibit addition of iodine to the double bond.



Scheme 4

Typical experimental procedure for the synthesis of α-carboxy-α-methyl-γ,γ-dimethyl-γ-butyrolactones **(2b)**[8] : Iodine (0.25 g, 1mmol) was added to a stirred solution of **1b** (0.86 g, 5 mmol) in dry dichloromethane. After stirring for 1 hour, the organic layer was quenched with a 5 % aqueous sodium thiosulfate solution to remove iodine. After usual extractive work-up, the crude product was purified by crystallization from hexane or preferably, by silica gel column chromatography (1/10 acetone / hexane) to give **2b** (0.82 g, 95 %).

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7. α,α-Diphenyl-γ-iodomethyl-γ-methyl-γ-butyrolactone (**3a**) ; a white solid; m.p = 151 °C ; ^{1}H nmr (20 MHz, $CDCl_3$) ; δ 1.51 (s, 3H), 2.99 (d, J = 13.9, 1H), 3.20 (d, J = 10.4, 1H), 3.31 (d, J = 10.4, 1H), 3.34 (d, J = 13.9, 1H), 7.22~7.43 (m, 10H). ; ms (70 eV) m/z (rel. intensity) 368 (M+, 7), 221 (15.4), 178 (11.2), 143 (38.5), 128 (24.3), 91 (100) ; IR : 1759 (s), 1499 (m), 1450 (m), 1296.7 (s), 1163 (s).
8. α-Carboxy-α-methyl-γ,γ-dimethyl-γ-butyrolactone (**2b**) ; a white solid; m.p = 126-127 °C ; ^{1}H nmr (200 MHz, $CDCl_3$) ; δ 1.50(s, 3H), 1.51(s, 3H),1.62(s, 3H), 2.08(d, 1H, J=13.6), 2.79(d,1H, J=13.6), 10.38 (br, 1H). ; ms (70 eV) m/z (rel. intensity) 173(M+, 21.9), 128(95.2), 113(56.5), 59(100) ; IR : 3179(s), 1769(s), 1725(s).

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