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Preparation of Seven-Membered and Medium-Ring Lactones by Iodo Lactonization

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Summary: Iodo lactonization of 6-heptenoic acid using bis(*sym*-collidine)iodine(I) hexafluorophosphate in methylene chloride led in high yield to 6-(iodomethyl)-hexanolide while with longer ω-ethylenic carboxylic acids the corresponding lactones were obtained in low yields; however, the presence of an oxygen atom in the carbon chain allowed the formation of medium-ring iodo lactones.

Lactonization of unsaturated acids mediated by iodine is a powerful process in synthetic organic chemistry.[1] Regio and stereoselective aspects of this reaction have been intensively studied and applied to the synthesis of complex organic molecules.[2] This methodology involves the treatment of metal carboxylates in either water[3] (sometimes in the presence of miscible[4] or nonmiscible[5] solvents) or organic solvents,[6] or carboxylic acids in organic solvents,[7] with electrophilic iodine sources such as iodine, *N*-iodosuccinimide, cyanogen iodide, or bis(*sym*-collidine)iodine(I) perchlorate. Formation of four-, five- and six-membered lactones has been reported. Attempts were made to obtain larger ring compounds;[8] however, only a few examples of seven-membered iodo lactones have been reported.[7c,9] The construction of medium rings by iodine-induced or, more generally, by an electrophile-induced cyclization[10] of alkenoic acids is rare.[2] In fact, the formation of medium rings remains as a significant problem in organic synthesis and lactonization methodology has proved difficult in this case,[11] owing to ring strain and transannular interactions.[12] The isolation of seven-membered and medium-ring lactones from natural sources[13] has heightened interest in developing new methods for preparing these compounds. In this paper we show that seven- to 11-membered lactones can be prepared by an iodonium-induced cyclization of simple unsaturated acids.

It has been reported that iodo lactonization of 4-oxa-6-heptenoic acid with bis(*sym*-collidine)iodine(I) perchlorate[14] led to the corresponding iodo lactone in 25% yield.[7c] We decided to explore the iodo lactonization of unsaturated carboxylic acids **2** using bis(*sym*-collidine)iodine(I) hexafluorophosphate (**1**)[15,16] for the formation of seven-, eight-, and 11-membered lactones. Reactions were conducted in methylene chloride at reflux (2 equiv of reagent **1**, 0.07 M solution), and the results are reported Table I. With 6-heptenoic acid (**2a**) we observed the formation of the ε-caprolactone (**3a**) in high yield. With 7-octenoic acid (**2b**) and 10-undecenoic acid (**2c**) cyclized and uncyclized oligomers were probably formed, according to TLC and ^{1}H NMR analysis. We have also checked the reactivity of 4-oxa-6-heptenoic acid (**4a**) with reagent **1**. Oxalactone **5a** has been obtained in 59% yield (see Table II). In fact, when reagent **1** (1.2 equiv) was stirred in methylene

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(15) The hexafluorophosphate anion was preferred to the perchlorate, owing to the explosive nature of perchlorate salts. Bis(*sym*-collidine)iodine(I) hexafluorophosphate (**1**) was prepared in two steps (91% overall yield) according to Lemieux and Morgan:[16] white solid mp 147 °C. Anal. Calcd for $C_{16}H_{22}F_6IP$: C, 37.35; H, 4.31; I, 24.69. Found: C, 37.42; H, 4.29; I, 24.66.

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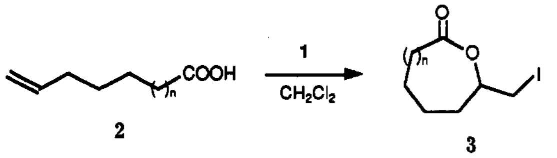
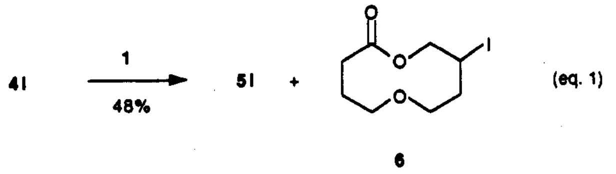
Table I. Iodo Lactonization of ω-Alkenoic Acids 2 Using Bis(*sym*-collidine)iodine(I) Hexafluorophosphate (1)

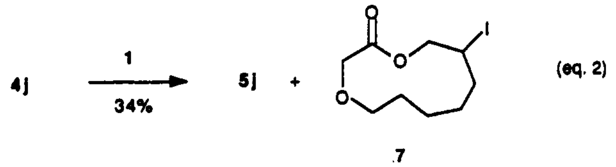


alkenoic acid		reaction time (h)	ring size	yield[a] (%)
n	no.			
1	**2a**	18	7	76
2	**2b**	4	8	5
5	**2c**	16	11	4

[a] Refers to material pure isolated by liquid chromatography (SiO_2).

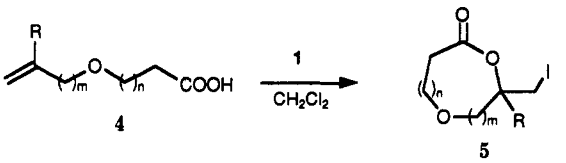
chloride (0.03 M solution) at reflux with n-oxa-ω-alkenoic acids **4**, seven- to 11-membered ring iodo lactones **5** were obtained as unique reaction products. Dilution of the reaction mixture (10^{-3} to 10^{-4} M solution) decreased the rate of the reactions without changing the yields appreciably. The examples in Table II attest to the generality of the method. The structures shown are supported by ^1H and ^{13}C NMR data (including DEPT or ^{13}C–^1H 2D correlation), as well as combustion analysis. Although chemical yields were not always high, it should be emphasized that these ring closures are made without resort to high dilution techniques. Except with acids **4i** and **4j**, the reaction shows a regioelectronic preference for an exo mode of closure, thus favoring the formation of products having the smaller ring sizes. This implies that for acids **4i** and **4j** the formation of the nine- and 10-membered lactones (**5i** and **5j** (eqs 1 and 2)) are probably disfavored due to nonbonding interactions.[17]





Comparison of the iodo lactone yields from acids **4a**, **4b** with those from acids **4c**, **4d**, **4e**, and **4g** shows the positional influence of the oxygen atom in the chain. The proximity of the oxygen atom to the carboxylic acid function seems favorable for cyclization. The low yield observed in the reaction of the acid **4h** is due to the competitive iodo etherification leading to a five-membered ether. Such competition is not observed with acids **4j**, **4k** since this would require the much more difficult formation of seven- or eight-membered ethers.

Table II. Iodo Lactonization of *n*-Oxa-ω-alkenoic Acids 4 Using Bis(*sym*-collidine)iodine(I) Hexafluorophosphate (1)



alkenoic acid				reaction time (h)	ring size	yield[a] (%)
R	m	n	no.			
H	1	1	**4a**	6	7	59
CH_3	1	1	**4b**	5	7	70.5
H	2	0	**4c**	6	7	75
CH_3	2	0	**4d**	7.5	7	75
H	2	1	**4e**	4	8	39
CH_3	2	1	**4f**	3.5	8	45
H	1	2	**4g**	10	8	8[b]
H	3	1	**4h**	15.5	9	2[c]
H	2	2	**4i**	10	9,10	48[d]
H	5	0	**4j**	9	10,11	34[e]
H	6	0	**4k**	22	11	21[f]

[a] Refers to material pure isolated by liquid chromatography (SiO_2). [b] 90% of **4g** was recovered. [c] 44% of 2-iodomethyloxolane was isolated. [d] 50:50 mixture of nine- and 10-membered iodo lactones (see eq 1). [e] 62:38 mixture of 10- and 11-membered iodo lactones (see eq 2). [f] formation of oligomers.

The improvement resulting from replacement of a methylene group by an oxygen atom has some precedent in the literature concerning the cyclization of chain molecules leading to the formation of medium- and large-ring compounds.[18] This effect is known also with normal ring compounds[19] and is probably due to relief of unfavorable CH···CH repulsions. In our case the relief of transannular interactions is one of the necessary conditions for cyclization. The second condition is, without doubt, the nature of the electrophile; reaction of bis(pyridine)iodine(I) hexafluorophosphate with acid **4a** gave only 20% of lactone **5a**, while acids **2a–2c** and **4a–4k** gave no lactone when iodine or NIS was used as the electrophile. This seems to imply that the mechanism of these cyclizations is different from that postulated for the iodine-induced cyclizations via a charge-transfer intermediate,[20] and the reaction may occur via an iodonium ion. However, details of the reaction mechanism are still being elucidated. This methodology will be applied to other electrophiles and to the preparation of medium ring ethers.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **3a–3c**, **5b–5k**, **6**, and **7** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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