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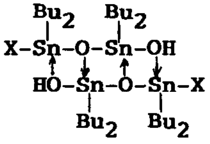
A Novel Template Effect of Distannoxane in Macrolactonization of ω-Hydroxy Carboxylic Acids

Junzo Otera,* Toru Yano, Yasuyuki Himeno, and Hitosi Nozaki
Department of Applied Chemistry, Okayama University of Science,
Ridai-cho, Okayama 700, Japan

Abstract: A novel template effect of 1,3-disubstituted tetrabutyldistannoxanes in macrolactonization of ω-hydroxy carboxylic acids has been disclosed.

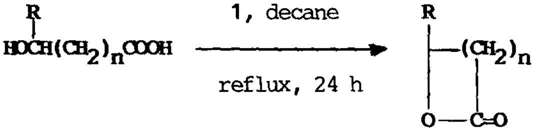
Intramolecular esterification of ω-hydroxy carboxylic acids provides the most direct synthetic method for macrolides.$^{1)}$ To this end, however, high dilution techniques or preliminary activations of functional groups are generally required for retarding intermolecular reactions. Recently, Steliou et al. disclosed that organotin oxides promoted direct macrolactonization of ω-hydroxy carboxylic acids$^{2a)}$ and later reported its successful synthetic application to macrolide antibiotics.$^{2b)}$ These papers prompted us to report here that 1-hydroxy-3-(pseudo)halotetrabutyldistannoxanes (**1**)$^{3)}$ serve as unique templates for macrolide formation by virtue of the characteristic dimeric structure shown below.



1a X = Cl
b = -NCS

The manipulation is quite simple. A decane solution (50 mL) of ω-hydroxy carboxylic acids (0.5 mmol) was heated at reflux in the presence of **1** (0.1 mmol) for 24 h. Evaporation of the solvent followed by column chromatography on silica gel furnished the desired lactones. Neither a high dilution technique nor a Dean-Stark apparatus was necessary. Commercial decane was

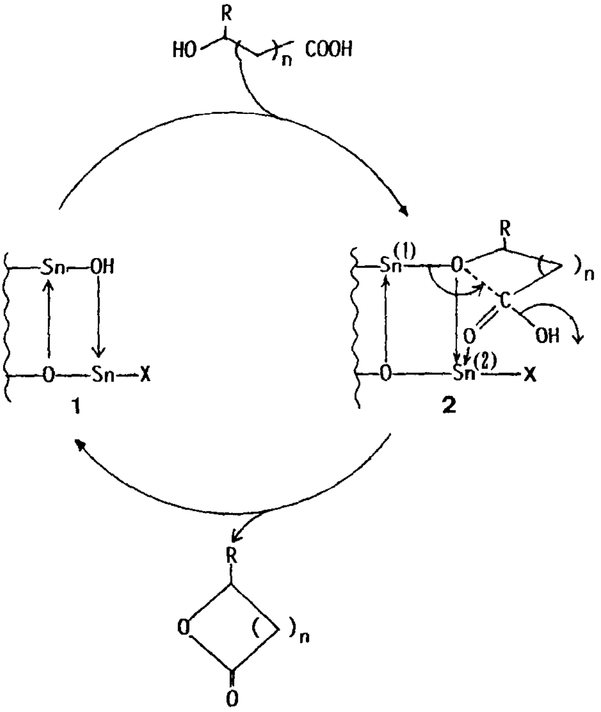
Table I. Distannoxane-catalyzed lactonization.



entry	n	R	cat.	isolated yields of lactones, %$^{a)}$	
1	14	H	**1a**	81	(60)$^{b)}$
2	13	H	**1a**	78	(43)
3	12	H	**1b**	19	
4		$\underline{n}$-C_6H_{13}		48	
5	11	H		20	
6		CH_3		--$^{c)}$	
7		$\underline{n}$-C_3H_7		--$^{c)}$	
8		$\underline{n}$-C_4H_9		63	(0)
9		$\underline{i}$-C_4H_9		56	
10		$\underline{n}$-C_6H_{13}		64$^{d)}$	
11	10	H	**1a**	--$^{e)}$	(22)
12		$\underline{n}$-C_6H_{13}		90	(0)

a) The products were identified by IR and MS spectra, and by comparison with authentic samples if available. b) Values in parentheses are yields with Bu_2SnO.^{2b} c) Pure monolide was not isolated. d) Diolide was obtained in 19% yield. e) Diolide was obtained in 82% yield.

employable without purification and the reaction proceeded under atmospheric as well as neutral conditions. Polar solvents such as diethyleneglycol dimethyl ether and DMF gave rise to complex side reactions. Table I reveals the yields of hexa- and pentadecanolides (entries 1 and 2) to be superior to those obtained with Bu_2SnO.$^{2b)}$ Of particular interest is that certain alkyl side chains attached on the hydroxyl carrying carbon exert a profound effect on lactonization. For example, exposure of 12-hydroxystearic acid to the present method resulted in clean monolide formation in 90% yield (entry 12), while 12-hydroxydodecanoic acid itself afforded no monolide but the corresponding diolide in 82% yield under the same reaction conditions (entry 11). Evidently, these surprising results are characteristic of distannoxanes since Bu_2SnO has been reported to give no monolide from 12-hydroxystearic acid at all.$^{2b,4)}$ The effect was further confirmed by other series of ω-hydroxy carboxylic acids as well (entries 3-10). The alkyl side chains bearing more than four carbon atoms



Scheme 1

proved effective. The smaller alkyl groups failed to afford monolides in detectable yields.

The catalysis can be explained by Scheme 1. We have already disclosed the facile formation of alkoxydistannoxanes simply on mixing the corresponding hydroxy derivatives with alcohols at room temperature,[5)] although organotin oxides or hydroxides react rather sluggishly with alcohols under analogous conditions.[5b,6)] The alkoxy group in the distannoxane molecules proved to be highly nucleophilic in the reaction with isocyanates.[5)] Moreover, coordination of the carbonyl group to the tin atom attached to X in **2** would facilitate the intramolecular esterification since the tin atom being bonded to a polarizable X group is highly susceptible to coordination by a carbonyl group.[5)] Then, thermolytic extrusion of the organotin template delivers lactones. In contrast to tri- or dibutyltin oxides whose esterification reaction has been shown to equilibrate with the reverse ester cleavage,[2a)] our process is virtually free from the reverse reaction. Heating hexadecanolide in decane at reflux in the presence of **1a** resulted in the complete recovery of the starting material after 24 h.[7)] This is why the use of a Dean-Stark apparatus was unnecessary.

In order to shed light on the role of the alkyl side chain, the degree of association of methyl 12-hydroxydodecanoate (**3**) and 12-hydroxystearate (**4**) was measured by means of a vapor pressure osmometer.8) In benzene, **3** was found to be constantly tetrameric in the concentration range of 0.122-0.589 wt%, while the degree of association of **4** proved to be much lower: 1.06 (c 0.118 wt%)-1.46 (c 0.146 wt%). Apparently, **4** shows a strong tendency to dissociate into a monomeric form. The alkyl side chain is effective to change an intermolecular hydrogen bonding of non-branched ω-hydroxy esters into an intramolecular fashion. Therefore, we assumed that the main skeleton in the ω-stannoxycarboxylic acid **2** is bent by the long alkyl side chain so that the terminal carboxylic group could arrive at the other end of the original ω-hydroxy carboxylic acid moiety. The approach of the carboxylic group is assisted by coordination to the tin, Sn (2), which possesses high acceptor property.

In summary, the present process is synthetically useful due to the simplicity of experimental operations, the mildness of reaction conditions, and the facile availability of **1**. Of further importance is the unusual template effect which has never been encountered with other promotors.

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(3) Distannoxanes **1** are readily prepared from commercially available Bu_2SnO and Bu_2SnCl_2. For their preparation and structural properties see, T. Yano, K. Nakashima, J. Otera, R. Okawara, Organometallics, **4**, 1501 (1985), and references cited therein.

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(7) Benzyl acetate was cleaved under the similar reaction conditions to give benzyl alcohol in 20% yield after aqueous workup.

(8) On account of poor solubility, the molecular weight of ω-hydroxy carboxylic acids could not be measured.

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