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Tin(IV)-catalyzed Lactonization of ω-Hydroxy Trifluoroethyl Esters

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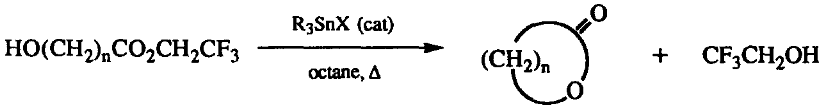
***Abstract:** 1,1,1-Trifluoroethyl esters of ω-hydroxycarboxylic acids were prepared and their conversion to macrocyclic lactones, including ricinelaidic lactone, was studied in the presence of catalytic quantities of tin(IV) reagents; a mechanism involving exchange of alkoxytrialkyltin species is proposed.*

A wide variety of methods have been described for the cyclization of ω-hydroxy acids and their derivatives to medium and large lactones,[1] yet this construction continues to present a significant challenge to synthetic methodology. As a frequently used final step in the synthesis of complex macrolide structures, efficient macrolactonization under mild conditions poses special problems which have been addressed by the search for novel means for carboxyl activation and cyclization.[2] We describe herein a new macrolactone synthesis employing 1,1,1-trifluoroethyl ω-hydroxycarboxylates **1** and various tin reagents in which the tin species can be used catalytically. The overall transformation is expressed in equation (i).



(i)

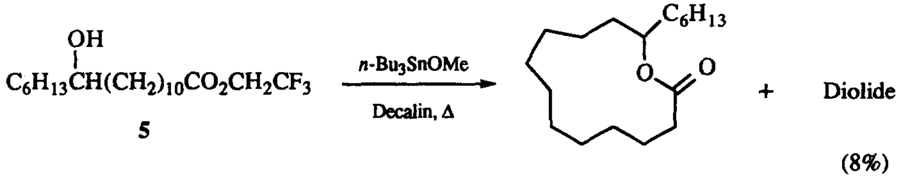
1 **2**

Alkoxytrialkyltin compounds undergo rapid exchange with alcohols.[3] The exchange also occurs with esters and can afford a facile means for transesterfication mediated by tin(IV).[4] Fluorine substitution in an alkoxy group attached to tin is known to stabilize the stannane[5] and can thus be used to assist an otherwise unfavorable reaction pathway. This reasoning led us to prepare trifluoroethyl esters of various ω-hydroxycarboxylic acids and examine their tin-promoted conversion to macrolactones **2**.[6] Reactions were carried out in octane at reflux (127 °C), which results in removal of trifluoroethanol and closure of the catalytic cycle in tin.

Trifluoroethyl esters **1** were obtained by a novel procedure in which the ω-hydroxy acid **3** was first activated with diethylphosphorochloridate[7] and then treated with potassium trifluoroethyl xanthate (**4**)[8] in DMF. This route, in which extrusion of CS_2 occurs, leads directly to pure **1** in *ca* 40% yield and is exceptionally mild. These esters were exposed to methoxytri-*n*-butyltin, di-*n*-butylstannoxane, hexa-*n*-butylditin, and tri-*n*-butylstannane in octane. Results are summarized in Table I.

$$\underset{\mathbf{3}}{HO(CH_2)_nCO_2H} \xrightarrow[\text{2. } CF_3CH_2OCS_2K\ (\mathbf{4}),\ DMF \quad -42\ ^\circ C \rightarrow \text{r.t.}]{\text{1. } ClPO(OEt)_2,\ Et_3N,\ THF} \mathbf{1}$$

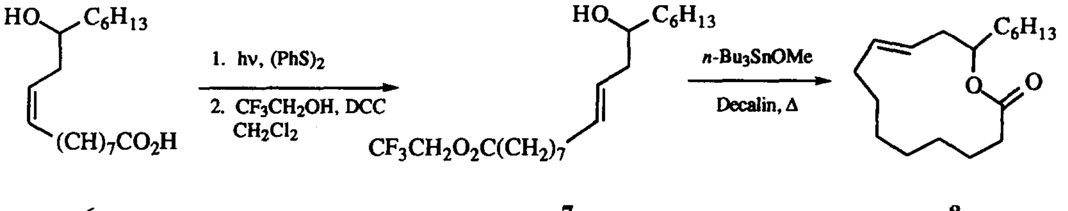
All of the tin reagents resulted in macrolactonization and/or diolide formation. No lactonization was observed in the absence of the tin reagent even after prolonged heating. 10-Hydroxydecanoate and shorter chain hydroxy esters gave only diolide accompanied by recovered starting material, whereas 16-hydroxyhexadecanoate and higher homologues afforded lactone in excellent yield. With tri-*n*-butylmethoxytin the reaction was relatively fast compared to tri-*n*-butyltin hydride (with AIBN as initiator), but the latter nevertheless furnished clean product. In all cases, lactonization and/or diolide formation could be effected with ≤ 0.1 equivalent of the tin reagent. Trifluoroethyl esters **1** gave significantly better yields of lactone than ethyl esters. Secondary alcohols, eg trifluoroethyl 12-hydroxystearate (**5**), require a higher temperature (ca 190 °C) to effect complete lactonization.



5

(33%)

(8%)



6 **7** **8**

(41%)

This procedure was applied to the synthesis of ricinelaidic lactone (**8**) from trifluoroethyl ricinelaidate (**7**), prepared by photochemical isomerization of ricinoleic acid (**6**)[9] followed by esterification with trifluoroethanol. Lactone **8** was obtained in moderate yield but, unlike the Steliou lactonization of **6**,[10] was not accompanied by diolide. Trifluoroethyl 16-*tert*-butyldimethylsilyloxyhexadecanoate failed to react in the presence of the tin reagent implying that formation of a ω-stannoxy compound **9** is a prerequisite for lactonization. The additional steric demand imposed by a secondary alcohol apparently retards this step. The sequence shown in Scheme I, where alkoxy group exchange involving catalytic tin species provides the mechanism for driving lactonization, accomodates these observations.

Table I. Lactonization of $HO(CH_2)_nCO_2CH_2CF_3$ with Tin(IV) Reagents

Entry	ω-Hydroxy Ester n	Tin(IV) Reagent	No. of Equiv.	Yield (%) Lactone	Yield (%) Diolide
1	15	A	0.1	81	14
2	15	B	0.1	76	19
3	15	C	0.1	62	9
4	15	D	0.1	67	
5	15	none	—	0	0
6	15	E	1.1	73	trace
7	15	D	1.1	70	0
8	14	A	0.1	74	17
9	14	D	0.1	59	16
10	12	A	0.1	60	22
11	11	A	0.1	45	40
12	11	D	0.1	42	19
13	11	D	1.1	21	23
14	9	A	0.1	0	82
15	9	D	0.1	0	65

Reagents: A = *n*-Bu_3SnOMe; B = (*n*-$Bu_3Sn)_2O$; C = (*n*-$Bu)_3Sn_2$; D = *n*-Bu_3SnH/AIBN;
E = *n*-Bu_3SnCl

Macrolactonization of trifluoroethyl ω-hydroxycarboxylates **1** resembles the di-*n*-butylstannoxane-mediated lactonization of ω-hydroxy acids described by Steliou,[10] for which a "template-driven" extrusion involving an alkoxystannylene carboxylate was postulated. In the present case, however, a tin template is probably not involved. Thermodynamic impetus is derived in the second step of the cycle from the formation of tri-*n*-butyltrifluoroethoxystannane (**10**) and overall from removal of trifluoroethanol.

$$\mathbf{1} + R_3SnX \rightleftharpoons \underset{\mathbf{9}}{R_3SnO(CH_2)_nCO_2CH_2CF_3} + HX$$

$$R_3SnO(CH_2)_nCO_2CH_2CF_3 \rightleftharpoons \mathbf{2} + \underset{\mathbf{10}}{R_3SnOCH_2CF_3}$$

$$R_3SnOCH_2CF_3 + \mathbf{1} \rightleftharpoons \mathbf{9} + CF_3CH_2OH\uparrow$$

Scheme I

Although the full scope of this tin(IV)-catalyzed macrolactonization remains to be established, it promises to be a useful alternative to conventional protocols, especially for those cases where a highly reactive acyl precursor is to be avoided.

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