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Reagents for Organic Synthesis: Use of Organostannyl Oxides as Catalytic Neutral Esterification Agents in the Preparation of Macrolides[1]

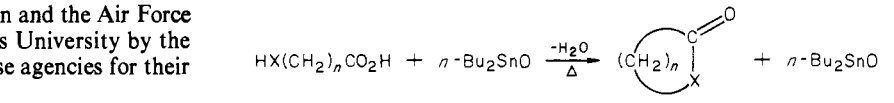
Sir:

Recent landmark achievements in the synthesis of natural products of the macrolide type[2-4] have necessitated the development of mild and efficient methods for ring closure to macrocyclic lactones, lactams, and related systems.[2-4] In several instances, macrolide formation has been the penultimate critical synthetic hurdle in a multistep sequence consisting of a meticulous assembly of functional groups on carbon chains containing multiple centers of chirality. Several techniques have recently been developed that are specifically addressed to this difficult synthetic problem, and these almost universally rely on high dilution and or some form of functional activation through prior derivatization.[4]

We herein report on a synthetically useful new approach toward the preparation of lactones and lactams including several macrocyclic types directly from ω-hydroxy and ω-amino carboxylic acids, respectively, by using catalytic amounts of various organotin oxides under neutral conditions and without resorting to high dilution techniques.[5] Thus, treatment of 15-hydroxypentadecanoic or 16-hydroxyhexadecanoic acid (10 mmol) with n-Bu_2SnO (1 mmol) in refluxing mesitylene (250 mL) for ~20 h by using a Dean-Stark apparatus gave the corresponding lactones in ~60% isolated yield. Diolides were also formed as minor products except for the case of the nine-membered lactone for which no monomer could be isolated. The procedure is also applicable to the formation to lactams in excellent to moderate yields (Table I).[6]

The mechanism by which these reactions proceed is particularly intriguing, since we could find no literature precedence for ester or amide formation with carboxylic acids and alcohols or amines,

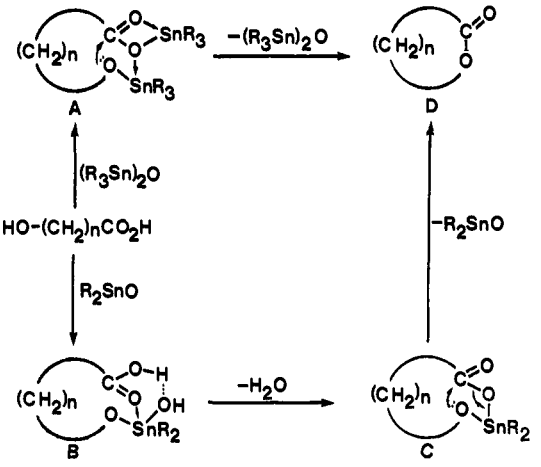
Table I



X	n	solvent[a]	reaction time, (h)	monolide,[b] %	diolide,[b] %
O	7	M	19	0	20
O	14	M	23	63	8
O	15	M	17	60	15
HN	3	X	12	>95	
HN	4	X	12	>95	
HN	5	X	20	>95	
HN	10	M	24	22	
HN	11	M	24	25	

[a] M = mesitylene, X = xylene. [b] Products were identified by comparing IR, MS, VPC, and melting point with commercially available authentic samples. The remaining products constituted polymeric residues which were uncharacterized.

Scheme I



respectively, using tin oxides. Indeed, the reverse reaction (ester cleavage) by various organotin oxides has been reported.[7a] We have found this type of reaction to be reversible such that the direction of equilibrium (ester formation or cleavage) is heavily dependent upon the nature of the substrate and, more importantly, on the concentration and type of the organotin oxide used. For example, treatment of methyl benzoate with an equivalent amount of $[n\text{-}Bu_3Sn]_2O$ in refluxing xylene gave a mixture of tri-n-butylstannyl benzoate and tri-n-butylstannyl methoxide. On the other hand, similar treatment of benzyl benzoate resulted in approximately 50% cleavage. When benzoic acid and benzyl alcohol were treated with an equivalent amount of $[n\text{-}Bu_3Sn]_2O$, an equal distribution of benzyl benzoate and the stannylated acid and alcohol were achieved, as with the previous reaction. It is important to note that both the acid and the alcohol are each readily stannylated and that an anhydride is not formed under these reaction conditions.[8] However, if benzoic acid and benzyl alcohol are treated with a 10% molar equivalent of $[n\text{-}Bu_3Sn]_2O$ or n-Bu_2SnO, a 90% yield of benzyl benzoate is readily obtained. Similarly benzoic acid and aniline yield benzanilide quantitatively. With lactones such as propiolactone[7b] or hexadecanolide, equimolar amounts of $[n\text{-}Bu_3Sn]_2O$ in refluxing mesitylene readily cause opening of the ring to yield the bis-stannylated hydroxy acid, but

(1) Presented in part at the 180th National Meeting of the American Chemical Society, Los Vegas, NV, August 1980; "Abstracts of Papers"; American Chemical Society: Washington DC, 1980; ORGN 299.

(2) (a) W. Keller-Schierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313 (1973); (b) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, 49 (1976).

(3) (a) S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, **16**, 585 (1977); (b) K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977); (c) T. G. Back, *ibid.*, 3041 (1977).

(4) See for example: (a) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974), and references therein; (b) G. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, **59**, 755 (1976); (c) S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975). See also: (d) T. Takahashi, S. Hashiguchi, K. Kasuga, and J. Tsuji, *ibid.*, **100**, 7424 (1978); (e) K. Naraska, K. Maruyama, and T. Mukaiyama, *Chem. Lett.*, 885 (1978); (f) B. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4743 (1980), and references cited therein.

(5) The preparation of macrolide type compounds using the coordinative ability of organotin derivatives by a procedure different from ours was published during the course of this study. A. Shanzer and N. Mayer-Shochet, *J. Chem. Soc., Chem. Commun.*, 176 (1980); A. Shanzer and E. Barman, *ibid.*, 259 (1980).

(6) For other recent methods of lactam formation see, for example,: (a) A. Bladé-Font, *Tetrahedron Lett.*, 2443 (1980); (b) R. Pellegata, M. Pinza, and G. Pifferi, *Synthesis*, 614 (1978); (c) L. Birkoffer and J. Schramm, *Justus Liebigs Ann. Chem.*, 2195 (1975).

(7) (a) A. G. Davies, T. N. Mitchell, and W. R. Symes, *J. Chem. Soc. C*, 1311 (1966); (b) K. Itoh, Y. Kato, and Y. Ishii, *J. Org. Chem.*, **34**, 459 (1969); (c) A. G. Davies, D. C. Kleinschmidt, P. R. Palan, and S. C. Vasishtha, *J. Chem. Soc. C*, 3972 (1971).

(8) Refluxing a solution of benzoic or capric acid in mesitylene with or without n-Bu_2SnO by using a Dean-Stark apparatus for several days did not give rise to the formation of any spectroscopically (IR) detectable anhydride.

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γ-butyro- or δ-valerlactone can be recovered essentially unchanged. Under the same conditions, n-Bu_2SnO was found to be more condescending to lactone stability (20% cleavage of hexadecanolide), hence its selection as the reagent of choice in the macrolide-forming reactions.

It is reported[7c] that when treated with alcohols, stannylated carboxylic acids *trans*-stannylate to produce the acid and the alkoxy stannyl ether. This process does not readily occur with amines,[9] nor are esters or amides formed under these reaction conditions. Thus, when a hydroxy carboxylic acid is treated with a catalytic amount of organotin oxide, a reactive stannylated intermediate (A or C in Scheme I) is formed in low concentrations and subsequently releases the tin reagent possibly by a template-driven extrusion process (Scheme I) to give the lactone. Hence, the method enjoys the intrinsic advantages of high dilution without resorting to the technique itself, since the tin reagent is continuously regenerated essentially under conditions of microscopic reversibility. The same scheme is operable with ω-amino carboxylic acids.

The ability of tin to enhance the nucleophilicity of heteroatoms bound to it and its capacity to expand its valency from four to five and six through coordination are well expressed in the literature[10a] and in some instances documented by X-ray structural analyses.[11] Thus, as a consequence of intramolecular coordination, a bis-stannylated complex (expression A in Scheme I) could form and, in effect, assume the geometry or template requirements for the extrusion[12] of the tin oxide to yield the macrolide. Some evidence in support of this proposal was obtained by reducing the ability of the tin substrates to coordinate through substitutent modification on tin.[10] Thus, considerably longer periods of time (~5 times) were required for reactions in which cyclohexyltin oxides were used over those of n-butyltin analogues, presumably due to the larger steric requirements of the cyclohexyl group and the weaker coordinating ability[10b] of the corresponding bis-stannylated intermediates.

Macrolide formation mediated by n-Bu_2SnO can be envisioned to take place through the intermediacy of structures B and C in Scheme I. Structure B could actually be favored due to the additional ionic interaction[13] by way of hydrogen bonding, although we have no experimental evidence in support of this argument.

We are currently investigating this reaction in greater detail to determine the effect of ring size and whether or not this approach can be extended to include ω-halo and ω-mercapto carboxylic acids for the preparation of lactones and thiolactones, respectively.

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(9) M. Frankel, D. Gertner, D. Wagner, and A. Zilkha, *J. Org. Chem.*, **30**, 1596 (1965).
(10) (a) *Adv. Chem. Ser.*, No. 157 (1976); (b) B. Y. K. Ho and J. J. Zuckerman, *Inorg. Chem.*, **12**, 1552 (1973).
(11) D. Moras and R. Weiss, *Acta Crystallogr., Sect. B.*, **25**, 1726 (1969).
(12) Extrusion of dialkyltin oxide has been postulated in some reactions of heterocyclic 2-stannacyclopentanes; S. Sakai, Y. Fujimura and Y. Ishii, *J. Organomet. Chem.*, *50*, 113 (1973).
(13) A similar type of an ionic interaction with other models has been put forth. See ref 4, and T. Kurihara, Y. Nakajima, and O. Mitsunobu, *Tetrahedron Lett.*, 2455 (1976), and W. H. Rastetter and D. P. Phillion, *J. Org. Chem.*, **45**, 1538 (1980).
(14) (a) Holder of UNIDO, CIDA fellowship; (b) Summer undergraduate research participant.

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Stereoelectronic Control in the Breakdown of Hemiorthothiol Esters, $RC(OR')_2SH$[1]

Sir:

The generation and breakdown of transient tetrahedral intermediates of the type $RC(OR')(OH)_2$, $RC(OR')_2(OH)$, and $RC(OR')(NR_2'')(OH)$ are subject to stereoelectronic control as evidenced by Deslongchamps' elegant studies on the ozonolysis of acetals,[2] carbonyl exchange reactions,[3] hydrolyses of cyclic ortho esters[4] and imidate salts,[5] and oxidative cleavages of vinyl ortho esters.[6] Sulfhydrolytic studies of imidates also have suggested the possible involvement of stereoelectronic effects in the breakdown of hemiorthothioamide intermediates, $RC(OR')(NR_2'')SH$.[7] We hereby report on the role of the stereoelectronic factor in the breakdown of hemiorthothiol esters—$RC(OR')_2SH$—under kinetic control. The model tetrahedral intermediates in question, *viz.*, **[1]**-**[4]** (Figure 1),[8] were generated *directly* by the ion-ion combination of dialkoxycarbonium cations **5**-**8** with hydrosulfide anion, under aprotic conditions, at zero or subzero temperatures.

According to the stereoelectronic theory,[9] a carbon-heteroatom bond, C-Y, in a tetrahedral intermediate RC(X)(Y)(Z), is severed relatively easily if there are *two* nonbonded electron pairs (one on X, one on Z) antiperiplanar to C-Y; other things being equal, the cleavage of C-Y is appreciably less facile if *one* or *no* antiperiplanar electron pair is present. Thus, for hemiorthothiol esters one predicts that (i) in tetrahedral intermediate **[1]** either C-O bond ought to cleave easily (each C-O is antiperiplanar to two electron pairs), (ii) neither C-O bond in model intermediate **[2]** would be severed with ease (each C-O is antiperiplanar to only one electron pair), and (iii) in each of the tetrahedral intermediates **[3]** and **[4]**, the *endocyclic* C-O bond should break in preference to the exocyclic one (the former C-O bond is antiperiplanar to two nonbonded electron pairs, while the latter, to only one).

Intermediate **[1]**, generated by the reaction of compound **5**[10] with anhydrous NaSH[11] in dry acetonitrile at 0 °C, under a nitrogen atmosphere, led to a mixture of two rather labile isomeric hydroxythionacetates—**9** and **10** (50.5% isolated yield; ~1.5:1 by integration of the respective $-CHOC(=S)$ ^1H NMR ($CDCl_3$) signals at δ 4.54 and 5.36; IR (neat) 3400, 1460, 1275, 1220, 1030 cm^{-1}; R_f 0.47 ($CHCl_3$-CH_3CN 5:1 v/v)).[12]

Treatment of **6**[13] with anhydrous NaSH under conditions identical with those for the generation of **[1]** gave no trace of compound **11a**;[14] the principal sulfur-containing (positive $PdCl_2$

(1) The Chemistry of Tetrahedral Intermediates. 5. For part 4, see: Khouri, F.; Kaloustian, M. K. *J. Am. Chem. Soc.* **1979**, *101*, 2249-2251.
(2) Deslongchamps, P.; Moreau, C.; Frehel, D.; Chênevert, R. *Can. J. Chem.* **1975**, *53*, 1204 and references cited therein.
(3) Deslongchamps, P.; Cheriyan, U. O.; Taillefer, R. J. *Can. J. Chem.* **1979**, *57*, 3262 and references cited therein.
(4) (a) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A. *Can. J. Chem.* **1972**, *50*, 3405. (b) Deslongchamps, P.; Chênevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. *Ibid.*, **1975**, *53*, 1601.
(5) Deslongchamps, P.; Taillefer, R. J. *Can. J. Chem.*, **1975**, *53*, 3029 and references cited therein.
(6) Deslongchamps, P.; Beaulieu, N.; Chênevert, R.; Dickinson, R. A. *Can. J. Chem.*, **1980**, *58*, 1051.
(7) Kaloustian, M. K.; de Gutierrez, M. I. Aguilar-Laurents; Nader, R. B. *J. Org. Chem.* **1979**, *44*, 666-668.
(8) All tetrahedral intermediates in the sequel, regardless of lifetime, are indicated with square brackets.
(9) (a) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463; (b) *Pure Appl. Chem.* **1975**, *43*, 351; (c) *Heterocycles* **1977**, *7*, 1271.
(10) Prepared from BF_3·Et_2O and the ortho ester derived from *trans*-2-(hydroxymethyl)cyclohexanol and triethyl orthoacetate (95% yield).
(11) Eibeck, R. E. *Inorg. Synth.* **1965**, *7*, 128.
(12) No attempts were made to separate the labile thionacetates **9** + **10**. Treatment of this mixture with NaH/CH_3CN (0 °C) gave **16** (35% isolated yield) which was quantitatively methylated (CH_3I) to yield ortho ester **17**; the latter proved to be identical (IR, ^1H NMR) with the product of the reaction of **5** with CH_3SLi.
(13) Synthesized from δ-valerolactone by sequential treatment with (i) LDA/THF (-78 °C, 30 min), (ii) 3-chloroiodopropane/HMPT (-78 °C; 15 h), (iii) $AgBF_4/Et_2O$ (27 °C, 3 h), (iv) MeONa/MeOH-*i*-PrOH (-78 °C, 2 h), (v) BF_3·Et_2O (-78 °C, 20 min); overall yield 20.2%. The last two steps were carried out in order to obtain silver-free, crystalline **6**.

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