Ring-Opening Reactions of Lactones with Alkylaminostannanes; A New Regioselective Route to ω-Stannoxyamides and Related Compounds

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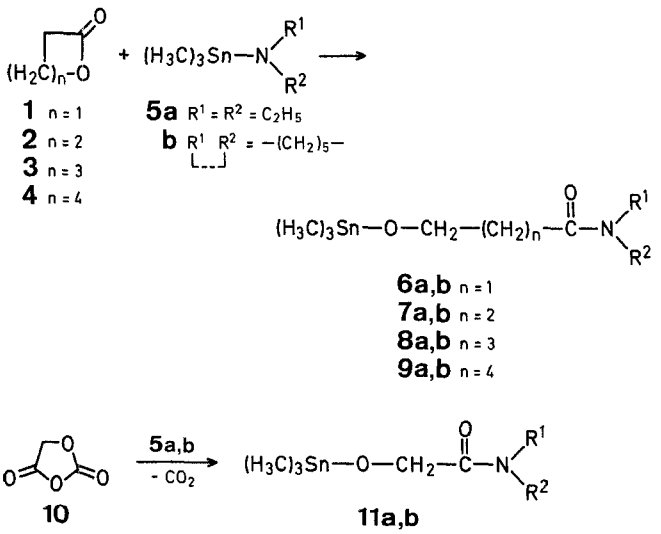
While the silyl group has drawn much attention as a synthetic tool in organic chemistry[1], the stannyl group has only recently been used in organic chemistry[2] and promises to open many new possibilities. Although silicon and tin derivatives may at first sight appear similar, there are pronounced differences which can be favourably exploited. Siloxanes, for example, are rather inert compounds and silicon may therefore be used as a protecting group for alcohols and related oxygen derivatives. Stannoxanes, on the other hand, are chemically reactive and may undergo a large range of condensation reactions with electrophiles. Tin derivatives may therefore be considered as activating groups for alcohols.

In this publication we demonstrate the possibility of this approach by describing the dual function of a tin derivative as a reagent and as an activating group. Specifically, we describe the regioselective ring-opening of saturated lactones **1–4** by alkylaminostannanes **5** affording a new general route to stannylated derivatives **6–9** which may further be transformed to a series of di- and trifunctional compounds.

N,N-Diethylaminotrimethylstannane **(5a)** and piperidinotrimethylstannane **(5b)** induce regioselective ring-opening in the β-propiolactone **(1)**, γ-butyrolactone **(2)**, δ-valerolactone **(3)** and ε-caprolactone **(4)** systems by means of acyl-oxygen bond fission to give the corresponding ω-stannoxyamides **6–9** in good yields. Analogously, 1,3-dioxolan-2,4-dione **(10)**, which behaves as a masked α-lactone, reacts with these organometallics with evolution of carbon dioxide. The products formed are the ω-stannoxyamides **11a** and **11b**.



Scheme A

Table 1. ω-Stannoxyamides **6–9, 11** prepared (Scheme **A**)

Lactone	Reagent (mmol)	Product	Reaction time	Yield [%][a]	Molecular formula[b]	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
1 (n=1)	**5a** (10)	**6a**	1 h	95	$C_{10}H_{23}NO_2Sn$ (308.0)	1641	0.31 (s, 9H); 1.09 (t, 6H, J=7 Hz); 2.32 (t, 2H, J=6 Hz); 3.28 (q, 4H, J=7 Hz); 3.79 (t, 2H, J=6 Hz)
1 (n=1)	**5b** (10)	**6b**	1 h	96	$C_{11}H_{23}NO_2Sn$ (320.0)	1635	0.53 (s, 9H); 1.6 (m, 6H); 2.60 (t, 2H, J=6 Hz); 3.5 (m, 4H); 3.85 (t, 2H, J=6 Hz)
2 (n=2)	**5a** (12)	**7a**	24 h	90	$C_{11}H_{25}NO_2Sn$ (322.0)	1630	0.3 (m, 9H); 1.0 (m, 6H); 1.6 (m, 2H); 2.20 (t, 2H, J=6 Hz); 3.3 (m, 4H); 3.50 (t, 2H, J=6 Hz)
2 (n=2)	**5b** (10)	**7b**	8 h	89	$C_{12}H_{25}NO_2Sn$ (334.0)	1645	0.45 (s, 9H); 1.7 (m, 6H); 1.9 (m, 2H); 2.47 (t, 2H, J=7 Hz); 3.6 (m, 4H); 3.80 (t, 2H, J=7 Hz)
3 (n=3)	**5a** (15)	**8a**	30 h	71	$C_{12}H_{27}NO_2Sn$ (336.1)	1630	0.23 (s, 9H); 1.0 (m, 6H); 1.4 (m, 4H); 2.25 (t, 2H, J=6 Hz); 3.2 (m, 4H); 3.57 (t, 2H, J=6 Hz)
3 (n=3)	**5b** (13)	**8b**	30 h	77	$C_{13}H_{27}NO_2Sn$ (348.1)	1640	0.4 (m, 9H); 1.6 (m, 10H); 2.38 (t, 2H, J=7 Hz); 3.5 (m, 4H); 3.75 (t, 2H, J=7 Hz)
4 (n=4)	**5a** (13)	**9a**	24 h	90	$C_{13}H_{29}NO_2Sn$ (350.1)	1650	0.25 (s, 9H); 1.0 (m, 6H); 1.3 (m, 6H); 2.16 (t, 2H, J=7 Hz); 3.2 (m, 4H); 3.50 (t, 2H, J=7 Hz)
4 (n=4)	**5b** (11)	**9b**	8 h	92	$C_{14}H_{29}NO_2Sn$ (362.1)	1635	0.37 (s, 9H); 1.6 (m, 12H); 2.25 (t, 2H, J=7 Hz); 3.4 (m, 4H); 3.58 (t, 2H, J=7 Hz)
10	**5a** (10)	**11a** (n=0)	10 h	70	—[c]	1650	0.30 (s, 9H); 1.19 (t, 6H, J=6 Hz); 3.36 (q, 4H, J=6 Hz); 4.26 (s, 2H)
10	**5b** (10)	**11b** (n=0)	10 h	70	—[c]	1648	0.38 (s, 9H); 1.6 (m, 6H); 3.6 (m, 4H); 4.29 (s, 2H)

[a] Yields of isolated products, except for **11a, b** which were estimated from ^{1}H-N.M.R. spectra.
[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.35, N ±0.35.
[c] Products undergo spontaneous destannylation.

Table 2. ω-Hydroxyamides **12–16** prepared (Scheme **B**)

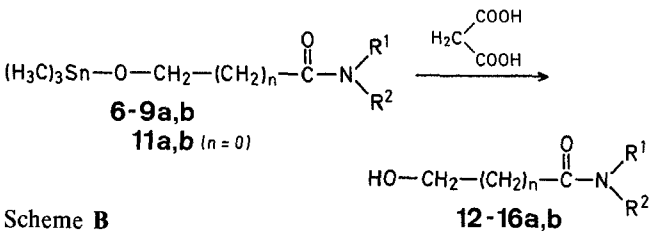
Substrate	Product	Yield [%][a]	b.p. [°C]/torr	Molecular formula[b] or Lit. b.p. [°C]/torr	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. *m/e*
6a	**12a** (n=1)	93	75–76°/0.5	80–81°/1[4]	1625	1.10 (t, 6H, J=7.5 Hz); 2.33 (t, 2H, J=6 Hz); 3.30 (q, 4H, J=7.5 Hz); 3.81 (t, 2H, J=6 Hz); 4.36 (s, 1H, OH)	145 (M^+); 126; 115, 100, 87, 72
6b	**12b** (n=1)	94	74–75°/0.03	$C_8H_{15}NO_2$ (157.2)	1620	1.6 (m, 6H); 2.66 (t, 2H, J=6 Hz); 3.2 (m, 1H, OH); 3.4 (m, 2H); 3.5 (m, 2H); 3.87 (t, 2H, J=6 Hz)	157 (M^+); 140, 139; 126, 112
7a	**13a** (n=2)	87	oil[c]	$C_8H_{17}NO_2$ (159.2)	1620	1.2 (m, 6H); 2.0 (m, 2H); 2.55 (t, 2H, J=6 Hz); 3.4 (m, 4H); 3.70 (t, 2H, J=6 Hz); 5.90 (s, 1H, OH)	159 (M^+); 142, 115; 100, 82, 72
7b	**13b** (n=2)	88	oil[c]	$C_9H_{17}NO_2$ (171.2)	1635	1.7 (m, 6H); 1.90 (t+t, 2H, J=6.5 Hz); 2.47 (t, 2H, J=6.5 Hz); 3.5 (m, 4H); 3.57 (t, 2H, J=6.5 Hz); 5.06 (s, 1H, OH)	171 (M^+); 154, 139, 126, 112
8a	**14a** (n=3)	63	oil[c]	$C_9H_{19}NO_2$ (173.2)	1625	1.1 (m, 6H); 1.5 (m, 4H); 2.32 (t, 2H, J=6 Hz); 3.2 (m, 4H); 3.71 (t, 2H, J=6 Hz); 4.91 (s, 1H, OH)	173 (M^+); 154, 115; 100, 87, 22
8b	**14b** (n=3)	73	oil[c]	$C_{10}H_{19}NO_2$ (185.3)	1620	1.6 (m, 10H); 2.38 (t, 2H, J=6 Hz); 3.45–3.75 (br. s, 6H); 5.58 (s, 1H, OH)	185 (M^+); 168, 139, 126, 112
9a	**15a** (n=4)	88	oil[c]	$C_{10}H_{21}NO_2$ (187.3)	1630	1.2 (m, 6H); 1.8 (m, 6H); 2.33 (t, 2H, J=6.5 Hz); 3.5 (m, 4H); 3.85 (t, 2H, J=6.5 Hz); 3.91 (s, 1H, OH)	187 (M^+); 168, 115, 100, 87, 72
9b	**15b** (n=4)	89	oil[c]	$C_{11}H_{21}NO_2$ (199.3)	1625	1.7 (m, 12H); 2.35 (t, 2H, J=6.5 Hz); 3.35–3.75 (br. s, 6H); 4.40 (s, 1H, OH)	199 (M^+); 152, 139, 126, 112
11a	**16a** (n=0)	65	68–70°/0.07	—[5]	1645	1.17 (t, 6H, J=7.5 Hz); 3.36 (q, 4H, J=7.5 Hz); 4.24 (s, 2H); 4.84 (s, 1H, OH)	131 (M^+); 114, 100, 72
11b	**16b** (n=0)	67	76–80°/0.05	$C_7H_{13}NO_2$ (143.2)	1640	1.6 (m, 6H); 3.6 (m, 4H); 4.30 (s, 2H); 4.48 (s, 1H, OH)	143 (M^+); 126, 112, 84

[a] Yields of isolated products based on starting lactones.
[b] Satisfactory microanalyses; C ±0.30%; H ±0.30%; N ±0.35%.
[c] Oils which could not be distilled without decomposition.

The products were identified by the I.R. absorption band in the carbonyl region at $\nu = 1625-1650\ cm^{-1}$ and by the ^1H-N.M.R. peaks near $\delta = 3.5-3.7$ ppm, diagnostic for the —CO—N—CH_2-system; the absence of I.R. carbonyl bands at frequencies above 1650 cm^{-1}, shows that the reaction follows the regiospecific pathway outlined above.

With compounds **1, 2, 4,** and **10,** the ring-opening takes place at room temperature in dichloromethane to give, after several hours the ω-stannoxyamides **6, 7, 9,** which can be isolated as practically pure oils, whereas for **10,** spontaneous destannylation prevents the isolation of the analytically pure stannoxyamide **11.** The insertion reactions are very clean and no by-products can be detected in the reaction mixture, with the exception of **4** where a small amount (not exceeding 3.5%) of polymeric material (m.p. 52–53 °C; M.W. 3666) was recovered. Compound **3,** on the other hand, needs more drastic reaction conditions (about 30 h in boiling *sym*-dichloroethane) and the corresponding stannoxyamides are obtained in somewhat lower yields. Piperidinotrimethylstannane **(5b)** is more reactive in the opening of the lactone ring and does not lead to any traces of polymeric by-product even with **4.** Experimental data are given in Table 1.

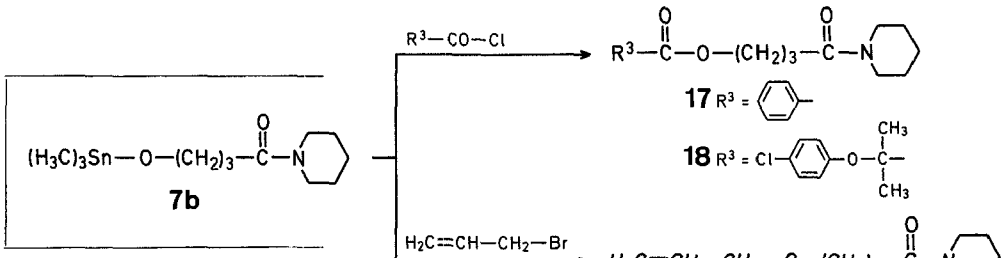
A synthetically attractive feature of this procedure is the reactivity of the tin-oxygen bond in the stannoxyamides. This bond can easily react with electrophiles through removal of the reactive trimethyltin-protecting group giving rise to further functionalisation at oxygen. Thus, on treatment with the appropriate amount of malonic acid, stannoxyamides **6–9** and **11** undergo destannylation affording in quantitative yields, as colourless oils, the corresponding ω-hydroxyamides **12–16,** most of which were previously unknown compounds.



Scheme **B**

Compounds **12–16** may be considered as precursors of physiologically active amino-alcohols[3]. As shown by T.L.C. analysis, they are obtained almost pure. Further purification can be achieved for **12** and **13** by vacuum distillation and for **14–16** by chromatography on silica gel with ethyl acetate/ethanol (2/1). The relevant data are collected in Table 2.

Moreover, stannoxyamides react with acyl and allyl halides under insertion into the tin-oxygen bond. This is exemplified by the reaction of **7b** leading under mild conditions and in high yields to the corresponding esters and ethers **17, 18, 19** with the typical skeletons of pharmacologically active compounds, such as hypolipidimic[6], anti-colinolitic[7], and hypotensive agents[8] (Table 3).



Scheme **C**

Further work is in progress to elucidate the mechanism of the insertion reactions and to extend the scope of the procedure to a wider range of electrophiles.

ω-Stannoxyamides 6–9 and 11; General Procedure:
The lactone **(1–4)** or 1,3-dioxolan-2,4-dione **(10)** (10 mmol) and the appropriate amount of alkylaminostannane **5** are dissolved in dry dichloromethane (10 ml) under nitrogen and the progress of the reaction monitored by ^1H-N.M.R. analysis. After several hours (Table 1), the solvent is evaporated, the excess stannane removed under high vacuum, and the resulting oil, characterised as the ω-stannoxyamide, is used for the next steps.

ω-Hydroxyamides 12–16; General Procedure:
The ω-stannoxyamide (10 mmol) is dissolved in the smallest amount possible of dry ether (~3 ml) and a 0.5 molar solution of malonic acid in dry ether (5 ml, 5 mmol) is added. After 2 h under reflux, bis-trimethylstannoxy-malonic ester is filtered off, the filtrate is evaporated to afford the product (yield: ~100%), which is subsequently purified by column chromatography on silica gel with ethyl acetate/ethanol (2/1) to give pure ω-hydroxyamide **12–16** (Table 2).

Reaction of 7b with Acyl Chlorides and Allyl Bromide; General Procedure:
The acyl chloride or allyl bromide (3 mmol) is added to an equimolar amount of **7b** and the mixture allowed to stand at room temperature

Table 3. Compounds **17, 18, 19** prepared (Scheme C)

Product	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[a]	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	^1H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
17	78	78–80°	$C_{16}H_{21}NO_3$ (275.4)	1720, 1640[b]	1.6 (m, 6H); 2.2 (m, 2H); 2.45 (t, 2H, J=6 Hz); 3.5 (m, 4H); 4.40 (t, 2H, J=6 Hz); 7.5 (m, 3H); 8.1 (m, 2H)
18	69	102–105°/0.03	$C_{19}H_{26}ClNO_4$ (367.9)	1735, 1630	1.56 (s, 6H); 1.7 (m, 2H); 2.12 (t, 2H, J=6 Hz); 3.2 (m, 2H); 3.5 (m, 2H); 4.21 (t, 2H, J=6 Hz); 6.8 (m, 2H); 7.2 (m, 2H)
19	45	oil[c]	$C_{12}H_{21}NO_2$ (211.3)	1640, 1074 (C—O)	1.7 (m, 6H); 2.00 (t, 2H, J=6 Hz); 3.5 (m, 6H); 3.95 (d, 2H, J=7 Hz); 5.3 (m, 2H); 5.9 (m, 1H)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.35, N ±0.35.
[b] In KBr.
[c] Colourless oil purified by T.L.C. (silica gel/ethyl acetate).

for 10 h. The mixture is then dissolved in ether (10 ml) and hydrolysed with 10% aqueous sodium hydrogen carbonate solution (25 ml). From the ethereal layer, after removing the solvent, compound **17, 18,** and **19** are recovered by recrystallisation from cyclohexane **(17),** fractional distillation **(18),** or preparative T.L.C. **(19)** (Table 3).

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[5] Compound **12a** has been reported only in some patents, e.g. F. M. Pallos, M. E. Brokke, D. R. Arnekley, *German Patent (DOS)* 2218097 (1972); *C. A.* **78,** 29282 (1973).

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