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Activation of hydroxyl groups in sugars using bis(tributyltin) oxide: retention of the organotin residues to give biologically active products *

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Abstract

Tributyltin ethoxide has been shown to react with cyclic anhydrides to give tributylstannyl ethyl esters of phthalic, maleic and succinic acids. Treatment of tris(tributylstannyl)-D-glucose with phthalic anhydride gave either the 1,6-di-*O*-phthalyl or the 6-*O*-phthalyl derivatives, respectively, depending on conditions, demonstrating that the stannyl group can be used for activation and subsequently retained in the product. This synthetic procedure seems preferable to that in which phthalation precedes stannylation.

Introduction

Use of stannylation to activate sugar hydroxyl groups towards electrophilic substitution is now well established. Introduction of tributyltin groups occurs selectively and increases the reactivity of the substituted hydroxyls [1]. Activation towards acyl halides and to certain reactive alkyl halides has been demonstrated in carbohydrate chemistry [1]. It has also been shown that simple alcohols can be activated by stannylation towards acetylation with acetic anhydride [2], but this reaction has not been exploited in carbohydrate chemistry. We have previously demonstrated that direct phthalation and succinylation of sugars gave mono esters which were converted to stannyl sugar esters having enhanced biocidal properties [3–7] (eq. 1). The aim of the work now reported was to examine the reaction of stannylated sugars with cyclic anhydrides, since it seemed likely that the stannyl groups used to activate the hydroxyls would be retained as biocidal centres in the products.

* Dedicated, with gratitude, to the memory of Jerry J. Zuckerman.

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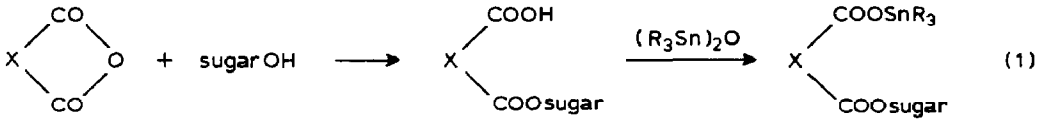
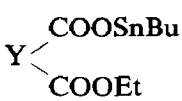


(X = o-C_6H_4, CH_2CH_2)

Preliminary experiments with simple alcohols were conducted to demonstrate that reaction occurred between the stannoxide and anhydride to give the required alkyl stannyl phthalate.

Results and discussion

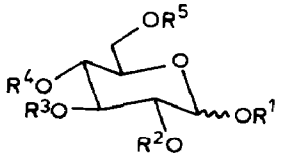
When tributyltin ethoxide was treated with phthalic anhydride and dimethyl formamide at room temperature for 16–18 h tributylstannyl ethyl phthalate (I) was obtained in 91% yield. Tributylstannyl ethyl succinate (II) and tributylstannyl ethyl maleate (III) were obtained similarly.



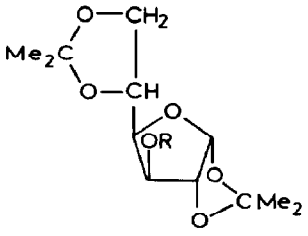
(I, Y = o-C_6H_4,
II, Y = CH_2CH_2,
III, Y = cis-CH=CH)

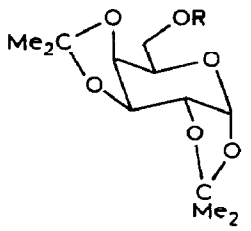
The ^1H and ^{13}C NMR and IR spectra of I–III were as expected, the positions and complexity of the carbonyl (COOSn) bands indicating 5-coordinate tin. This could not be confirmed from the magnitude of the J(Sn–C–H) coupling constants as the splittings were masked, but the Mössbauer parameters for compounds I–III (isomer shifts, relative to barium stannate, 1.04–1.07, quadrupole splittings 3.68–3.76 mm sec^{-1}) are consistent with 5-coordinate tin atoms and bidentate carboxylate groups [8].

Heating D-glucose and excess bis(tributylstannyl) oxide in toluene with azeotropic removal of water is reported [9] to give 1,4,6-tri-O-tributylstannylglucopyranoside (IV), and this compound was treated with three molar proportions of phthalic anhydride in dimethylformamide at room temperature. The product contained two stannylated phthalate residues, and structure V, with substituents in the 1 and 6 positions, is most likely. Purification of V was difficult because of a tendency to lose the metal and so it was destannylated by treatment with trifluoroacetic acid and acetylated and methylated to give 2,3,4-tri-O-acetyl-1,6-di-O-(2′-methoxycarbonylbenzoyl)-D-glucose (VI). The mass spectrum of VI shows peaks corresponding to $[M - MeOCOC_6H_4COO]^+$ and $[M - MeOCOC_6H_4COO - 2AcOH - CH_2CO]^+$ which is strong evidence for the proposed structure [10].



(IV: $R^1 = R^4 = R^5 = Bu_3Sn$, $R^2 = R^3 = H$;
V: $R^1 = R^5 = o$-$COC_6H_4COOSnBu_3$, $R^2 = R^3 = R^4 = H$;
VI: $R^1 = R^5 = o$-COC_6H_4COOMe, $R^2 = R^3 = R^4 = Ac$;
VII: $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = o$-$COC_6H_4COOSnBu_3$;
VIII: $R^1 = R^2 = R^3 = R^4 = Ac$, $R^5 = o$-COC_6H_4COOMe)





(IX : R = H ,
X : R = $SnBu_3$,
XI : R = $SnPh_3$)

(XII : R = Bu_3Sn ,
XIII : R = o-$COC_6H_4COOSnBu_3$)

When IV was treated with a one molar proportion of phthalic anhydride in benzene the product was 6-*O*-(2′-tributylstannyloxycarbonylbenzoyl)-D-glucose (VII). Destannylation followed by acetylation and methylation as before gave 1,2,3,4-tetra-*O*-acetyl-6-*O*-(2′-methoxycarbonylbenzoyl)-D-glucose (VIII). The mass spectrum of VIII showed the $[M - AcO - 2AcOH - CH_2CO]^+$ peak expected for a 6-*O*-phthalated derivative [10]. These reactions demonstrate that a tributyltin group can have a dual function, first to activate sugar hydroxyl groups towards phthalation and second to confer high biological activity on the product.

When free D-glucose was treated directly with one molar proportion of phthalic anhydride a mixture was obtained which was shown by TLC examination and column chromatography to consist of unchanged glucose, two monophthalates, and a number of diphthalates. The monophthalate and diphthalate fractions were acetylated and methylated, and the products purified further by column chromatography to give, as principal components, the 6-*O*-phthalyl and 1,6-di-*O*-phthalyl derivatives VIII and VI, obtained by the other route. Thus, although essentially the same compounds are produced by the two methods, prior stannylation gives higher yields and mixtures which are much easier to purify.

Stannylated sugars are considerably more stable to hydrolysis than stannoxides of simple alcohols, and we confirmed that if all but one of the hydroxyl groups in a sugar are protected then the stannyl derivative is very moisture sensitive. Treatment of 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (IX) with bis(tributyltin) oxide in toluene and azeotropic removal of water appeared to give only unchanged starting materials, though very rapid hydrolysis of the desired product X may have occurred. Under the same conditions the triphenylstannoxide (XI) was apparently formed but underwent hydrolysis rapidly on exposure to moist air. The absence of a nearby oxygen stereochemically disposed to coordinate to tin may explain the lability of these stannoxides [11]. The previously reported [9] preparation of 1,2 : 3,4-di-*O*-isopropylidene-6-*O*-tributylstannyl-α-D-galactopyranose (XII) was repeated and the somewhat less moisture-sensitive product reacted with phthalic anhydride to give XIII.

Experimental

250 MHz ^1H and all ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument with tetramethylsilane as internal standard. Mass spectra were recorded

on a Kratos MS-25 spectrometer by electron impact at 70 eV with a DS 50 data processing system. Infrared spectra were recorded on a Perkin–Elmer 398 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 141 automatic polarimeter or on a Bellingham and Stanley manual polarimeter. Mössbauer spectra were measured on the U.L.I.R.S. instrument at Birkbeck College; isomer shifts refer to barium stannate.

Reactions were monitored by TLC on silica gel coated aluminium plates (Merck 5554). Carbohydrates were detected by spraying the plates with a 5% solution of sulphuric acid in ethanol followed by charring on a hot plate. Tin compounds were detected by exposure to iodine vapour followed by spraying with a 0.1% solution of Catechol Violet.

Column chromatography was carried out under pressure (5–15 psi) using Kieselgel 60 (23–400 mesh ASTM).

Tributylstannyl ether phthalate (I)

A solution of tributyltin ethoxide (0.50 g, 1.5 mmol) phthalic anhydride (0.22 g, 1.5 mmol) in dry DMF (20 ml) was stirred at room temperature for 24 h. Removal of the DMF under reduced pressure at 30 °C left an oil which solidified on standing. Purification on a silica gel column (eluant: ethanol/carbon tetrachloride 1/3) gave I (0.66 g, 91%) as a cream solid with no characteristic m.p. ^{1}H NMR (CCl_4): δ 0.7–2.0 (m,3H), 4.1–4.6 (q,2H), 7.3–7.8 (m,4H); ^3J(Sn–C–H) 36.56 Hz. ^{13}C NMR ($CDCl_3$) (* = tin satellite): δ 171.81, 168.79, 133.48, 133.15, 130.45, 130.29, 129.63, 128.08, 61.33, 28.01 *, 27.85, 27.70 *, 27.63 *, 27.11, 26.58 *, 19.51 *, 19.39 *, 16.68, 14.15, 13.98 *, 13.86 *, 13.66; ^1J(Sn–C) 19.781 Hz, ^2J(Sn–C–C) 65.661 Hz, $^3J(^{117,119}$Sn–C–C–C) 339.987/355.50 Hz. IR: ν(C=O)$_{(COOC)}$ 1727, ν(C=O)$_{(COOSn)}$ 1645, 1596, 1573 cm^{-1}. Mössbauer spectra $\delta = 1.05 + 0.01$, $\Delta = 3.76 + 0.02$ mm s^{-1}. Anal. Found: C, 54.5, H, 7.3. $C_{22}H_{36}O_4Sn$ calcd.: C, 54.7; H, 7.5%.

Tributylstannyl ethyl succinate (II).

Using identical conditions a solution of tributyltin ethoxide (0.50 g, 1.5 mmol) and succinic anhydride (0.15 g, 1.5 mmol) in dry DMF (20 ml) was stirred for 24 h at room temperature. Removal of solvent under reduced pressure left a solid which was purified by column chromatography to give II (0.57 g, 88%), m.p. 50–53 °C. ^{1}H NMR ($CDCl_3$): δ 0.7–1.9 (m, 3H), 2.6 (s, 4H, 3.9–4.4 (q, 2H). IR, ν(C=O)$_{(COOC)}$ 1726, ν(C=O)$_{(COOSn)}$ 1644, 1591, 1561 cm^{-1}. Mössbauer spectrum, $\delta = 1.04 + 0.01$, $\Delta = 3.68 + 0.01$ mm s^{-1}. Anal. Found; C, 49.7, H, 8.3. $C_{18}H_{36}O_4Sn$ calcd.: C, 49.7; H, 8.3%.

Tributylstannyl ethyl maleate (III).

A similar procedure starting from tributyltin ethoxide (2.51 g, 7.5 mmol) and maleic anhydride (0.74 g, 7.5 mmol) in dry DMF (40 ml) gave, after chromatographic purification, III (3.11 g, 96%), m.p. 72–73 °C. ^{1}H NMR (CCl_4) δ 0.6–1.9 (m,3H), 3.9–4.4 (q,2H), 5.8–6.4 (q,2H). IR ν(C=O)$_{(COOC)}$ 1728, ν(C=O)$_{(COOSn)}$ 1644, 1573 cm^{-1}. Mössbauer spectra, $\delta = 1.07 + 0.1$, $\Delta = 3.76 + 0.02$ mm s^{-1}.

1,6-Di-O-(2'-tributylstannyloxycarbonylbenzoyl)-D-glucose (V).

A solution of IV [9] (3 g, 2.9 mmol) and phthalic anhydride (1.3 g, 9 mmol) in dry DMF (30 ml) was stirred at room temperature for 4 h in a flask protected from atmospheric moisture by a calcium chloride drying tube. Diethyl ether (30 ml) was

added and the mixture extracted with 3×10 ml portions of aqueous sodium bicarbonate (0.1 g in 100 ml water). The ethereal layer was concentrated to constant weight in vacuo to give VIII as an amber oil (2.8 g, 66%). IR: $\nu(C{=}O)_{(COOC)}$ 1720, $\nu(C{=}O)_{(COOSn)}$ 1620, ν(SnOC) 1060, ν(OH) 3410 cm^{-1}. Anal. Found: C, 52.3, H, 7.6. $C_{46}H_{72}O_{12}Sn_2$ calcd.: C, 52.4, H, 6.9%.

2,3,4-Tri-O-acetyl-1,6-di-O-(2′-methoxycarbonylbenzoyl)-D-glucose (VI).

Compound V (0.59 g, 4 mmol) was treated with trifluoroacetic acid (2 ml) in iced water (25 ml) for 30 min, the mixture was extracted with four portions (15 ml) of chloroform, and the aqueous phase reduced to constant weight in vacuo to give 1,6-di-*O*-(2′-carboxybenzoyl)glucose (0.19 g, 77%). Acetylation and methylation of this product (30 mg) by standard methods gave VI (19 mg, 48%). Pure VI, m.p. 41–42.5 °C, was obtained by column chromatography (diethyl ether). MS, *m/z* 451 (4.5, $[M - MeOOCC_6H_4COO]^+$), 289 (1.6, $[M - MeOOCC_6H_4COO - CH_2O - 2AcOH]^+$), 163, (100, $[MeOOCC_6H_4CO]^+$), 149 (4.5, $[HOOCC_6H_4CO]^+$). Anal. Found: C, 56.4; H, 5.2. $C_{30}H_{30}O_{15}$ calcd.: C, 57.1; H, 4.8%.

6-O-(2′-Tributylstannyloxycarbonylbenzoyl)-D-glucose (VII).

A solution of IV (1.0 g, 0.95 mmol) and phthalic anhydride (0.14 g, 0.95 mmol) in dry (sodium) benzene (10 ml) was stirred at room temperature for 2 h. The mixture was washed with three portions (10 ml) of aqueous sodium carbonate (0.1 g in 200 ml water) reduced to constant weight under reduced pressure to give VII as on oil (0.42 g, 71%). IR, $\nu(C{=}O)_{COOC}$ 1720, $\nu(C{=}O)_{(COOSn)}$ 1630, ν(SnOC) 1070, ν(O–H) 3400 cm^{-1}. Anal. Found: C, 51.2; H, 7.2. $C_{26}H_{42}O_9Sn$ calcd.: C, 50.6, H, 6.9.

1,2,3,4-Tetra-O-acetyl-6-(2′-methoxycarbonylbenzoyl)-D-glucose (VIII)

A solution of VII (0.42 g, 0.7 mmol) and trifluoroacetic acid (2 ml) in iced water (25 ml) was kept at room temperature for 30 min. The mixture was washed with four portions (15 ml) of chloroform and the aqueous layer evaporated to constant weight under reduced pressure to give 6-*O*-(2′-carboxybenzoyl)-D-glucose as a white solid (0.30 g).

Acetylation by standard procedures gave the crude tetraacetyl derivative, which was purified by column chromatography (eluants: 1 ethyl acetate, 2 methanol) and then methylated to give the mixed anomers of VIII as a syrup (0.10 g). MS, *m/z* 451 (4.4, $[M - AcO]^+$), 331 (0.6, $[M - AcO - 2AcOH]^+$), 289 (0.7, $[C_6H_6O_3COC_6H_4COOMe]^+$). Anal. Calcd for $C_{23}H_{26}O_{13}$: C, 54.1; H, 5.1. Found: C, 54.0; H, 5.2%.

Attempted preparation of 1,2 : 5,6-di-O-isopropylidene-3-O-tributylstannyl-α-D-glucofuranose (X).

A solution of IX (1 g, 3.8 mmol) and bis(tributyltin) oxide (1.14 g, 1.9 mmol) in toluene or *m*-xylene (55 ml) was refluxed during 20 h as water was removed azeotropically with a Dean and Stark separator. The solvent was removed in vacuo. IR: ν(SnOSN) 750 cm^{-1}, ν(O–H) 3240 cm^{-1}.

Attempted preparation of 1,2 : 5,6-di-O-isopropylidene-3-O-triphenylstannyl-α-D-glucofuranose (XI)

A solution of IX (1 g, 3.8 mmol) and triphenyltin hydroxide (1.41 g, 3.8 mmol) in toluene (40 ml) was refluxed for 8 h as water was removed azeotropically with a

Dean and Stark separator. Water was evolved and reaction appeared to have occurred, but when the solvent was removed in vacuo to leave a syrup the IR spectrum still showed the presence of free hydroxyl groups, ν(O–H) 3240 cm^{-1}.

1,2 : 3,4-Di-O-isopropylidene-6-O-tributylstannyl-α-D-galactopyranose (XII)

1,2 : 3,4-Di-*O*-isopropylidene-α-D-galactopyranose (1 g, 3.8 mmol) and bis(tributyltin) oxide (1.14 g, 1.9 mmol) in toluene (55 ml) was refluxed for 15 h with the usual azeotropic removal of water. The solvent was removed in vacuo leaving an oil, and distillation gave pure XII (1.7 g, 82%). B.p. 175–177 °C/0.21 mmHg (lit. [9] value 160–162 °C/0.06 mmHg). IR, ν(Sn–O–C) 1070 cm^{-1}.

1,2 : 3,4-Di-O-isopropylidene-6-O-(2'-tributylstannyloxycarbonylbenzoyl)-α-D-galactopyranose (XIII)

A solution of XII (1 g, 1.8 mmol) and phthalic anhydride (0.3 g, 2 mmol) in dry DMF (7.5 ml) was kept at 80 °C for 15 h with stirring in a flask protected from atmospheric moisture by a calcium chloride drying tube. Diethyl ether (25 ml) was added, and the mixture extracted 4 times with water (5 ml). The ethereal extract was dried over magnesium sulphate, filtered, and evaporated in vacuo to give XIII as a syrup (1.0 g, 83%). IR, $\nu(C{=}O)_{COOC}$ 1720, $\nu(C{=}O)_{COOSn}$ 1640 cm^{-1}.

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