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SHORT COMMUNICATION

Polymer-supported tin carbohydrate chemistry

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It was anticipated that stannylation of carbohydrates could be achieved using tin on a polymer-support. Such immobilization simplifies the purification of the carbohydrate because the toxic tin reagent can be removed by filtration. In this case an alkene linker (3-buten-1-ol) was added to chloromethylated 2% cross-linked polystyrene by etherification. Photochemical hydrostannylation with dibutyltinchlorohydride gave a polymer bound trialkyl tin chloride. The Sn-Cl could be hydrolysed with NaOH to yield a resin with terminal Sn-O bonds. Highly regioselective acylation of methyl α-D-mannopyranoside (αMeMan) to its 3-*O*-benzoyl derivative was achieved. Traces of the mono 6-*O*-benzoate and the 3,6-di-*O*-benzoate were also obtained. Methyl α-D-glucopyranoside was also selectively acylated to its 2-*O*-benzoate but this reaction gave a more complex mixture. The isolated yields (10–30% based on sugar) were disappointingly low. The yields were improved to about 60% with 5% cross-linked resin.

***Keywords*: polymer-support, tin, stannylation**

Introduction

Several reports of using Sn(IV) functionalized polymeric supports as organic reagents have been made [1, 2]. Polymer-supported reagents have two practical advantages over the analogous soluble reagents, namely that toxic materials are easier to handle and the work-up of the reaction products is by simple filtration and washing procedures. Although Sn reagents particularly dibutylstannyl oxide and bis(tributylstannyl) oxide have been widely used in carbohydrate chemistry for regioselective acylation and alkylations [3, 4] only the one report of using polymer supported reagents for carbohydrate chemistry has been made [5]. In this preliminary study we outline the preparation of a Sn functionalized polymer and its application to acylations of monosaccharides.

Methods

General

Dibutyltindihydride was prepared from dibutyltindichloride according to van der Kerk *et al.* [6]. The 5% cross linked chloromethyl polystyrene resin was a gift from the Mitsubishi corporation. The Merrifield resin and the 3-buten-1-ol were purchased from Aldrich and all other reagents were commercially available from standard sources. IR spectra were run as KBr pellets on a Shimadzu Fourier-Transform, FT-IR spectrometer. All sugar derivatives were identified by ^{1}H NMR using a Jeol EX-270 spectrometer. For literature values for α-MeMan derivatives see [7–9], and for α-MeGlc derivatives see [10–12].

Preparation of chlorostannylated polystyrene resin – PS-Sn-Cl

3-Buten-1-ol (1.032 ml; 12 mmol) and dry tetrahydrofuran, THF, (20 ml) were added to a RB flask under an N_2 atm. To this solution at 0 °C was added n-BuLi (12 ml of 1.6 M in hexane; 12 mmol). After vigorous stirring for 1 h, 2% cross linked chloromethylpolystyrene resin (4 g; 2 mmol) was added quickly as a solid and the whole mixture was left to shake and warm to RT overnight. The resin after neutralization with solid NH_4Cl was recovered by filtration with washings with CH_3OH (3 ×), H_2O (4 ×), CH_3OH (3 ×) and Et_2O (3 ×). Drying at high vacuum yielded 3.65 g. This resin was swelled in freshly distilled benzene (40 ml) and dibutyltindichloride (2.22 g; 7.7 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 250 mg; 1.5 mmol) were added followed by dropwise addition of dibutyltindihydride (1.72 g; 7.7 mmol). The resulting mixture was left shaking under irradiation with a 150 W lamp and under a N_2 filled balloon for 3 d. Periodically aliquots of AIBN (25 mg) were added. The

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resin was recovered by filtration after rinsing with C_6H_6 (3×), THF (2×), H_2O (5×), THF, CH_3OH (3×), C_6H_6 (2×) and Et_2O. After drying this yielded 3.6 g of a slightly grey coloured resin, PS-Sn-Cl. IR spectrum was compared to starting resin and differences at 2960 (C–H), 1480 and 1150–1050 (C–O) cm^{-1} were found as well as disappearance of bands at 1260 (C–Cl) cm^{-1}. Anal. Cald. for C, 78.6; H, 7.71; Cl, 2.7; Sn, 9.0. Found C, 81.9; H, 7.08; Cl, 0.70; Sn, 9.35.

Preparation of 5% cross linked chlorostannylated polystyrene resin – PS-Sn-Cl

Derivitization of the 5% cross linked chloromethylated polystyrene resin followed the same procedure as outlined above.

Preparation of hydroxystannylated polystyrene resin – PS-Sn-OH

PS-Sn-Cl resin (2 g) was swollen in THF (20 ml) and 2 M $NaOH_{aq}$ (20 ml) was added slowly dropwise over 1.5 h. The mixture was left to stir gently overnight and the resin recovered by filtration with rinsing THF, H_2O (5×), THF, THF:H_2O (5×), THF, CH_3OH (3×), THF (2×) and Et_2O. After drying at high vacuum yielded 1.74 g of a white resin. IR spectrum was compared to starting PS-Sn-Cl resin and differences at 1150–1050 (C–O) and 860 cm^{-1} were found as well the appearance of broad band at about 3200 (OH) cm^{-1}. Anal. Cald. for C, 78.8; H, 7.7; Cl, 0.0; Sn, 9.0. Found C, 87.1; H, 7.6; Cl, 0.27; Sn, 7.2.

Method A. Regioselective Benzoylation of α-MeMan using PS-Sn-Cl Resin

Methyl α-D-mannopyranoside (16 mg; 0.08 mmol) was suspended in dry THF (3.5 ml) and NaH (8 mg 60% in mineral oil; 0.2 mmol) was added under an atm of argon. After stirring for 1.5 h, the PS-Sn-Cl resin (220 mg; nominally 0.2 mmol) was added and the mixture left to stir overnight. The resin was collected by filtration and rinsed with THF (20 ml). The resin was transferred to a fresh RB flask and dry THF (3 ml) was added. After stirring gently for 15 min at 0 °C, benzoyl chloride (BzCl 0.05 ml; 0.4 mmol) was added dropwise and the mixture left to stir overnight. The filtrate was collected by filtration and rinsing with THF, CH_3OH and THF. The residue after evaporation was purified by preparative TLC on 20 × 20 cm × 0.5 mm SiO_2 plates using 10% $CH_3OH/CHCl_3$ as eluent. The main product $R_f = 0.3$ was methyl 3-*O*-benzoyl-α-D-mannopyranoside (**1A**, 2.6 mg; 11%). Some $R_f = 0.85$ methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside (**1C**, < 1 mg) and $R_f = 0.25$ methyl 6-*O*-benzoyl-α-D-mannopyranoside (**1B**, < 1 mg) were also isolated.

A preparation using 5% cross linked resin (110 mg; nominally 0.1 mmol) and α-MeMan (5 mg; 0.025 mmol) yielded **1A** (4.7 mg; 60%), **1A** mixed with **1B** (2 mg) and **1C** (< 1mg).

Method B. Regioselective Benzoylation of α-MeMan using PS-Sn-OH Resin

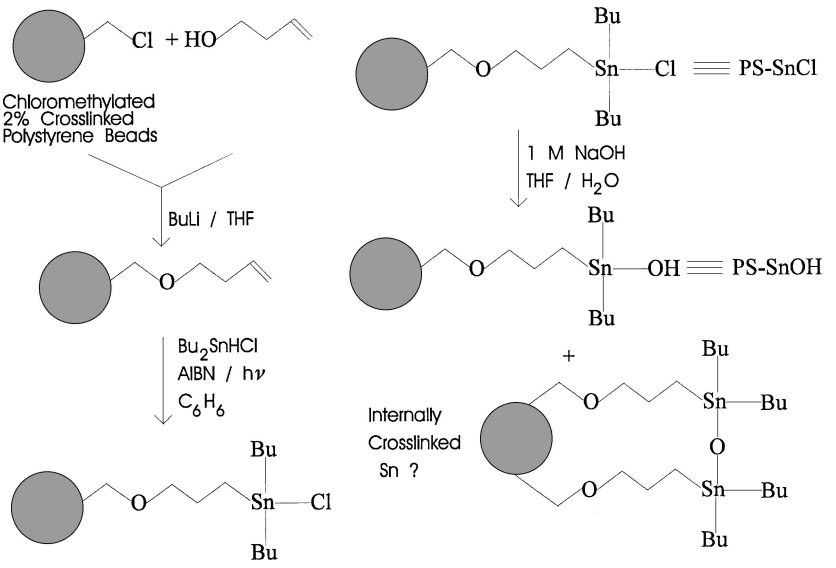
Methyl α-D-mannopyranoside (5 mg; 0.025 mmol) was suspended in C_6H_6 (30 ml) along with PS-Sn-OH resin (132 mg; nominally 0.1 mmol) and heated to reflux under azeotropic conditions overnight. The solvents were removed or concentrated by evaporation and the resin was either resuspended in THF (3 ml) or left in about 3 ml of C_6H_6. To the resulting mixtures was added BzCl (0.04 ml; 0.23 mmol) and the mixtures left to stir under an argon atm overnight. From THF **1A** (2.6 mg; 33%) and from C_6H_6 **1C** (2.2 mg; 22%) were isolated along with traces of **1B** and **1C** or **1A** and **1B** respectively. From THF the **1A** : **1B** ratio was > 7 : 1.

Methyl α-D-glucopyranoside and phenyl-β-D-glucopyranoside were treated under the conditions of method B.

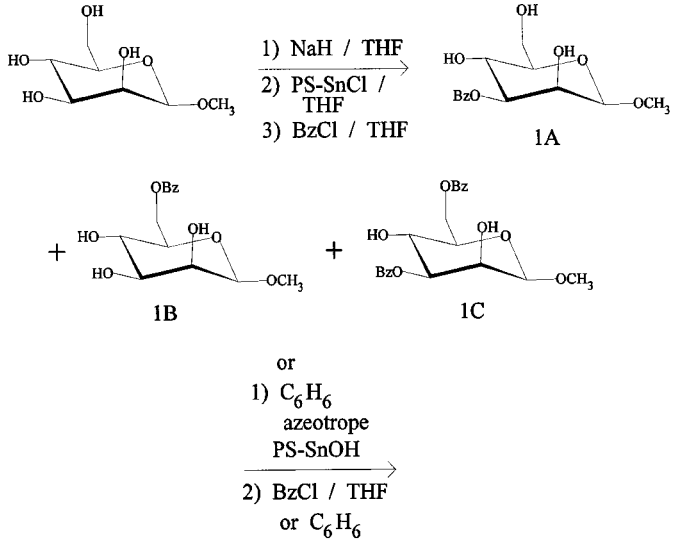
Results and discussion

The polymer supported Sn reagent was prepared from 2% cross linked 1 mmol g^{-1} chloromethyl polystyrene (Merrifield Resin) by treating the chloromethyl polymer with lithium 3-butenyloxide in THF followed by photolytic hydrostannylation [13] with dibutyltinchlorohydride [14] (see Scheme 1). The resulting PS-CH_2–O–$(CH_2)_4$–Bu_2Sn–Cl (PS = polystyrene and Bu = *n*-butyl) subsequently abbreviated to PS-Sn-Cl could be used with sugar alkoxides but was more conveniently hydrolysed with 1 M NaOH in THF/water [15] to the corresponding PS-Sn-OH polymer.

One question that arises which impacts directly on the reactivity of the resin is whether or not Sn-O-Sn bridges exist in this polymer? It is anticipated that only Sn-OH or Sn-Cl sites will be reactive (Scheme 1). As a test reaction methyl α-D-mannopyranoside (α-MeMan) was reacted with benzoyl chloride. Classical solution Sn chemistry gives predominantly the 3,6-di-*O*-benzoate **1C** [7]. Polymer bound Sn-alkoxides were prepared by either treating the PS-Sn-Cl resin with the sodium alkoxide of the sugar in THF (from NaH + sugar) followed by filtration and rinsing with THF and then resuspension and treatment with BzCl or by treating the PS-Sn-OH polymer (0.1 mmol, based on original chloromethyl content) under azeotropic conditions with benzene overnight, followed by solvent exchange and treatment with benzoyl chloride (see Scheme 2.). Either procedure yielded 10–30% of the known mono-3-*O*-benzoate [7] of α-MeMan **1A**. This fraction was contaminated with a small amount of the known mono-6-*O*-benzoate [9] (3-Bz:6-Bz > 7 : 1). Also a small amount of pure 3,6-di-*O*-benzoate was isolated (total mono:di > 5:1). Experimentation revealed that 5 mg of α-MeMan (about 0.025 mmol) almost completely reacted under these conditions. Some material must be lost during filtration and purification because the final mass balance is less than 100%. Larger amounts of sugar did not increase the absolute yield or change the



Scheme 1. Preparation of polymeric Sn reagent and hydrolysis of Sn-Cl to Sn-OH and possible formation of cross links.



Scheme 2. Regioselective benzoylation of *α*-MeMan.

apparent regioselectivity or the di-benzoate to mono-benzoate ratio significantly. The original protocol included a filter and rinsing with THF step, after the azeotropic treatment but before treatment with BzCl. However, higher yields were obtained by simple evaporation to dryness followed by addition of THF then BzCl. Under these conditions almost no starting material was recovered. Interestingly, concentrating the benzene to about 3 ml instead of to dryness and, after cooling, adding BzCl (*ie* no THF) led to predominantly 3,6-di-*O*-benzoate **1C** formation, although under these conditions significant amounts of α-MeMan were recovered. This observation requires further experimentation to verify this solvent effect. Two separate preparations of this polymer gave very similar activities.

Further controls included treating underivatized chloromethyl resin, PS-CH_2Cl, with the standard protocol and led to a small yield ($< 5\%$) of a complex mixture of monobenzoylated α-MeMan isomers. A polymer prepared by a similar hydrostannylation protocol except that a shorter alkene side chain PS-$CH{=}CH_2$ was used. This was not active as a catalyst. The progress of the solid phase derivitization was followed by FT-IR of the PS beads as KBr pellets [16]. Also, the disappearance or presence of Cl and Sn were tested by elemental analysis. The incorporation of Sn was close to what was expected on the basis of the original chloromethyl content (about 9% Sn). However, the amount of Cl was low suggesting that Sn-O-Sn bridges had been formed.

Treatment of α-MeGlc under the azeotropic conditions (method B, see Methods) which gave a mixture of mono and di-*O*-benzoates in a ratio of approximately 2:1. The di-*O*-benzoate was mostly the known 2,6-di-*O*-benzoate [7, 10] but the mono benzoate fraction contained several components although the main ones were the 2-*O*-benzoate and the 6-*O*-benzoate [11]. Treatment of phenyl-*β*-D-glucopyranoside gave only trace quantities of its 6-*O*-benzoate under these conditions. Similar reactions with a 5% cross linked chloromethyl polystyrene yielded 3-*O*-benzoyl-α-MeMan **1A** in 60% isolated yield in addition to some recovered starting material and traces of **1B** and **1C**.

Thus, the preliminary results suggest a preference for regioselective reaction at vicinal cis-diols (*ie* α-MeMan O-2 and O-3 or α-MeGlc O-2 and O-1) leading to preferential formation of the mono-acyl derivative at the equatorial position [17]. Much work remains to be done to optimize the yields and reaction conditions.

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