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Tin(IV)-functionalised polymer supports; non-toxic and practical reagents for regioselective acetylation of sucrose

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Abstract

Polymer-supported butyltin(IV) reagents have been surveyed for regioselectivity in acetylation of sucrose. Polymer-supported butyltin(IV) dichloride 8 catalysed the acetylation of sucrose to give a 59% yield of 6-O-acetyl sucrose 3, the precursor of sucralose. The yield is close to that of a previously reported process involving dibutyltin(IV) oxide (Bu_2SnO). The spent polymeric resin could readily be regenerated and can be subsequently used in further synthetic reactions.

Keywords: Sucralose; Butyltin(IV) dichloride, polymer-supported; Acetylation, regioselective; 6-O-Acetyl sucrose; Regenerated polymer

1. Introduction

Synthetic sucrose derivatives have widespread applications in the cosmetic, plasticiser and food industries [1,2]. Sucralose (4,1',6'-trichloro-4,1'6'-trideoxygalactopyrano-syl-(1 \rightarrow 1)- β -D-fructofuranoside, 1), a high-intensity sweetener, may be obtained by tritylation of sucrose, acetylation and detritylation, followed by C-4 \rightarrow C-6 acetyl migration [3,4], to give 2,3,6,3',4'-penta-O-acetyl sucrose (2); chlorinating the 4,1'- and 6-hydroxyl groups of 2, then deacetylation gives sucralose [5]. The route is circuitous and is not suitable for large-scale synthesis. Alternatively 6-O-acetylsucrose 3 may be

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chlorinated and subsequently deacetylated to afford 1 in good yield [6,7]. Provided 3 is readily available, the latter process has good potential for large-scale synthesis.

Several regioselective chemical esterifications of sugar substrates have been developed over the years. The selectivity of these reactions is based on (i) the regioselective enhancement of the nucleophilicity of hydroxyl groups by use of dibutyltin(IV) oxide [8,9], tributyltin(IV) oxide [10] or via cobalt chelates [11], (ii) selectivity for primary hydroxyls associated with the use of bulky reagents, and by application of the Mitsunobu reaction [12] or (iii) minimizing the extent of intramolecular acyl migration by forming the corresponding thiazolidine-2-thione sugar [13]. Strategies for obtaining **2** include selective removal of acetyl groups from the corresponding octaacetate by chemical [14] and enzymatic methods [15–17], and by biological acetylation [18,19].

We are interested in the acetylation of sugar substrates by regioselective considerations. Dibutyltin(IV) reagents hold excellent potential for regioselective acetylation of sugars. The effects of their toxicity [20] may be alleviated by use of a polymer support which would combine the regioselective enhancement of the tin(IV) reagent with ease of operation, work-up and regeneration of reagent and the avoidance of malodours and toxic vapours. We report the preparation of such polymer-tin supports and compare their effectiveness in regioselective acetylation of sucrose.

X-ray studies by David et al. [21] have established that in the dibutylstannylene adduct of methyl 4,6-O-benzylidene- α -D-glucopyranoside, tin atoms are positioned as a trigonal bypyramid forming part of a dimer. In Bu₂SnO-mediated acetylation of sucrose, the stannylene adduct was ascertained by elemental analysis to be a dimer; however, on the basis of the latter giving rise to pure isomeric formation of 6-acetate 3, dimer 5 was proposed as a putative structure [22,8]. In principle, therefore, we proposed that the polymer-supported butyltin(IV) oxide 6 could form a polymer-bound di-tin equivalent 7 by a two-point attachment of sucrose to the polymer (Scheme 1), and a similar level of regioselectivity should result in monoacetylating the latter intermediate as in acetylation



Scheme 1.



Scheme 2.

of 5 (Scheme 2). It turned out in practice, however, that regioselective synthesis of 6-O-acetylsucrose using the polymer-supported reagent 8 rather than 6 compared excellently with that (60% yield) employing dibutyltin oxide [8].

2. Results and discussion

The polymer-supported butyltin reagents 6, 8, 9, 10 and 11 were prepared from polystyrene resin via bromide 12 and lithium salt 13 or Grignard reagent 14 [23]; they were employed in a methodology which is akin to a procedure for solution-phase dibutyltin(IV) oxide mediated acetylation of sucrose [8], and the results are combined in Table 1. The dichloride 8 is the preferred reagent on the basis of its being most efficient in sucrose monoacetate conversion and relatively straightforward to prepare and regenerate. Control experiments were carried out whereby an amount of non-polymeric dibutyltin reagent, equivalent to the level of SnX_2 groups present in the polymeric case, was used in the solution-phase reaction for monoacetylation of sucrose and gave in similar yields, a sucrose monoacetate product which had similar NMR and IR characteristics as for the polymer case (a 65% isolated yield of sucrose monoacetate was obtained in the case of dibutyltin dichloride being the reagent). Blank experiments employing the above conditions, either in the presence or absence of non-functionalised polystyrene resin, did not yield any sucrose acetate product.

Good yields of sucrose acetates obtained from a 1:65 mole ratio of pendant SnX_2 groups to sucrose indicate that the polymeric species is acting catalytically. Any attempts to obtain a sucrose acetate product by directly reacting polymer 8 with sucrose in DMF were thwarted by the apparent unreactive nature of the polymer-supported

Observations ^b
Low conversion to sucrose monoacetate; major spot sucrose.
Both sucrose mono- and di-acetate were detected in roughly equal amounts with trace amounts of sucrose; good conversion to sucrose monoacetate product observed.
Small conversion to sucrose mono- and di-acetate; mostly sucrose.
Sucrose mono- and di-acetate were detected in roughly a 1:2 proportion, respectively; a significant amount of sucrose remained.
Both sucrose mono- and di-acetates detected; poor level of conversion was observed for monoacetate.

Qualitative screening of polymeric tin(IV) reagents for monoacetylation of sucrose ^a

^a The general experimental protocol is given in the text.

^b Observations were made by examining TLC plates of the corresponding reactions.

^c Polymer-supported reagent can be easily regenerated by refluxing with acetyl chloride.

^d Regeneration easier than for the non-polymeric tin(IV) reagent, but more difficult than for 6, 8, and 11.

butyltin dichloride species in such media. Therefore, refluxing polymer $\mathbf{8}$ with sucrose in methanol and pyridine seems necessary for attaining polymer-supported stannyl ether sugar functions. Thus mechanistically it is supposed that at the stage of the latter intermediate being converted to acetate product, polymer reaction sites are being replaced by an equivalent amount of sucrose substrate.

Studies with varying molar ratios of tin(IV) groups to sucrose indicated that virtually all the sucrose is converted to mono- and di-acetate product when the polymer **8** is employed in the ratio 1:28 with a mole ratio of sucrose to acetic anhydride set at 1:3. A reduced diacetate yield is obtained for polymer **8** when sucrose and acetic anhydride are present in almost equimolar amounts without appreciable loss of monoacetate product; the filtrate from this polymer suspension after flash chromatography gave an isolated product **3** in 59% yield based on sucrose. The standard perdeuteroacetylation-¹H NMR procedure [24] indicated that the monoacetate **3** is the 6-isomer with minor amounts of other isomers present. The isomeric impurities of this 6-*O*-acetyl sucrose sample could be eliminated by performing acetyl group migration and then adsorbing the crude product onto non-polar Amberlite XAD resins, followed by elution with aqueous methanol (vide infra) [18].

The main component 4, contained in the diacetate product formed from acetylation catalysed by polymer 8, probably arises from a cyclic stannylene intermediate 15. We attempted to achieve exclusively monoacetylation by use of polymer 11. However, considerable amounts of sucrose diacetate were also produced, and it is speculated that this occurs via a two-site binding of the sugar to the polymer 16 or by further polarisation of a neighbouring sucrose hydroxyl oxygen atom after mono-binding to the polymer 17 [25] (Scheme 3). A surprising result was that polymer-supported butyltin(IV) oxide 6 showed no regioselectivity towards acetylation at the C-6 position of sucrose, unlike solution-phase monoacetylation using $Bu_2 SnO$ [8].

It should be noted that even after six cycles, the regenerated polymer 8 could monoacetylate sucrose to the same extent as determined by TLC and product isolation.

In conclusion, the solid-phase method yields gram quantities of 6-O-acetylsucrose in

Table 1



Scheme 3.

59% yield. Producing this level of 6-O-acetylsucrose in successive cycles of executing the solid-phase strategy has the advantage over its solution-phase equivalent in that (i) separation of acetate product from spent tin reagent can be simply carried out by filtration, (ii) there is no exposure to a toxic tin(IV) reagent, and (iii) the spent polymer can be readily regenerated by refluxing with acetyl chloride. In addition, the solid-phase technique seems to include a catalytic function. The recycling property of polymer **8** gives excellent potential for a continuous process, although resorting to other purifica-

tion methods to avoid using flash chromatography may be an important practical consideration in large-scale synthesis.

3. Experimental

General.-Melting points were determined with a Kofler apparatus and are uncorrected. NMR spectra were recorded with a Jeol GX 270 for both ¹H (270 MHz) and ¹³C (90 MHz) nuclei using ca. 10% solutions in the deuterated solvents indicated (internal Me₄Si). IR spectra were recorded with a Perkin–Elmer 683 IR spectrophotometer. The IR spectra of all tin-functionalised polymers prepared in this study were checked against the IR spectrum of a blank sample of non-functionalised resin. The purity of products was determined by TLC on Silica Gel 60 F_{254} (E. Merck) with detection by charring with sulfuric acid. Elemental analyses were performed with a Carlo Erba CHN instrument. Flash column chromatography was performed using silica gel (Wakogel C-300) as adsorbent. The tin-functionalised polymers were prepared from microporous 2% cross linked Pontybond 2166 polystyrene resin (100 mm particle size). Tetrahydrofuran was removed of its peroxides by passing it through a column of basic alumina, and the solvent was dried by refluxing over calcium hydride under nitrogen and distilled prior to use. Anhydrous pyridine was obtained by refluxing in the presence of barium oxide, fractionally distilling under a dry atmosphere, with storage over KOH pellets. Methanol was dried by treatment with magnesium metal activated with iodine. Anhydrous Me₂NCHO was purchased from Aldrich Chemical Company. The sucrose (analytical grade) was grounded to a fine powder prior to use. Acetic acid was dried by adding 10%/wt of Ac₂O, refluxing the mixture in CrO₃, and then fractionally distilling. All other reagents were used as commercially received.

Polymer-supported butyltin(IV) dichloride (8).—The preparation was carried out as according to the method of Crosby et al. [23] without modification. After air drying and then drying under vacuum (2 Torr), the resin was refluxed in 20%/v of an acetyl chloride-benzene (Na dried) solution for 12 h, filtered, washed with CH_2Cl_2 (4×50 mL) and then dried under vacuum overnight. Sn content: 0.038 mmol/g; IR ν_{max} (Nujol mull): 595, 505(w) (Sn–C), 350, 335 (Sn–Cl) cm⁻¹.

Polymer-supported butyltin(IV) oxide (6).—To 6.32 g of polymer 8 in a 250 mL conical flask, 100 mL of 5 N NaOH solution was added, and the resulting suspension stirred for 6 h at room temperature. The hydrolysed polymer was collected using a grade 3 sintered glass funnel and washed with the following solvents: MeOH (4×50 mL), acetone (4×50 mL) and CH₂Cl₂ (4×50 mL) and then air dried. The polymer was transferred to a Dean–Stark apparatus, and a suspension of the polymer in toluene (Na dried) was refluxed at 120 °C overnight. Finally the polymer was filtered, washed with CH₂Cl₂ (4×50 mL) and air dried; Sn content: 0.0388 mmol/g; IR ν_{max} (Nujol mull): 1425, 1050, 865(m) (Sn=O), 675 (Sn-C) cm⁻¹.

Polymer-supported butyltin(IV) dimethoxide (9).—Polymer 8 (5.00 g) was stirred in a methanolic solution of NaOMe (391 mmol in 250 mL of MeOH) at room temperature overnight. The mixture was filtered and washed; dry MeOH (4×50 mL), dry Et₂O

 $(4 \times 50 \text{ mL})$. After drying it was stored under vacuum over self-indicating silica gel. Sn content: 0.0328 mmol/g; IR ν_{max} (Nujol mull): 565 (Sn–OMe) cm⁻¹.

Polymer-supported butyltin(IV) diacetate (10).—Lithium aluminium hydride (1.21 g, 31.9 mmol) was dissolved in 20 mL of dry THF (1.6 M). Polymer 8 (6.0 g) was then added to the latter solution, and the mixture was stirred at room temperature for 6 h in a round-bottom flask connected to a glass-fritted Schlenk tube assembled according to the method of Fyles and Leznoff [26] for inert atmosphere filtration. The resulting polymeric butyltin(IV) dihydride was filtered under nitrogen and washed with dry THF (4 × 50 mL). Then 100 mL of dry acetic acid was added, and the suspension was stirred for 24 h at room temperature under nitrogen. Finally the resulting polymeric butyltin diacetate was filtered, washed with CH₂Cl₂ (4 × 50 mL), dried in vacuo and stored in a vacuum desiccator over calcium chloride; Sn content: 0.0365 mmol/g; IR ν_{max} (Nujol mull): 1680(m) (C=O), 555(w) (Sn-O) cm⁻¹.

Polymer-supported dibutyltin(IV) chloride (11).—This polymer-supported reagent was prepared by the method employed for the reagent 8 but employing dibutyltin(IV) dichloride. The material had a tin content of 0.040 mmol/g; IR ν_{max} (Nujol mull): 605 (Sn-C), 351, 336 (Sn-Cl) cm⁻¹.

Acetylation of sucrose; procedure for qualitative screening of polymer-supported tin(IV) reagents (see Table 1).—A mixture of sucrose (4.32 g, 12.62 mmol), polymer-supported butyltin(IV) species (to give a 1:65 mole ratio of pendant tin groups to sucrose), dry MeOH (100 mL) and pyridine (2.26 mL, 28.0 mmol) was refluxed under nitrogen for 12 h. Once the mixture was removed from the heat and cooled, the solvent was removed in vacuo, then dry Me₂NCHO (50 mL) and acetic anhydride (1.34 mL, 14.2 mmol) were added in sequence, and the suspension was left to stir at ambient temperature for 1 day. Filtrates were evaporated in vacuo and triturated with CH₂Cl₂; the resulting syrup of crude sucrose acetates was subjected to TLC (10:1 acetone–water), ¹H NMR and IR analyses.

6-O-Acetyl sucrose (3).—The above procedure was employed using polymer 8 at a ratio of 1:28 (tin groups to sucrose). TLC (10:1 acetone-water) showed monoacetate as the major product ($R_f = 0.37$) with sucrose diacetate ($R_f = 0.63$), and traces of sucrose. The suspension was filtered, and the polymer was washed with dry Me₂NCHO (4 × 20 mL) and dry MeOH (4 × 50 mL). The combined washings and filtrate were evaporated in vacuo. The crude sucrose monoacetate syrup was purified by flash chromatography (100:1 acetone-Et₃N, pH 7-8) to afford the crude compound 3 (2.86 g, 59%) and sucrose diacetate (0.43 g, 8%) in yields based on starting sucrose (4.32 g, 12.62 mmol).

Crude 3: white solid, mp 93–96 °C; IR: ν_{max} (Nujol mull) 3500(br) (OH), 1720(m), 1650(s) (C=O) cm⁻¹; ¹H NMR (270 MHz, CD₃OD): δ 4.86 (s, 7 H, OH), 4.6–3.4 (m, 14 H, pyranoid and furanoid), 2.12 (s, COCH₃), 2.11 (s, COCH₃) 2.10 (s, COCH₃), 2.09 (s, COCH₃) and 2.08 (s, COCH₃), (total 3 H). After perdeuteroacetylation; (1:1 C₆H₆-Pyr-d₅): δ 6.04 (d, 1 H, J 3.6 Hz, 1CH), 5.92 (t, 1 H, J 9.9 Hz, 3CH), 5.86 (d, 1 H, J 5.8 Hz, 3'CH), 5.69 (t, 1 H, J 5.8, 5.5 Hz, 4'CH), 5.45 (dd, 1 H, J 9.9, 10.2 Hz, 4CH), 5.21 (dd, 1 H, J 3.6, 10.4 Hz, 2CH), 4.64–4.39 (m, 5 H, 6'CH, 1'CH, 6CH, 5'CH, 5CH), 2.019, 1.971, 1.911, 1.885, 1.833, 1.827, 1.803, 1,796 (s, 3 H, C-3', 2, 6, 6', 1', 3, 4, 4', 1:1:100:4:5:2:4:4, COCH₃). ¹³C NMR (90 MHz, CD₃OD): δ 105.2 (C-2'), 93.3 (C-1), 83.9 (C-5'), 79.4 (C-3'), 76.0 (C-4'), 74.5 (C-2), 74.2 (C-3), 73.2

(C-5), 71.8 (C-4), 64.7 (C-6'), 63.9 (C-1'), 61.9 (C-6), 20.8 (CH₃ of COCH₃). Anal. Calcd for $C_{14}H_{24}O_{12} \cdot 1.5H_2O$: C, 40.87; H, 6.62. Found: C, 41.29; H, 6.59.

Sucrose diacetate containing mainly the 4,6-diacetate isomer (4): white solid, mp 51-53 °C; IR ν_{max} (Nujol mull) 3450(br) (OH), 1710(m), 1640(s) (C=O) cm⁻¹; ¹H NMR (270 MHz, CD₃OD): δ 4.82 (s, 6 H, OH), 4.6–3.4 (m, 14 H, pyranoid and furanoid), 2.109 (s, COCH₃), 2.076 (s, COCH₃), (total 6 H). After perdeuteroacetylation: (1:1 C₆D₆-Pyr-d₅): δ 6.08 (d, 1 H, J 3.6 Hz, 1CH), 5.94 (d, 1 H, J 10.4 Hz, 3CH), 5.89 (d, 1 H, J 5.7 Hz, 3'CH), 5.72 (dd, 1 H, J 5.7, 5.4 Hz, 4'CH), 5.48 (dd, 1 H, J 10.4, 9.7 Hz, 4CH), 5.25 (dd, 1 H, J 3.6, 10.4 Hz, 2CH), 4.75–4.54 (m, 8 H, 6'CH, 1'CH, 6CH, 5'CH, 5CH), 2.095, 2.050, 2.035, 1.984, 1.964, 1.943, 1.919, 1.904 (8d, 6 H, J 8.1 Hz, C-3', 2, 6, 6', 1', 3, 4, 4', 2:5:40:11:10:4:39:2, COCH₃). ¹³C NMR (90 MHz, CD₃OD): δ 105.2 (C2'), 90.8 (C1), 83.8 (C5'), 79.4 (C3'), 76.0 (C4'), 74.4 (C2), 73.2 (C3), 71.8 (C5), 71.4 (C4), 64.2 (C6'), 63.2 (C1'), 61.9 (C6), 21.1 (CH₃ of COCH₃), 20.8 (CH₃ of COCH₃). Anal. Calcd for C₁₆H₂₆O₁₃ · 3H₂O: C, 40.00; H, 6.71. Found: C, 40.15; H, 6.27.

Acetyl migration and purification of 3.—Acetyl migration of 3 was carried out by treating a 1.0 g sample at 150 °C for 24 h in a Me₂NCHO solution (10 mL) containing 5% Bu₃N and 5% water. The cooled solution was diluted with toluene, and repeated coevaporation of the volatiles in vacuo with the latter solvent gave a residue. Dissolving this residue in the minimum of MeOH and then adsorption onto an Amberlite XAD-2 column [18] (500 g), followed by elution with 80% aq MeOH, gave 3, which after perdeuteroacetylation-¹H NMR analysis [24] was shown to be isomerically pure. Further corroboration of the purity of 3 was provided by comparing the latter spectrum with that of the same compound synthesised from the solution-phase method employing Bu₂SnO [8].

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