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Tin-mediated regioselective acylation of unprotected sugars on solid phase

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Abstract

Methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and methyl β-D-galactopyranoside bound on O-6 to a copolystyrene–DVB resin through a trityl ether linker, have been regioselectively acylated with benzoyl chloride after treatment with Bu_2SnO and stannylene formation on solid phase. The benzoylation reactions proved to be highly regioselective affording 2-*O* benzoyl derivatives for glucose and 3-*O* benzoyl derivatives for galactose and mannose with high yield. © 2000 Published by Elsevier Science Ltd.

Tin-mediated esterification, alkylation,[1] and other transformations of the hydroxyl groups, including glycosylation,[2,3] have been extensively exploited for the regioselective functionalisation of sugars in solution. The stannylene derivative of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside has been characterised by X-ray analysis in the solid state as a dimer composed of two sugars linked through the Sn_2O_2 parallelogram[4] and the methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside has been crystallised as a pentamer constituted by a repeat of dioxystannacyclopentane units.[5] The consequent nucleophilic enhancement of the oxygen atom in the equatorial position in the oligomer may provide a plausible explanation of the regioselectivity observed in the subsequent functionalisation of the OH groups.

We present here an extension of this chemistry to the regioselective acylation of solid-phase bound monosaccharides with unprotected secondary hydroxyl groups. The emerging use of sugars as chiral multi-dimension-diversity scaffolds for combinatorial chemistry demands convergent and efficient solid-phase chemical methods for the selective functionalisation of the resin-bound sugar.[6,7] The preparation of monosaccharides protected with a set of orthogonal groups is a laborious but necessary step in obtaining a multifunctional carbohydrate-derived scaffold. The solid-phase universal pharmacophore-mapping libraries are then generally pre-

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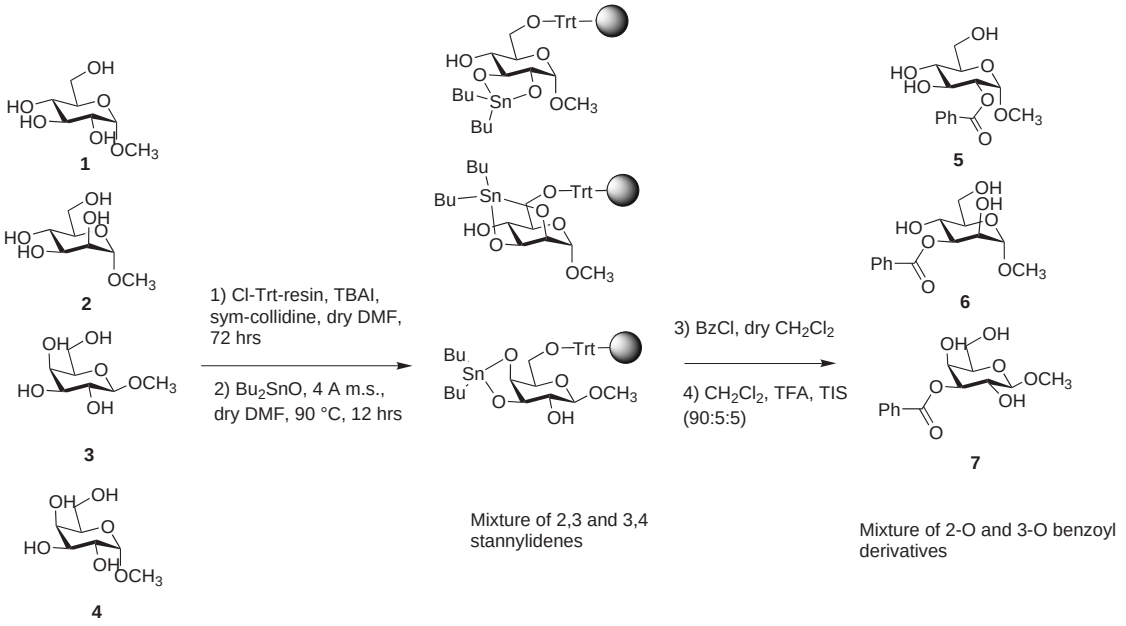
pared by covalently linking the sugar to a resin, by deprotecting one of the hydroxyl groups and by introducing pharmacophores at this position. The regioselective functionalisation of one of the unprotected hydroxyl groups of a sugar directly on solid phase could be an elegant and efficient alternative to shorten this procedure.

Methyl α-D-gluco-, manno- and galactopyranosides (**1**, **2** and **4**) and methyl β-D-galactopyranoside (**3**) were anchored to a trityl chloride polystyrene–DVB resin by trityl ether formation at O-6 (Scheme 1).[†]



Scheme 1. Solid-phase stannylene-promoted benzoylation of monosaccharides **1**, **2**, **3** and **4**

To determine the loading, part of the resin (50 mg) was swelled in dry CH_2Cl_2 and shaken at rt in a CH_2Cl_2–TFA–TIS[‡] (90:5:5) mixture for 1 h in a plastic syringe with a polypropylene filter and a Teflon valve in the bottom (the cleavage was repeated twice), the effluents were collected, concentrated and methyl glycosides were purified by FC on silica gel (AcOEt–MeOH–H_2O 70:30:1). A loading of 0.81 mmol/g after purification resulted from the average of the values obtained for the four monosaccharides.

[†] Experimental conditions: Trityl chloride polystyrene–DVB resin (Novabiochem, 2 g, 2.5 mmol) was swollen for 30 min in dry CH_2Cl_2 under argon in a glass flask with a sintered glass filter and a Teflon valve in the bottom. This was then suspended in dry DMF (20 mL) under argon atmosphere, methyl-glycopyranosides (1.97 g, 10.2 mmol), TBAI (4.03 g, 10.2 mmol), *sym*-collidine (2.03 mL, 15.2 mmol) were added and the mixture was shaken in the dark for 72 h at rt. The resin was then washed with dry CH_2Cl_2 (20 mL, three times), dry THF (20 mL, three times), dry CH_2Cl_2 (20 mL) and dried overnight in a desiccator in vacuo and stored under argon at −25°C.

[‡] Abbreviations: FC: flash chromatography; TBAI: tetrabutylammonium iodide; TFA: trifluoroacetic acid; TIS: tris-isopropylsilane.

For the stannylene formation, the resin (200 mg, 0.16 mmol) was suspended in dry DMF[§] (1 mL), Bu_2SnO (80 mg, 0.32 mmol) and powdered 4 Å m.s. (50 mg) were added and the suspension was heated without shaking in a glass vessel sealed with a Teflon cap at 100°C for 12 h. The resin was separated from the solids by decanting in CH_2Cl_2, transferred to a plastic syringe, washed twice in dry CH_2Cl_2, suspended in dry CH_2Cl_2 (1 mL), benzoyl chloride (30 μL, 0.24 mmol) was added and the suspension was shaken at rt for 1 h. The resin was then washed with CH_2Cl_2, THF, CH_2Cl_2 and cleaved with CH_2Cl_2–TFA–TIS (90:5:5). The HPLC and TLC analyses of the effluents revealed the absence of unreacted sugars and the presence of only one monobenzylated product in the case of α-gluco-, α-manno- and β-galactopyranosides corresponding, respectively, to compounds **5**, **6** and **7**. The regioselectivity of the benzoylation reactions was nearly complete (more than 98% according to HPLC analysis) for the three sugars. The reaction on methyl α-D-galactopyranoside **4** was neither complete (40% of unreacted sugar was recovered after cleavage) nor regioselective (a complex mixture of mono and dibenzoylated compounds was formed). Pure monobenzoylated sugars **5**, **6** and **7** were purified by FC on silica gel (AcOEt–EtOH 9:1) and their regiochemistry was elucidated by ^{1}H NMR.[¶] The benzoylation reactions were accomplished without added base in very high yields (Table 1).

Table 1

Compound	Acylation position	Regioselectivity (%)	Yield (%)[a]
1	O-2	>98	94
2	O-3	>98	98
3	O-3	>98	96
4	Mixture		60[b]

[a] Yields of products purified by FC.
[b] Yield of the mixture of acylated products.

As a control, the benzoylation reaction was done without added base on methyl α-D-glucopyranoside bound to trityl resin omitting the stannylene formation step. Unreacted sugar was recovered after cleavage indicating that acylation does not take place on solid phase without stannylene activation of the hydroxyl groups. Some practical and theoretical considerations are derived from these results. There are no examples, to our knowledge, of stannylene formation on solid phase. The possibility of regioselectively acylating unprotected sugars bound to a resin paves the way to more convergent solid-phase synthesis of sugar-based libraries avoiding the extensive use of protecting groups. More generally, all synthetic transformations of sugars on solid phase involving ester formation from diols can take advantage of this procedure. The yield and regioselectivity for O-2 observed in the acylation of resin-bound methyl-α-D-glucopyra-

[§] Using dry benzene as solvent the stannylene formation proceeded as well giving similar results to that reported in the paper.

[¶] Mondimensional ^{1}H NMR (300 MHz) in D-MeOH were diagnostic for the determination of the acylation positions. The protons on the carbon atoms that were benzoylated are downshifted by more than 1 ppm: in compound **5** (α-glucose), $\delta = 4.89$ ppm, H-2 (dd, $J_{1-2} = 3.7$ Hz, $J_{2-3} = 9.8$ Hz); in compound **6** (α-mannose), $\delta = 5.22$ ppm, H-3 (dd, $J_{2-3} = 3.3$ Hz, $J_{3-4} = 9.9$ Hz), in compound **7** (β-galactose), $\delta = 4.97$ ppm, H-3 (dd, $J_{2-3} = 10.0$ Hz, $J_{3-4} = 3.4$ Hz).

noside is comparable to that observed in solution for the 4,6-*O*-benzylidene analogue[8,9] and can be explained with formation of a 2,3-*O*-dibutylstannylene and consequent O-2 selective activation. The acylation of the resin-bound methyl α-D-mannopyranoside was selective for O-3, as observed for the methyl 6-*O*-trityl α-D-mannopyranoside in solution[10] with 2,3-*O*-stannylene formation. The acylation on O-3 of methyl β-D-galactopyranoside is comparable in yield and regioselectivity to the same reaction on the 4,6-*O*-benzylidene analogue in solution[11] with stannylene formation in 3,4 position. The axial orientation of the anomeric methoxy group in the methyl-α-D-galactopyranoside can favour the formation of the stannylidene in the 2,3 positions because of additional coordination of tin to the anomeric oxygen. In this case both 3,4-*O*- and 2,3-*O*-stannylenes are probably formed, thus explaining the lack of regioselectivity of the subsequent benzoylation.

It is noteworthy that two resin-bound sugars cannot associate in solid phase forming the dimeric units observed for stannylenes of monosaccharides in solution. The regioselectivity of the acylation reactions described here need to be explained with a different rationale than that based on the nucleophilic enhancement of the apical oxygen in the Sn_2O_2 parallelogram of the dimer.[4,5] Further theoretical and applied studies are needed to elucidate this aspect of the stannylene chemistry on solid phase. We are currently developing other regioselective reactions of unprotected or partially protected sugars on solid phase via stannylene formation to demonstrate the general utility of this technique.

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