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Solvent incorporation during *N*-iodosaccharin mediated glycosylation: facile synthesis of acetal linked disaccharides†

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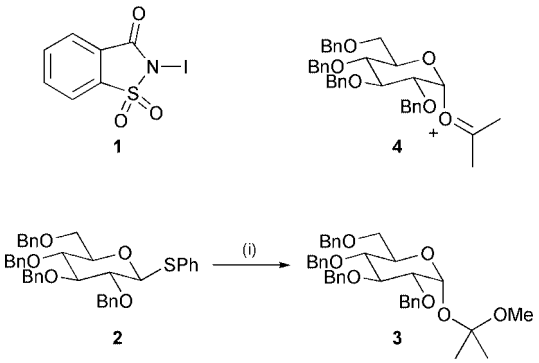
Solvent incorporation between glycosyl donor and acceptor occurs during glycosylation reactions initiated by *N*-iodosaccharin (NISac) performed in acetone and cyclohexanone solvents to stereoselectively produce acetal linked α-glycosides.

Considerable work has been performed to understand the role of solvent during the glycosylation process[1,2] However the situation is complicated by the identity of anomeric leaving group, the activator and the protecting groups on the donor. Therefore although there are several general 'guiding principles' as to how the choice of solvent may affect the stereochemical outcome of glycosylation for donors with non-participating OH-2 protecting groups, there is still requirement for further mechanistic insight into each particular glycosylation reaction.

One of the best-established examples of solvent participation during the glycosylation process is the preferential formation of β-glycoside products observed when using acetonitrile as solvent.[3] This β stereoselectivity has been ascribed to trapping of the glycosyl cation formed during the glycosylation reaction by solvent to produce an intermediate α-nitrilium ion, which then undergoes S_N2 type glycosylation, resulting in preferential formation of the β-product.[4] The isolation of α-nitrilium trapped species has provided substantial supporting evidence for this hypothesis.[5] Reported herein are investigations into glycosylation reactions performed in ketone solvents, in which solvent incorporation invariably occurs to produce good yields of mixed acetal linked α-glycosides and α-disaccharides, in an entirely stereoselective manner.

We recently reported the use of *N*-iodosaccharin (NISac) **1** for the activation of thiophenyl glycosides under mild conditions.[6] During the course of these studies it became clear that reduced yields of disaccharide products were obtained by saccharin trapping of the glycosyl cation, which is probably produced during the glycosylation reaction. In an attempt to promote *O*-glycosylation, and in particular increase yields of disaccharide products, studies turned to the use of more polar solvents. Use of acetonitrile as solvent[7] resulted in an increase in the yield of disaccharides, but saccharin trapping was still observed. For this reason acetone was also investigated as the solvent for glycosylation. Although acetone has frequently been employed as an organic co-solvent for enzyme catalysed glycosylation, it has not been particularly widely used for chemical glycosylation reactions.[8]

Glycosylation of perbenzylated thioglycoside **2** was undertaken with methanol as glycosyl acceptor in acetone with *N*-iodosaccharin (NISac, **1**) as activator. Quite surprisingly none of the desired methyl glycoside was observed, and the sole reaction product was identified as the pure α-glycoside **3** (Scheme 1). Moreover, **3** was produced entirely as the α-anomer. Formation of **3** can be explained by initial formation of the α-acetonium ion **4**, by solvent participation in a manner



Scheme 1 *Reagents and conditions*: (i) NISac **1**, MeOH (3 equiv.), acetone, −78 to 0 °C, 2.5 h, 76%.

analogous to glycosylation in acetonitrile. Nucleophilic attack on **4** by methanol then yields the mixed acetal. To the best of our knowledge solvent participation by acetone during a glycosylation reaction has only been observed on two previous occasions.[9,10] Investigations then turned to the use of carbohydrates as glycosyl acceptors to investigate if solvent trapping would occur to produce disaccharides linked as mixed acetals. Reaction of thioglycoside **2** with diacetonide galactose **5**, in acetone with NISac activation, produced acetal-linked disaccharide **6** in an excellent 84%, as the pure α-anomer (Scheme 2).‡§ Carbohydrates with secondary hydroxy groups also produced good yields of acetal-linked products. Thus reaction of donor **2** with the *manno* acceptor **7** produced the mixed acetal linked disaccharide **8**, as the pure α-anomer, in 78% yield.

Investigation then turned to the use of other solvents to determine the potential generality of the process. Initial attempted reaction of **2** with methanol and NISac as activator in butanal as an aldehyde solvent produced a complex mixture of products and no appreciable amount of acetal glycoside. However with cyclohexanone as solvent again good yields of pure α-glycoside products were isolated. Thus reaction of donor **2** with methanol in cyclohexanone initiated by NISac produced a good yield of the α-mixed acetal **9** (Scheme 3). Carbohydrate acceptors also reacted well; diacetonide galactose **5** produced the acetal linked α-disaccharide **10** in 73% yield.

In summary we have demonstrated that NISac[11] activation of thioglycosides in ketone solvents[12] leads exclusively to the formation of α-mixed acetal products, in which a solvent molecule is incorporated between the anomeric centre of the glycosyl donor and the hydroxy group of the glycosyl acceptor. Formation of these mixed acetal products probably occurs by trapping of an incipient α-acetonium ion **4** by the glycosyl acceptor, and provides substantial evidence for the intermediacy of such species during glycosylation reactions performed in acetone as solvent. Furthermore this synthetic route to pure α-acetal glycosides, which have been proposed as potential anti-cancer prodrugs, compares favourably with the other published routes.[13,14]

Further investigations into the generality of this novel glycosylation reaction, and its development for the synthesis of

† Electronic supplementary information (ESI) available: spectral data for compounds **3**, **6** and **8**–**10**. See http://www.rsc.org/suppdata/cc/b1/b104196g/

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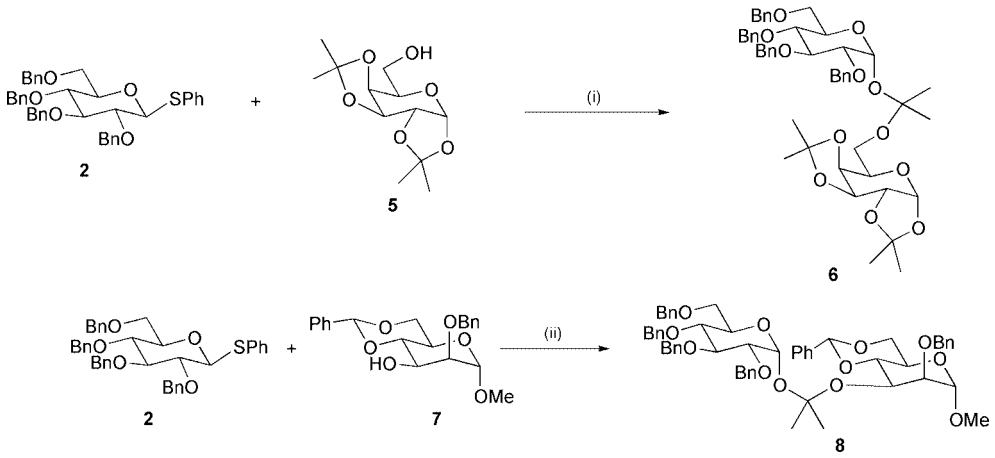
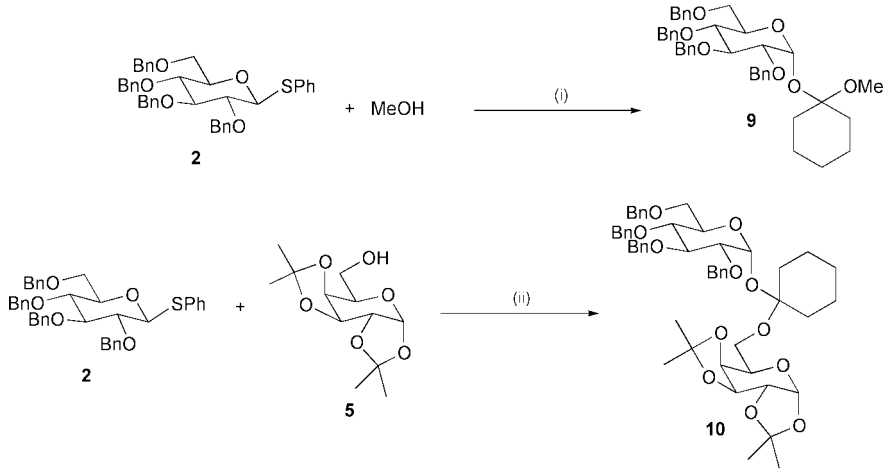


Scheme 2 *Reagents and conditions*: (i) NISac **1**, acetone, −78 to 0 °C, 2.5 h, 84%; (ii) NISac **1**, acetone, −78 to 0 °C, 3 h, 78%.



Scheme 3 *Reagents and conditions*: (i) NISac **1**, acetone, −78 to 0 °C, 2.5 h, 84%; (ii) NISac **1**, cyclohexanone, −40 to 5 °C, 3 h, 62%; (ii) NISac **1**, cyclohexanone, −40 to 0 °C, 2 h, 73%.

glycomimetics are currently in progress and will be reported in due course. We gratefully acknowledge financial support from the Leverhulme Trust (postdoctoral fellowship to M. A.), and also the use of the Chemical Database Service (CDS) at Daresbury, UK, and the EPSRC National Mass Spectrometry Service at Swansea.

Notes and references

‡ Typical experimental procedure: a mixture of the perbenzylated phenyl thioglucoside **2** (0.091 g, 0.14 mmol), diacetonide galactose **5** (0.056g, 0.21 mmol) and molecular sieves 4 Å (0.2 g) were stirred in dry acetone (3 ml) under an atmosphere of argon at −78 °C. *N*-Iodosaccharin **1** (0.066 g, 0.021 mmol) was then added rapidly. The reaction mixture was then stirred with warming to 0 °C until TLC (R_f 0.44, ethyl acetate–petroleum ether, 1:3) indicated complete consumption of the thioglycoside (*ca*. 2.5 hours). Triethylamine (1 ml) was added and stirring was continued for a further 15 minutes at 0 °C. The reaction mixture was then diluted with dichloromethane (30 ml) and then filtered through Celite®. The filtrate was then washed with 10% aqueous sodium thiosulfate (10 ml), saturated aqueous sodium bicarbonate (10 ml) and water (10 ml). The organic extracts were then dried (anhydrous sodium sulfate), filtered, and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography (ethyl acetate–petroleum ether, 1:4) to give the acetal-linked disaccharide **6** (0.102 g, 84 %), as a colourless oil.

§ All new compounds possess NMR and high-resolution mass spectral data consistent with their structures.

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