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Regioselective C-3-*O*-acylation and *O*-alkylation of 4,6-*O*-benzylidene-β-D-glucopyranoside derivatives displaying a range of anomeric substituents

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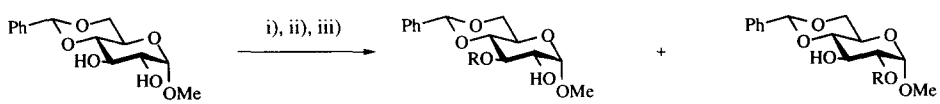
Abstract: Regioselective C-3-*O*-acylation and *O*-alkylation of ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside, phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside and phenyl 4,6-*O*-benzylidene-1-seleno-β-D-glucopyranoside is described. Regioselectivity is obtained by first treating the benzylidene diols with sodium hydride and copper (II) chloride to form a THF soluble copper chelate.

INTRODUCTION

As our understanding of the vital roles of oligosaccharides as mediators of biological events increases, so does our need for efficient methods for their total syntheses.[1] As a consequence, a whole range of new oligosaccharide assembly strategies have been developed which allow efficient one-pot synthesis of oligosaccharides.[2] For example, orthogonal glycosidation strategies have recently been developed which utilise a range of glycosyl hermaphrodites (i.e. molecules which can act as donors or acceptors depending on the reaction conditions) which display different groups at the anomeric positions.[3] If access to individual isomers of biologically important oligosaccharides is to be possible then orthogonally protected hermaphrodites must be available. Such differentially protected hermaphrodites are generally available for manno- and galactopyranosides, but not for glucopyranosides.[4] For example, although it is generally possible to access glucopyranoside hermaphrodites with a free hydroxyl group at C-3, access to the isomeric hermaphrodites with a free hydroxyl group at C-2 is more difficult.[5]

The regioselective alkylation and acylation of methyl 4,6-*O*-benzylidene-α- and -β-D-glucopyranoside to afford acceptors with a free hydroxyl group at C-2 has been described in the literature.[6] Thus the dianion of methyl 4,6-*O*-benzylidene-α- and -β-D-glucopyranoside is treated sequentially with anhydrous copper (II) chloride and an alkylating or acylating agent to afford, with good regiocontrol, acceptors with a free hydroxyl group at C-2 (Scheme 1).

For example



R = Me 66%
R = Ac 80%

R = Me 20%
R = Ac 15%

i) NaH (2 eq.), THF or DME; ii) $CuCl_2$ (1 eq.); iii) Alkylating or acylating agent

Scheme 1

To the best of our knowledge this reaction has not been investigated using 4,6-*O*-benzylidene-β-D-pyranoside substrates displaying a range of anomeric substituents. If successful, this would allow access to previously elusive glucopyranoside hermaphrodites with a free hydroxyl group at C-2. We have therefore recently investigated the viability of using copper chelates of a range of 4,6-*O*-benzylidene-β-D-glucopyranosides to access hermaphrodites useful for orthogonal glycosidation strategies.

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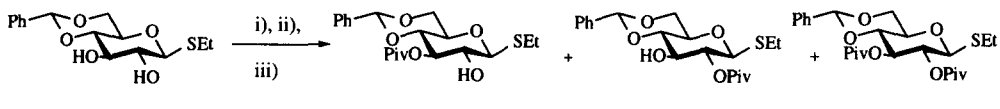
RESULTS AND DISCUSSION

We initially wished to determine whether a pivaloyl group could be introduced onto the C-3 hydroxyl group of thioethyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**1**) to afford hermaphrodite (**2**) (Scheme 2).



(1) (2) (3) (4)

i) NaH (2 eq.); ii) $CuCl_2$ (1 eq.); iii) PivCl (1.2 eq.), rt, 24h

Scheme 2

The glucopyranoside substrate (**1**) was first treated with two equivalents of sodium hydride at room temperature for 1 hour to form the dialkoxide as a thick white slurry. One equivalent of copper (II) chloride was then added to afford a clear dark green solution of the copper chelate. After 10 minutes this was treated with pivaloyl chloride and stirred at room temperature for 24 hours. Although some regioselectivity was attained, the reaction was found to be more capricious and lower yielding than the original reaction reported in the literature for the analogous methyl glucopyranoside derivative. Thus the reaction conditions were varied in a number of ways and the effect on the yield and regioselectivity of the reaction noted (Table 1).

Solvent	Mole eq. of NaH	Mole eq. of PivCl	(**2**) (%)	(**3**) (%)	(**4**) (%)	(**1**) (%)
THF	2	1.2	42	3	0	54
THF	2	2.0	35	6	16	43
THF	2	4.0	32	8	19	41
THF	3	1.2	3	2	3	92
DME	2	1.2	28	18	11	43

Table 1

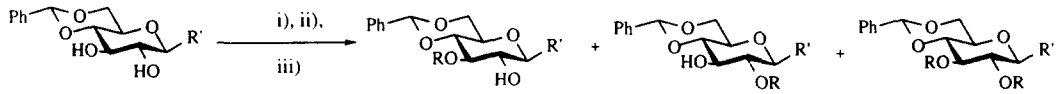
These experiments highlighted the importance of using THF as solvent and one equivalent of NaH per free hydroxyl group. A slight excess of acylating reagent was also optimum for attaining good yields. As the yield and regioselectivity of this reaction were still lower than those reported in the literature for the analogous methyl glucopyranoside substrate a further series of experiments was performed using copper (II) chloride from different sources. The data obtained in this way is described in Table 2.

Source of anhydrous copper (II) chloride	(**2**) (%)	(**3**) (%)	(**4**) (%)	(**1**) (%)
Commercially available[a]	19	10	10	61
Freshly prepared[b]	26	10	5	59
Commercially available, dried 24 h[c]	29	10	6	55
Freshly prepared, dried 24 h	43	3	0	54

[a] Purchased from Aldrich Chemical Company; [b] Prepared from Cu(II)O and HCl to afford $Cu(II)Cl_2.H_2O$ which was then heated at 90°C, 15 mm Hg to give anhydrous $Cu(II)Cl_2$;[7] [c] Dried at 200°C, 0.1 mm Hg

Table 2

Best yields and regioselectivities were clearly obtained when freshly prepared[7] and rigorously dried copper (II) chloride was employed. Hence although the yield of reaction remained moderate, the regioselectivity obtained was excellent. The next stage of our research programme then involved application of these conditions to a range of substrates[8] as well as utilising a range of alkylating and acylating agents. The results of this are shown below (Scheme 3, Table 3).[9]



R'=SEt (**1**)
R'=SePh (**5**)
R'=OPh (**9**)

R'=SEt (**2**)
R'=SePh (**6**)
R'=OPh (**10**)

R'=SEt (**3**)
R'=SePh (**7**)
R'=OPh (**11**)

R'=SEt (**4**)
R'=SePh (**8**)
R'=OPh (**12**)

i) NaH (2 eq.), THF; ii) $CuCl_2$ (1 eq.); iii) Alkylating or acylating agent (1.2 eq.)

Alkylating or acylating reagent	R'	(**2**), (**6**) or (**10**) (%)[a]	(**3**), (**7**) or (**11**) (%)[a]	(**4**), (**8**) or (**12**) (%)[a]	(**1**), (**5**) or (**9**) (%)[a]
BzCl	SEt	52 (48)	0	9 (7)	39 (37)
BzCl	SePh	69 (65)	0	0	31 (28)
BzCl	OPh	62	19	8 (7)	11 (9)
PivCl	SEt	43	3	0	54 (53)
PivCl	SePh	42 (39)	0	0	58 (55)
PivCl	OPh	60	17	9 (8)	14 (11)
AcCl	SEt	76 (74)	0	23 (21)	1 (1)
AcCl	SePh	86 (81)	0	3 (3)	11 (10)
AcCl	OPh	63	19	0	18 (15)
MeI	SEt	6	0	0	94 (90)
MeI	SePh	77 (75)	0	0	23 (21)
MeI	OPh	64	23	0	13 (10)

[a] Ratios estimated from the ^1H nmr of the crude reaction mixtures; isolated yields in brackets

Scheme 3, Table 3

Acylation reactions were stirred at room temperature for 24 hours whilst alkylation reactions were heated at reflux for 24 hours. In all cases the ratio of the reaction components was determined from the ^1H nmr of the crude reaction mixture, and, where possible, by isolation of the pure products by column chromatography. Of the glucopyranosides examined, optimum results were obtained with phenylselenopyranosides. Furthermore, a wide range of acyl protecting groups could be introduced onto the C-3 hydroxyl group of the substrates, with optimum results being obtained with acetyl chloride. Interestingly, although the corresponding alkylation reaction worked well with methyl iodide, limited success was achieved with alternative alkylating agents, with yields and regioselectivities remaining variable. We are therefore currently optimising these reactions in our laboratories.

In this paper we have described an extension of a previously reported but rarely cited method for acylation and alkylation of the C-3 hydroxyl group of benzylidene protected glucopyranosides. The full scope of this methodology will be reported in due course.

ACKNOWLEDGEMENTS

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9. *Example of experimental procedure* : Glucopyranoside (**1**) (0.14 g, 0.5 mmol) was dissolved in THF (10 cm^3 distilled over sodium / benzophenone) at room temperature under argon. Sodium hydride (0.04 g, 1.0 mmol, 60% dispersion in oil) was added and the reaction mixture left to stir for one hour. After this time a thick white slurry resulted and hydrogen evolution ceased. Anhydrous copper (II) chloride (0.067 g, 0.5 mmol) was added to the slurry which immediately went to complete dissolution as a dark green solution. Benzoyl chloride (0.07 cm^3, 0.6 mmol) was added dropwise to the solution and the mixture stirred at room temperature for 24 hours. Water (3 cm^3) and aqueous ammonia solution (3 cm^3) were then added to afford a dark blue solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 10cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow oil. This oil was purified by column chromatography on silica gel (hexane : ethyl acetate, 3:1 plus 1% triethylamine) to afford glucopyranoside (**2**) (0.10 g, 48%) as a white solid.