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FACILE SYNTHESIS OF SILYLATED THIOGLYCOSIDES

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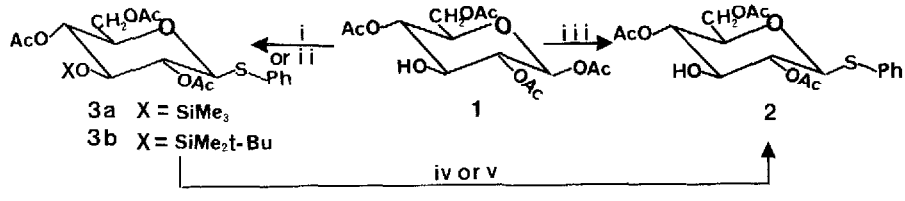
Abstract: The one pot conversion of 1,2,4,6-tetra-O-acetyl-β-D-glucopyranose, **1**, into phenyl 2,4,6-tri-O-acetyl-3-O-trialkylsilyl-1-thio-β-D-glucopyranosides, **3**, is described. The method is applicable to use with galactopyranosyl-, 2-deoxyglucopyranosyl-, and ribofuranosyl-starting materials.

Thioglycosides have proven to be valuable intermediates in the efficient construction of O-glycosidic linkages under mild conditions.[1] The widespread occurrence of the O-glycosidic bond in natural products has spurred interest in the facile synthesis of thioglycosides.[2] The utility of silyl groups in protection reactions employed in natural product synthesis is well known.[3] Herein we describe a method which accomplishes thioglycosidation and silylation in one pot, an approach which we believe will be of value in the synthesis of oligosaccharides.[4]

Scheme I indicates the method by which thioglycosidation and silylation of 1,2,4,6-tetra-O-acetyl-D-glucopyranose **1**[5] was accomplished to give compounds **3a** or **3b** in 74%[6] and 69%[6] yield, respectively.

Scheme I



i) PhSH (2.4 mequiv), pyridine (3.4 mequiv), TfOX (X = $SiMe_3$, $Si(Me)_2tBu$) (7.0 mequiv), $(ClCH_2)_2$ (5 mL), 0°→25°C, 12 h; $(ClCH_2)_2$ (5 mL), 0°C, pyridine (3.4 mequiv), 1 h, 69%.

ii) $TfOSiMe_3$ (2.4 mequiv), $PhSSiMe_3$ (3.0 mequiv), $(ClCH_2)_2$ (5 mL), 0°→25°C, 12 h; then 0°C, pyridine (5.4 mequiv), 74%.

iii) TfOX (X = $SiMe_3$, $Si(Me)_2tBu$) (2.4 mequiv); $PhSSiMe_3$ (3.0 mequiv), $(ClCH_2)_2$ (5 mL), 0°-25°C, 12 h, 75%.

iv) $BF_3{\cdot}OEt_2$ (2.0 mequiv), CH_2Cl_2 (5 mL), 18 h, 0°→25°C, 80%.

v) PhSH (5.0 mequiv), $TfOSiMe_3$ (4.0 mequiv), $(CH_2Cl)_2$ (5 mL), 45°C, 4 h, 80%.

While carrying out the thioglycosidation of **1** with excess TMS triflate and thiophenyl-TMS, we discovered that the addition of 2,6-lutidine to the reaction mixture after the thioglycosidation was complete gave the 3-O-trimethylsilylglucoside **3a** in high yield (Scheme I, reaction ii).

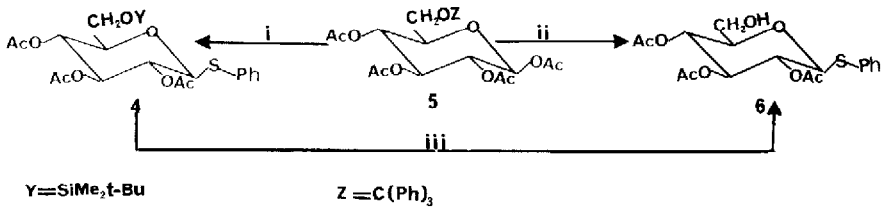
Introduction of the more rugged and versatile tert-butyldimethylsilyl (TBDMS) group simultaneously with thioglycosidation was not as straightforward because the preferred thiol transfer agent, thiophenyl-TBDMS, is not commercially available. Our approach to circumvent

the problem was based on the observation that the thioglycosidation of glucose pentacetate with thiophenol and TMS-triflate appeared to be more facile in the presence of pyridine. We attributed this to the in situ formation of phenylthio-TMS, which is probably a more efficient thiol transfer agent than thiophenol.[8] Accordingly, for the synthesis of **3b** we used TBDMS-triflate as Lewis acid (and subsequent silylating agent), thiophenol for glycosidation, and we added pyridine in two stages, first to accelerate the thioglycosidation, and then to catalyze the silylation reaction.[9] After chromatographic purification, 78% conversion to **3b** (α,β-anomers) was observed. Crystallization from ether-methanol yielded pure **3b**[7] (69%).

The identity of the intermediate **2**[7] was determined by its isolation from the reaction mixture after the thioglycosidation step. This was confirmed by comparing its properties[7] to the desilylated product obtained from the reaction of **3b** with $BF_3 \cdot OEt_2$.[10] Compound **3b** could also be desilylated using thiophenol and TMS triflate in greater than 80% yield. These successful desilylations give **3b** strong potential as a block synthon[11] for β-1,3-oligosaccharides. Likewise the 6-O-silylated analog, **4**, was synthesized from the commercially available 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose in 70% yield.

A logical extension of the method detailed above has led to a novel, detritylation-thioglycosidation-silylation sequence that also was accomplished in one pot (Scheme II).

Scheme II



i) Reaction i from Scheme I; TfOX (X=Si(Me)$_2$tBu);68%.

ii) Reaction iii from Scheme I; 68%.

iii) NBu_4NF, THF, 0°-25°C; 80%.

Table - Substrates, Products and Yields of the Detritylation-Thioglycosidation-Silylation Reaction Sequence.

Substrate[a]	Product[b]	Yield[c]
1,2,3,4 Tetra-O-acetyl-6-O-trityl β-D-galactopyranose, **7**	Phenyl 2,3,4 tri-O-acetyl 6-O-(TBDMS)-1-thio-D-galactopyranoside, **10**	72%
Methyl 3,4 di-O-acetyl-2-deoxy 6-O-trityl-β-D-glucopyranoside, **8**	Phenyl 3,4 di-O-acetyl 2-deoxy-6-O-(TBDMS)-1-thio-β-D-glucopyranoside, **11**	74%
Methyl 2,3 di-O-benzyl-5-O-trityl-D-ribofuranoside, **9**	Phenyl 2,3 di-O-benzyl 5-O-(TBDMS)-1-thio-D-ribofuranoside, **12**	74%

(a) Anomeric mixtures of the substrates **8** and **9** were employed. (b) Anomeric mixtures of the products were usually obtained. In the case of products **4** and **10**, the β anomer predominated and could be crystallized. (c) Isolated yields.

The protected starting materials of the Table, analogous to **5** of Scheme II, are readily prepared in high yield from commercially available precursors. The high regioselectivity of the tritylation reaction justified its use as the initial blocking group of primary OH positions.[12] However, the significantly greater flexibility of TBDMS protection under the range of reaction conditions usually employed for oligosaccharide synthesis dictated its use as replacement of the initial trityl protection. The table shows additional results of this three step-one pot reaction sequence.

Lewis acid catalyzed 4 to 6 O-acyl migrations are well known in glucose and galactose chemistry. The site of silylation in the final products was determined by ^{1}H NMR spectroscopy: for example, the expected, and observed, upfield shifts of the H-6 protons (δH-6S = 3.62; δH-6R = 3.57) in **4** relative to those of the H-6 protons in phenyl 2,3,4,6 tetra-O-acetyl-1-thio-β-D-glucopyranoside (δ=4.0) confirmed the presence of the silyl group at O-6. Other ^{1}H NMR (C_6D_6) resonances for **4**: δ (H-3, m) = 5.35; δ (H-4, m) = 5.2; δ (H-1, d) = 4.5; δ (H-5, m) = 3.17; δ (H-2, m) = 5.25. In a similar fashion, galacto derivative **10** (mp 90-91°C) displayed signals for H-6R and H-6S at δ3.68 and 3.58 respectively. The H-6 signals of 6-O-acylated galactose derivatives resonate at > δ4.1.[13] Other ^{1}H NMR (C_6D_6) resonances for **10** (mp 90-1°C); δ (H-1, d) = 4.54; δ (H-2, m) = 5.63; δ (H-3, m) = 5.19; δ (H-4, m) = 5.62; δ (H-5, m) = 3.28. (Chemical shift assignments were made using correlation spectroscopies.)

In a final extension of the approach we found that exposure of 2,3,4-tri-O-benzyl-1,6-anhydro-β-D-glucopyranose, **13**,[14] to reaction conditions ii of Scheme I gave phenyl 2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranoside, **14**, in 85% yield (mp 93-4°C).[7a] Further, when **13** was subjected to reaction iii (X=Si(Me)$_2$tBu) of Scheme I, phenyl 6-O-TBDMS-2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranoside[7a], **15**, was obtained in 76% yield.

The ease of desilylation[15,16] of these thioglycosides under mild conditions enhances their potential as block synthons for oligosaccharide synthesis.

In conclusion, we have developed a short and efficient synthetic route to silylated thioglycosides from readily available starting materials . Our approach circumvents the undesirable desilylations that often accompany the thioglycosidation of silylated precursors[4c]. The silylation of 'sensitive' substrates that are susceptable to acetate migrations has been achieved successfully. The reagents used are handled quite easily, employing the usual precautions, and are compatible with common protecting groups.

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6. Crystalline β-anomer; reactions i, ii, and iii yielded mixtures of α,β-anomers in 80% yield. The conversion of the α-anomer of **1** to **2** was accomplished in good yield at 60°C in $(CH_2Cl)_2$ (12 h).
7. (a) All new compounds exhibited satisfactory elemental analysis and spectral data. (b) **2** mp: 104°-105°C; ^1H NMR (C_6D_6): $J_{1,2}$ = 10.2 Hz, δ(H-3) = 3.7, δ(OH-3) = 3.05. **3a** mp: 124°-125°C; δ(H-3) = 3.6, δ(Me_3Si) = 0.1. **3b** mp: 110°-111°C; δ(H-1, d) = 4.45, δ(H-2, m) = 5.1, δ(H-3, m) = 3.68, δ(H-4, m) = 4.95, δ(H-5, m) = 3.15, δ(H-6, 6', m) = 4.1.
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9. TLC of the reaction mixture before the addition of base showed trace amounts of **3** using Method ii, Scheme I. Significant amounts of **3** were detectable by TLC before the second addition of base using Method i, Scheme I.
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14. Compound **13** was prepared by the benzylation (NaH, $C_6H_5CH_2Br$, DMF, 25°) of commercially available 1,6-anhydro-β-D-glucopyranose.
15. Desilylation of **4** for example was accomplished under the following conditions: n-Bu_4NF, THF, 0°C, 25°C, 80%. (b) See also Nicolaou, K.C., Dolle, R.E., Papahatjis, D.P., and Randall, J.L., J. Am. Chem. Soc. **1984**, 106, 4189-92.
16. Since both anomers of thioglycosides can be converted to fluorosugars for glycosidic coupling using NBS and DAST[15b] the present 2 step syntheses of **14** and **15** appear particularly attractive.

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