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Preliminary communication

Chemistry of the glycosidic linkage. Direct conversion of glycosides into 1-thioglycosides by use of [alkyl(or aryl)thio]trimethylsilanes‡

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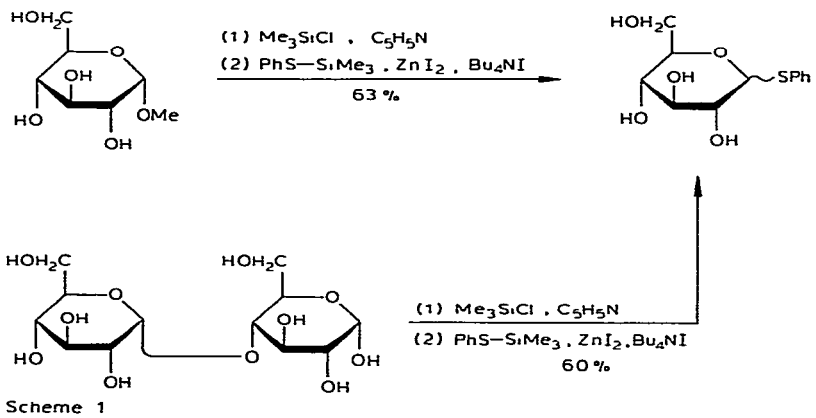
The formation and cleavage of the glycosidic linkage are processes whose paramount importance is, perhaps, surpassed only by the efficiency with which such events take place in Nature[2]. Whereas a significant number of chemical methods of glycoside synthesis have emerged in the recent past[1,3], little has been developed in the area of glycosyl–O cleavage beyond the well known, standard procedures[3]. Such a process may be quite important when dealing with the structure elucidation of antibiotics containing sugars[4]. Indeed, in several cases, the sugar portion is decomposed in the process of attempted cleavage, or it is recovered in low yield only. Mild methods of glycoside cleavage are also in demand in the area of oligosaccharides and biopolymers[3].

As regards these problems, we report herein a possible solution that consists of the efficient, one-step conversion of a glycoside into a 1-thioglycoside. Compounds of the latter type are known to be readily hydrolyzed to the free sugars by several methods[5] including metal-assisted hydrolysis. The reaction consists of the treatment of a glycoside or saccharide derivative with trimethyl[methyl**(or phenyl)thio]silane[6] in the presence



Scheme 1

‡For a previous paper in this series, see ref. 1.
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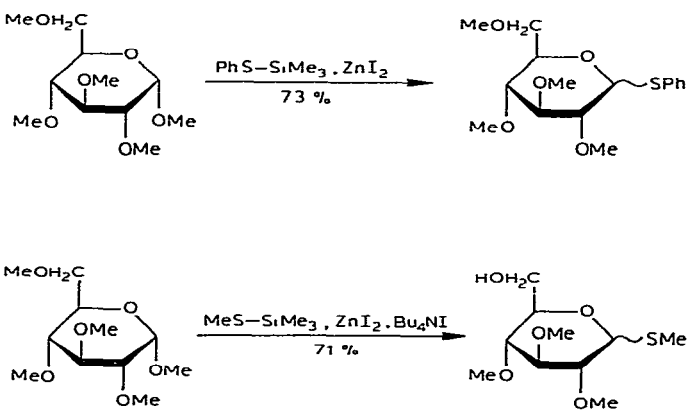
of zinc iodide and tetrabutylammonium iodide[7], whereupon the corresponding 1-thioglycoside is formed under essentially neutral, aprotic conditions (see Scheme 1). The reaction is applicable to 1,2-*cis*-, as well as 1,2-*trans*-, glycosides.

In a typical procedure, methyl α-D-glucopyranoside (0.39 g, 2 mmol) was converted into its per-*O*-(trimethylsilyl) derivative in the usual way, with Me_3SiCl, hexamethyldisilazane, and pyridine. The syrupy trimethylsilyl derivative was dissolved in 1,2-dichloroethane (10 mL) containing trimethyl(phenylthio)silane (1.8 g, 10 mmol); zinc iodide (1.91 g, 6.0 mmol) and tetrabutylammonium iodide (0.74 g, 2 mmol) were added, and the suspension was heated at 60°, with stirring. After 8 h, the mixture was filtered, and the filtrate was washed with aq. $NaHCO_3$, and processed as usual, to give a pale-yellow syrup. Chromatographic purification gave phenyl 1-thio-D-glucopyranoside as a 10:1, α/β mixture (0.34 g, 63%). Crystallization from ethanol–ethyl acetate gave pure phenyl 1-thio-α-D-glucopyranoside (0.3 g, 55%), m.p. 155–157°, $[\alpha]_D$ +252° (C_5H_5N)*, in accord with literature values[8]. The mother liquors contained additional quantities of anomeric glycosides, and were not processed further; treatment of an aliquot with a solution of mercuric chloride in aq. acetone gave D-glucose.

Similar treatment of maltose gave, by scission thereof, a mixture of phenyl 1-thio-D-glucopyranosides (α/β ratio 5:1, by n.m.r. spectroscopy), in >60% yield.

Permethylated glycosides are notoriously resistant to acid hydrolysis. For example, hydrolysis of methyl tetra-*O*-methyl-α-D-glucopyranoside requires heating in 1:1 2M HCl–1,4-dioxane under reflux for 2 days**, to give 2,3,4,6-tetra-*O*-methyl-D-glucose[9]. Treatment of the aforementioned glycoside (1 mmol) with trimethyl(phenylthio)silane (3 mmol) and zinc iodide (3 mmol) in 1,2-dichloroethane during 7 h at 60° led to a 2:1 mixture of anomeric phenyl 2,3,4,6-tetra-*O*-methyl-1-thio-D-glucopyranosides in 73% yield (see Scheme 2). Chromatographic separation gave the α anomer (48%), $[\alpha]_D$ +25° ($CHCl_3$); δ 4.5 (d, $J_{1,2}$ 9 Hz, H-1), and the β anomer (22%).



Scheme 2

*Melting points are uncorrected. All products were studied by ^{13}C-n.m.r. spectroscopy, and the data were in agreement with the structures proposed.

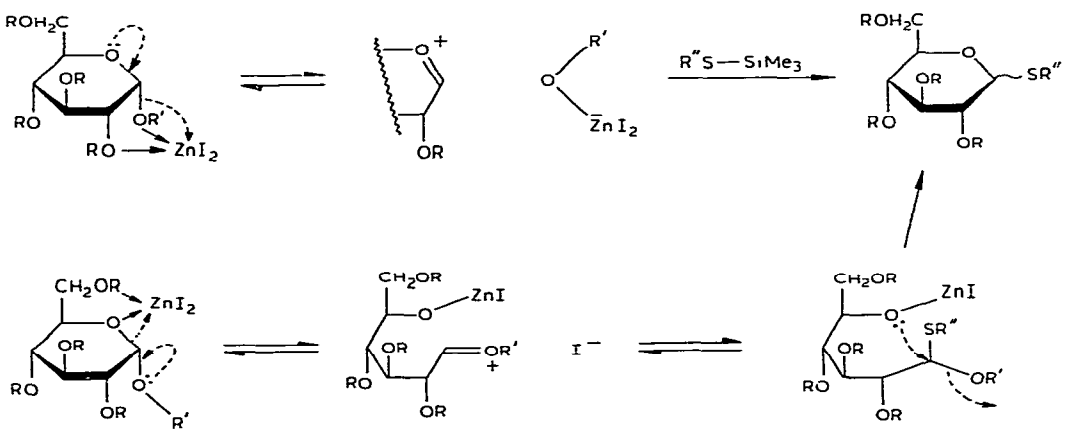
**Conditions established in this laboratory by R. Roy and G. Rancourt.

The corresponding β-D-glucoside gave similar results, except for a shorter reaction time (3–4 h), and the anomeric mixture of 1-thioglycosides could be readily hydrolyzed to 2,3,4,6-tetra-*O*-methyl-D-glucose, in the presence of Hg^{2+} ions.

Use of trimethyl(methylthio)silane, with inclusion of tetrabutylammonium iodide, in the aforementioned reactions, resulted in partial, selective *O*-demethylation[7] of the primary methoxyl group, in addition to 1-thioglycoside formation. Thus, treatment of methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (0.125 g, 0.5 mmol) with trimethyl(methylthio)silane (5 mmol; 10 mL of 0.5M solution), zinc iodide (0.8 g, 2.5 mmol), and tetrabutylammonium iodide (0.4 g, 1.1 mmol) in refluxing 1,2-dichloromethane during 6 h, followed by chromatographic separation, gave an α/β mixture of methyl 2,3,4,6-tetra-*O*-methyl-1-thio-D-glucopyranosides (15%) and the anomeric methyl 2,3,4-tri-*O*-methyl-1-thio-D-glucopyranosides [α/β ~3:2, n.m.r. data: δ 5.4 (d, $J_{1,2}$ 3 Hz, H-1, α anomer) and 4.3 (d, $J_{1,2}$ 7 Hz, H-1, β anomer)]. Tritylation of the mixture gave the corresponding trityl ethers. Prolonged refluxing periods resulted in further demethylation, to give an as-yet-unidentified, monomethyl ether derivative[7].

The reactions described herein provide easy access to 1-thioglycosides, without recourse to use of thiols as reagents. This novel trans-thioglycosidation reaction should find application in the cleavage of various naturally occurring glycosides, including oligosaccharides and carbohydrate biopolymers.

In the absence of zinc iodide, no reaction takes place, and the mechanism could involve initial coordination of oxygenophilic species[7], containing zinc or silicon, or both, to the glycosides. In this regard, it is interesting that the vicinal disposition of hydroxyl or alkoxyl groups in carbohydrates in general, and the glycosides under study in particular, provides a choice "ethylenedioxy" (and related two-carbon units[10]) for effective coordination and activation at the anomeric center[11]. Two plausible, mechanistic pathways are shown in Scheme 3.



Scheme 3

ACKNOWLEDGMENTS

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