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Preliminary communication

Chemistry of the glycosidic linkage. Exceptionally fast and efficient formation of glycosides by remote activation*

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Numerous methods for the formation of the biologically important O–glycosyl linkage have been reported since the turn of the century[1]. In connection with our own studies in this area[2], we became interested in the prospects of developing a method that would lead to simple, as well as relatively complex, glycosides, but avoid two preparatively cumbersome operations, namely, the formation of glycosyl halide and the protection of hydroxyl groups.

We reasoned that the incorporation, into an unprotected sugar molecule, of an appropriate anomeric substituent, and its subsequent activation to act as an efficient leaving group, would overcome these two problems, particularly if the reaction with the alcohol were a fast process. The presence in the anomeric substituent of atom X (preferably a "soft base", such as sulfur) and atom Y (preferably a "hard base", such as nitrogen) in a three-atom arrangement could provide the functional requirements for the remote activation desired. This concept is shown in two idealized situations, A and B (see Scheme 1), where, in A, a proton-mediated process** can be envisaged, whereas, in B, activation is initiated by reaction with an electrophilic species, or coordination with an appropriate, metal ion. Both processes should be energetically favored, in view of the nature of the resulting products, A′ and B′, respectively, and the prospects of stereocontrolled glycosidation could be viewed with optimism, provided that the reactions were SN2-like in character.

These concepts were put into practice with studies on three readily available models, namely pyridin-2-yl 1-thio-β-D-glucopyranoside[3] (1), pyrimidin-2-yl 1-thio-β-D-glucopyranoside[4] (2), and imidazolin-2-yl 1-thio-β-D-glucopyranoside[5] (3), all of which satisfy the criteria for functional requirements already discussed. The results reported were obtained with 1, although qualitatively similar results were given by 2 and 3.

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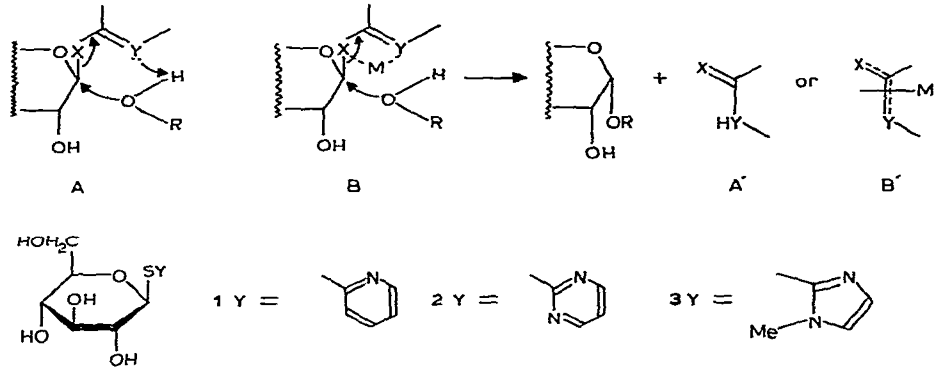
**Expression A does not necessarily imply a cyclic, concerted process. The proton could be provided by an appropriate acid.



Scheme 1

Compound **1** was prepared by an improved procedure, as follows. A suspension of 2-pyridinethiol (13.34 g, 0.12 mol) and potassium carbonate (11.6 g, 0.12 mol) in acetone (200 mL) was stirred for 1 h. The homogeneous solution was added dropwise to a solution of tetra-*O*-acetyl-α-D-glucosyl bromide (41.1 g, 0.1 mol) in toluene (100 mL). After being stirred for 1 h, the mixture was diluted with toluene, washed with water, and processed as usual, to give the desired per-*O*-acetylated 1-thioglycoside derivative[3] in 86% yield. Deacetylation in the usual way (NaOMe–MeOH) gave **1** (ref. 3) as the crystalline hydrate*.

Heating a solution of **1** in methanol for several hours gave only unchanged starting-material. The corresponding *N*-oxide[3] was also unaffected by such treatment**. However, in the presence of methanol and methanesulfonic acid (1 equiv. under reflux for 10 h), **1** was converted into methyl α-D-glucopyranoside*** in virtually quantitative yield under essentially neutral conditions.

Similar treatment of **1** (1 mmol) in 1 : 1 2-propanol–acetonitrile containing *p*-toluenesulfonic acid (*p*-TsOH; 1.2 equiv.) under reflux for 2 h, gave, after acetylation, a 3:2 mixture of the acetylated 2-propyl D-glucopyranosides (64%, isolated). Treatment of phenyl 1-thio-β-D-glucopyranoside with 2-propanol containing a catalytic amount of *p*-TsOH under reflux resulted in very little, if any, glycosidation, thus demonstrating the virtue of proton-mediated, hetero-atom, remote activation. These results were, however, undermined by the knowledge that the protonated pyridin-2-thiyl group is an excellent leaving-group, and that, in solution, the pyridine-2-thiol so produced is more stable in the thione than in the thiol form (*i.e.*, thioamide *vs.* thioimidate)[6]. The enhanced reactivity of **1** compared to its

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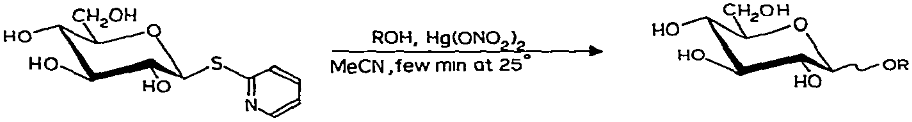
*The crystalline hydrate could be used for such simple alcohols as MeOH, or, preferably, dehydrated by treatment *in vacuo* for 30 min at 100°. A stock solution in warm acetonitrile can be made, and is stable under argon for prolonged periods of time.

**Rearside attack by oxygen in a 6-membered transition-state, as depicted in Scheme 1, is, in fact, geometrically unfavorable. Presumably, lack of reactivity in the geometrically more favorable *N*-oxide due to the much lower basicity of the *N*-oxide function.

***All glycosides were characterized by comparison (m.p., mixture m.p., and $[\alpha]_D$) with authentic samples.

phenyl analog could also be due, at least in part, to the presence of hydrogen-bonded structures involving the 2-hydroxyl group and the pyridinyl unit[7]. In fact, rate enhancements in both acid and enzymic hydrolysis of **1**, compared to related systems, have been known for some time[8].

Metal-ion-promoted, remote activation was achieved by the use of silver nitrate, or, preferably, mercuric nitrate. Thus, treatment of **1** (275 mg, 1 mmol) in acetonitrile (10 mL) containing various alcohols (3–10 mL) with mercuric nitrate* (0.17 g, 1.1 equiv.) resulted in the formation of the corresponding alkyl D-glucopyranosides *essentially within a few minutes*, regardless of the structural complexity of the alcohols investigated** (see Scheme 2 and Table I).



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Scheme 2

TABLE I

FORMATION OF ALKYL D-GLUCOPYRANOSIDES AND A DISACCHARIDE[a]

ROH	*Yield*[b] (%)	$\alpha:\beta$ *ratio*[c]
Methanol	95	70:30
Ethanol	85	68:32
2-Propanol	77	62:38
2,2-Dimethyl-1-propanol	47	58:42[d]
Cyclohexanol	75	51:49
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose	35[e]	55:45

[a] For the general procedure, see text. [b] Yields of *O*-acetylated D-glucosides. [c] Individual anomers were isolated by column chromatography on silica gel with 7:3 hexane–EtOAc, and their ratios were determined by weight. Ratios were also confirmed by gas-chromatographic analysis of crude O-Me_3Si derivatives on 5% of SE-30. [d] Reaction done at reflux temperature; for 3 min at 25°, the ratio was found to be 45:55 (isolated). [e] Mercuric nitrate in acetonitrile was added slowly, using a pump-driven syringe during 3 h, to **1** and the alcohol (4 equiv.) in acetonitrile (2 mL; total volume 12 mL). Reaction at reflux, or by mixing the components at once (see text), gave essentially the same results.

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*Commercial $Hg(NO_3)_2 \cdot H_2O$ was heated at 55–60° at 10^{-2} torr. The dehydrated salt is hygroscopic, but can be handled easily. Alternatively, a stock solution (15 mg/mL) can be made in dry acetonitrile.

**On addition of the salt, a dense precipitate is formed almost immediately; this may initially consist of the mercury complex of the 1-thioglycoside. The relatively low yields in the case of complex alcohols may, in fact, be due to inefficient contact with the activated complex. Also, in the presence of adventitious water, D-glucose is formed. In the absence of an alcohol, the main product (other than D-glucose) was found to be 1,6-anhydro-β-D-glucopyranose, isolated as the crystalline triacetate.

In view of the variable proportions of alkyl β-D-glucopyranosides formed, particularly with increase in the steric bulk of the alcohol, we studied the effect of changing several reaction parameters (metal, solvent, and temperature), and structural features of the substrate. Thus, the 6-*O*-*tert*-butyldiphenylsilyl derivate[9] (a syrup) of **1** was subjected to the same D-glucosidation with 2-propanol in dichloromethane. However, the low polarity of the solvent did not significantly alter the α:β ratio (compare Table I). The 4,6-*O*-benzylidene derivative of **1**, prepared in the usual way with PhCHO and $ZnCl_2$, was intended to provide a certain degree of conformational rigidity, thus favoring axial attack by the alcohol on a presumed, oxonium ion or ion-paired intermediate. In a reaction with 2-propanol, the α:β ratio of the corresponding acetylated 2-propyl D-glucopyranosides isolated remained essentially the same. It appears, therefore, that, in all of the metal-ion-promoted glycosidations of pyridin-2-yl 1-thio-β-D-glucopyranoside and its derivatives, extremely reactive, metal-coordinated intermediates are being dealt with, and a proportion of these may undergo "direct" displacement by the alcohol to give the α-D-glucopyranoside. It is also possible that, with bulkier alcohols, reaction is proportionately slower, allowing some charge-separation to occur, and hence the larger proportion of β-attack*.

From the preparative standpoint, two related transformations should be brought to focus. Recently, Mukaiyama and co-workers[10] reported the formation of D-glucosides by using *O*-benzylated β-D-glucopyranosylbenzothiazole in the presence of cupric triflate. The ratios of α- to β-D-glucosides were found to be reasonably high, even with complex alcohols**. Ferrier and co-workers[11] had earlier reported that the mercury-assisted reaction of 2-propanol with phenyl 1-thio-β-D-glucopyranoside is complete after 96 h (compare Table I), giving the desired 2-propyl α-D-glucopyranoside (isolated as the tetraacetate in 55% yield).

The versatility, in glycosidations, of aglycons containing a hetero-atom, as exemplified by the 2-pyridylthio group, can be shown by other types of remote activation involving electrophilic species (see Scheme 3). Thus, treatment of **1** (1 mmol) with 2-chloroethanol for 18 h under reflux gave the corresponding 2-chloroethyl α-D-glucopyranoside (80%), characterized as the known[12] crystalline tetraacetate (m.p., mixed m.p.). A control experiment using 1-chloropentane (0.5 mL) and 2-propanol (5 mL) gave, after similar treatment, a 70% yield of the anomeric 2-propyl-D-glucopyranosides (α:β = ~1 : 1, isolated as the individual tetraacetates), thus indicating that, in both cases, activation had taken place by initial *S*- or *N*-alkylation. The corresponding phenyl 1-thioglycoside was recovered unchanged from such experiments.

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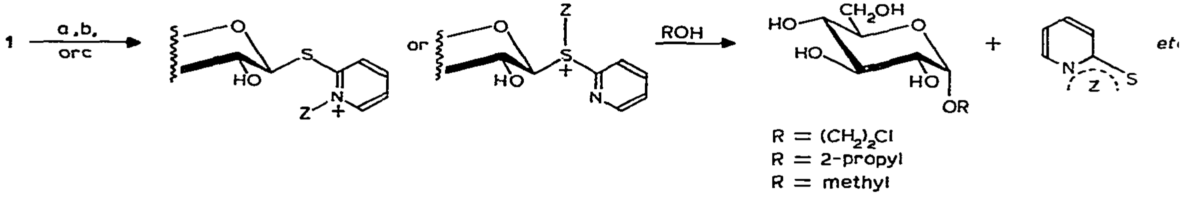
*Although kinetic studies have not yet been conducted, the reaction of methanol or 2-propanol is, for all practical purposes, immediate. With higher alcohols, such as cyclohexanol, such additional parameters as viscosity could alter the process; see, for example, the effect of temperature for 2,2-dimethylpropanol (Table I). Also, anomerization of initially formed glycosides, or the intervention of anhydro sugar intermediates, can be excluded, based on control studies. It should, however, be noted that the solutions are acidic when once they have been treated with water.

We have also briefly investigated the reaction of *O*-benzylated **1 with methanol in the presence of $Hg(NO_3)_2$ during 2 min at 25°, and have obtained the corresponding methyl α- and β-D-glucopyranosides (90%), in the ratio of 7:3.



a, 2-chloroethanol ; b, 2-propanol—1-chloropropane; c, methanol—NBS.

Scheme 3

Treatment of **1** (1 mmol) with *N*-bromosuccinimide (NBS; 1.5 mmol) in 1 : 1 acetonitrile–methanol during 5 h under reflux gave a 4 : 1 mixture (n.m.r.) of the methyl α- and β-D-glucopyranosides (80%). In this regard, West and Schuerch[13] had reported on the methanolysis of *O*-protected β-D-glycopyranosyl-sulfonium, -ammonium, and -phosphonium salts, prepared by reaction of the corresponding D-glucopyranosyl halide with the appropriate nucleophile (for example, Me_2S).

The exceptionally fast, metal-ion-promoted reactions of **1** and related derivatives, as well as the other forms of anomeric activation described herein, are clearly a consequence of the functional design inherent in the structure of the anomeric, heterocyclic substituent. Undoubtedly, other combinations of hetero-atoms in cyclic or acyclic modifications can be devised and subjected to suitable, remote activation in order to provide even more efficient glycosidations, with improved stereocontrol and substrate–alcohol ratios. The prospects of effecting *C*- and *N*-glycosylic coupling by these methods are also evident. Moreover, such novel derivatives could have relevance in various enzymic, and related biological, processes.

ACKNOWLEDGMENTS

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