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Note

Synthesis of *O*- and *S*-glucosides using glucosyl halides and zinc salts

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The widespread occurrence of *O*-glucosides in nature and their importance in biochemical processes is well known. Thioglycosides are known to accumulate in some plant tissues as storage reserves for thiol groups [1] and they are useful as specific enzyme inhibitors [2] and as glycosyl donors [3]. Methodologies for the synthesis of *O*- and *S*-glycosides [4–6], particularly those suitable for large-scale preparations, are thus of great interest to organic chemists.

Nucleophilic substitution of S_N1-active halides (*tert*-alkyl, allylic and benzylic) using zinc salts has been successfully used in this laboratory to develop preparative methods of access to several functional groups [7,8]. The zinc salts of nucleophiles are easily prepared in situ and the process, which is essentially a one-pot synthesis, can be carried out under both solvolytic and non-solvolytic conditions. The facility with which the substitution occurs — in competition with elimination reactions, especially with sterically hindered *tert*-alkyl substrates — has earlier been explained by invoking an ion-quadruplet intermediate [7]. We have now attempted extension of the scope of this general reaction to the substitution of glucopyranosyl halides with alcohols, phenols and mercaptans.

A systematic study of the reaction of tetra-*O*-acetyl-D-glucopyranosyl halides with benzyl alcohol was undertaken. It included variation of parameters such as the choice of halogen (Cl or Br) and its anomeric configuration, solvent and temperature. The results are summarized in Table 1. Understandably, tetra-*O*-acetyl-α-D-glucopyranosyl bromide

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Table 1
Reaction of tetra-*O*-acetyl-D-glucopyranosyl halides with zinc salt of benzyl alcohol in different solvents under reflux

Entry no.	Halide	Solvent	Time (h)	Glucoside [a] yield (%)	(α:β)
1	β-Chloride	CH_2Cl_2	36	55	(40:60)
2	α-Chloride	CH_2Cl_2	24	83	(10:90)
3	α-Bromide	CH_2Cl_2	8	81	(11:89)
4	α-Bromide	$CH_2Cl_2 + C_5H_5N$	48	55 [b]	(54:45)
5	α-Bromide	$CHCl_3$	4	54	(56:44)
6	α-Bromide	C_6H_6	3	75	(35:65)

[a] Glucoside yield and isomeric composition were determined by GC; the rest was accounted as glucose penta-acetate.
[b] Reaction incomplete; unreacted starting material 40%.

(acetobromoglucose) (Table 1, Entry 3) reacted faster than the corresponding chloro derivative (Entry 2) and β-glucosides were formed predominantly in high yield. On the other hand, the reaction with tetra-*O*-acetyl-β-D-glucopyranosyl chloride was relatively slow and led to a mixture of α- and β-glucosides (Entry 1). Aprotic solvents like haloalkanes and benzene were found to be ideally suited as reaction medium. Lower reaction temperature favoured the formation of the β-glucoside (Entry 3). However, the influence of acetoxyl group at C-2 (the neighbouring group effect) on the course of glucosylation as well as on the stereochemistry of products was not evident. Use of pyridine as an acid scavenger retarded the reaction (Entry 4). On the other hand, separate experiments showed that both acetobromoglucose (glucosyl donor) and benzyl glucopyranosides (products) were not anomerized in the presence of zinc bromide, the by-product. Also, under these conditions, zinc chloride or zinc bromide did not promote the condensation of benzyl alcohol with α- or β-D-glucopyranose pentaacetate. Thus, the present method is at variance with the Helferich method which involves rather drastic conditions. The latter is employed for the preparation of aryl glucopyranosides from glucopyranose peresters using zinc halide melt [9] or mercuric cyanide [10]. The glucosides so obtained are mixtures of anomers, of which the α anomer is usually predominant [11].

Under non-solvolytic conditions, the present glucosylation method worked best in refluxing dichloromethane, with acetobromoglucose as the glucosyl donor. The crude product was peracetylated before chromatographic separation of the glucoside anomers. The structures and stereochemistry of the glucosides were determined by physical and ^{1}H NMR analysis. In order to find the general applicability of this method for the preparation of alkyl or aryl glucosides, reactions with a number of representative substrates were carried out. The results are summarized in Table 2. When the substrate was a low-molecular-weight alcohol, the reaction could be carried out under solvolytic conditions. It was exceedingly fast and afforded glucosides in high yields. Thus, methyl β-D-glucopyranoside was formed exclusively in methanol (Entry 1). The reactions carried out under non-solvolytic conditions, with *n*-octanol, cholesterol and benzyl alcohol as substrates (Entries 2, 3, and 5), were equally easy and gave the corresponding glucosides in 80% overall yield, β anomers being the major components. The yield was

Table 2
Yield and physical constants of alkyl (aryl) per-*O*-acetyl-D-glucopyranosides

Entry no.	Substrate [a]	Time (h)	Yield % (α:β)	α β	mp (°C)	[α]$_D$	Ref.
1	Methanol	2	85 (0:100)		–	–	–
					104–105 (104) [c]	− 18.4 (− 19) [c]	[16]
2	*n*-Octanol	6	85 (20:80)		[b]	+ 102.4 [d]	–
					54 (54)	−23.8 (−22)	[17]
3	Cholesterol	16	73 (12:88)		191–192 (193)	+90.2 (+92)	[18]
					155–156 (157)	−27.4 (−26)	[18]
4	Menthol	11	58 (25:75)		[b]	+39.3 (+40)	[19]
					130–131 (131)	−54.1 (−53)	[19]
5	Benzyl alcohol	8	81 (11:89)		110–112 (111)	+ 143.8 (+ 143)	[20]
					97–98 (98)	43.4 (−44)	[21]
6	Phenol	2	70 (50:50)		115 (114)	+ 168.8 (+ 168)	[16]
					124 (125)	−22.4 (−23)	[16]
7	β-Naphthol	4	65 (40:60)		127 (128)	+208.0 [d]	[22]
					137 (135)	−91.8 [d]	[22]
8	Thymol	5	43 (36:64)		111–112 (112)	+ 124.5 [d]	[22]
					114–115 (115)	−20.5 [d]	[22]
9	Eugenol	5	75 (31:69)		[b]	+88.8 [d]	–
					123–124 (123)	−25.4 (−26)	[23]
10	Vanillin	12	25 (O:100)		–	–	–
					142 (144)	−51.4 (−50)	[24]
11	Z-3-Hexen-1-ol	8	87 (15:85)		[b]	+88.3 [d]	–
12	Allyl alcohol	8	60 (16:84)		[b]	+ 113.9(+ 115)	[25]
					87 (88)	−24.2 (−25)	[26]
13	Cinnamyl alcohol	8	0		–	–	–
14	Nerol	8	0		–	–	–

[a] Entry 1 under solvolytic conditions; rest in refluxing CH_2Cl_2.
[b] Syrup; could not be crystallized.
[c] Literature values are in parenthesis.
[d] Analytical data:

Entry	for	Calcd		Found	
		C	H	C	H
2α	$C_{22}H_{36}O_{10}$	57.37	7.88	57.25	7.92
7α	$C_{24}H_{26}O_{10}$	60.75	5.52	60.93	5.60
7β	$C_{24}H_{26}O_{10}$	60.75	5.52	60.92	5.44
8α	$C_{24}H_{32}O_{10}$	59.99	6.71	59.86	6.73
8β	$C_{24}H_{32}O_{10}$	59.99	6.71	59.90	6.67
9α	$C_{24}H_{30}O_{11}$	58.29	6.11	58.38	6.15
11β	$C_{20}H_{30}O_{10}$	55.81	7.02	55.68	7.08

Table 3
Yield and physical constants of alkylthio (aryl) per-*O*-acetyl-D-glucopyranosides

Entry no.	Substrate [a]	Time (h)	Yield % (α:β)	α β	mp (°C)	$[\alpha]_D$	Ref.
1	*n*-Propyl mercaptan	4	68 (40:60)		107–108	+190.9 [e]	–
					80–82 (79) [d]	−23.6 (−22) [d]	[27]
2	*sec*-Butyl mercaptan	3	66 (50:50)		[b]	+172.6 [e]	–
					100–102	−20.0 [e]	–
3	*tert*-Butyl mercaptan	24	No reaction		–	–	–
4	Allyl mercaptan	24	Intractable mixture		–	–	–
5	Benzyl mercaptan	6	50 (20:80)		[c]	–	–
					100–101 (102)	−91.5 (−92)	[16]
6	Thiophenol	4	45 (40:60)		89–90 (91)	+232.5 (+234)	[28]
					115–116 (117)	−16.9 (−16)	[16]

[a] In refluxing CH_2Cl_2.
[b] Syrup; could not be crystallized.
[c] Decomposes.
[d] Literature values in parenthesis.
[e] Analytical data:

Entry	for	Calcd		Found	
		C	H	C	H
1α	$C_{17}H_{26}O_9S$	50.24	6.45	50.32	6.48
2α	$C_{18}H_{28}O_9S$	52.42	6.71	51.36	6.73
2β	$C_{18}H_{28}O_9S$	51.42	6.71	51.35	6.75

somewhat lower in the case of menthol (Entry 4), perhaps due to steric hindrance. With phenoxide nucleophiles (Entries 6, 7, and 9), yields of the glucosides were moderate (60–70%). But, thymol (Entry 8) afforded only 43% of the glucoside, again due to steric reasons. The reaction with vanillin (Entry 10) afforded β the glucoside in only 25% yield.

The reactions involving allylic alcohols were not smooth and led to unexpected results. Allyl alcohol, the simplest example of this class, gave the corresponding glucoside in only 60% yield (Entry 12), whereas nerol and cinnamyl alcohol (Entries 13 and 14) failed to yield any glucosides at all. The actual products obtained were intractable mixtures of bromides (that are derived from the allylic alcohols), besides D-glucose tetra-acetate. This behaviour was typical of allylic alcohols only; the presence of double bonds elsewhere in the nucleophile did not affect the course of the reaction (e.g., *Z*-3-hexen-1-ol, Entry 11).

S-Glucosides were synthesized using mercaptans/thiophenol as substrates in the reaction (Table 3). The yields were moderate (45–70%) and the products were usually 1:1 anomeric mixtures except in the case of benzyl 1-thioglucopyranoside (Entry 5) where the more stable β anomer was formed predominantly. *tert*-Butyl and allyl mercaptans failed to yield the corresponding glucosides, probably due to their inability to form the ion-quadruplet intermediate.

Direct condensation of sugar peresters with mercaptans in the presence of zinc chloride, tin(IV) chloride, boron trifluoride or *p*-toluene sulfonic acid (under either solvolytic conditions or in a homogeneous solvent medium, Helferich procedure [12]) is known to give the β anomer of *S*-glucosides in 50–70% yield, but not consistently in all the cases. While from thiophenols the aryl β-thioglycosides are obtained exclusively [12], in the case of alkyl mercaptans, the initially formed β-alkyl thioglycosides anomerize under the influence of the catalyst, to give a 7:3 α/β mixture [13]. The present finding confirms this observation.

We have demonstrated the application of zinc salt-mediated substitution reaction to the synthesis of *O*- and *S*-glucosides. The glucosides so obtained contain both α and β anomers. But it is possible to obtain predominantly β-glucosides, at least in the case of alkoxy nucleophiles, by choosing the right conditions. Zinc salts being inexpensive and innocuous, this method is suitable for large-scale preparations.

1. Experimental

General method.—Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 200 or a 270 MHz instrument using tetramethylsilane as the internal standard. Optical rotations were measured at 22 °C and 589 nm. GC conditions: 6 ft. × 1/8 in. (o.d.) stainless steel column, OV-17 (10%) on Chromosorb W; N_2 30 mL/min; H_2 FID; injection and oven temp: 250 °C; detector temp: 300 °C. For TLC, 5 × 20 cm plates coated with Kieselgel G — type 60 (E. Merck) were used.

Tetra-*O*-acetyl-α-D-glucopyranosyl chloride, tetra-*O*-acetyl-β-D-glucopyranosyl chloride and tetra-*O*-acetyl-α-D-glucopyranosyl bromide were prepared according to the standard procedures of Lemieux [14].

General procedure for the preparation of zinc salts.—Substrate (alcohol/phenol/thiol) (10 mmol) was stirred with ZnO or $ZnCO_3$ (5 mmol) in dry C_6H_6 under reflux for 6 h in a Dean–Stark apparatus to remove water as it is formed. For small scale preparations it was convenient to use a Soxhlet apparatus filled with anhydrous Na_2SO_4 or molecular sieve 4 Å, so that the condensed solvent was dried before it returned to the reaction flask. Then the solvent was removed under reduced pressure and the residual zinc salt dried over P_2O_5 in a vacuum desiccator.

General procedure for O- *and* S-*glucosylation.*—A tetra-*O*-acetyl-α/β-D-glucopyranosyl halide (10 mmol) was added in parts under stirring to the zinc salt of the substrate, suspended in an appropriate solvent, and the mixture was refluxed. Refluxing was continued till the bluish-green spot due to glucopyranosyl halide disappeared on the TLC plate [spraying with the *O*-tolidine reagent (Fluka, 1% soln in acetone) and exposure to sunlight]. The reaction products were filtered and the residue washed with the solvent. Combined filtrates were washed repeatedly with distilled water and dried over anhydrous Na_2SO_4. Then the solvent was distilled off to yield a gummy residue. The residue was dried over P_2O_5 in vacuo and treated with a mixture of Ac_2O (20 mmol) and pyridine (10 mmol) for 24 h at room temperature. After the usual work up, the product mixture was subjected to column chromatography on SiO_2 (100–200 mesh) using hexane–EtOAc mixtures as eluents. Pure fractions containing *O*/*S*-alkyl/aryl-

Table 4
^1H NMR spectral data for new *O*/*S* alkyl tetra-*O*-acetyl-D-glucopyranosides

O/*S*-Alkyl	(α/β)	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	-OAc	Aglycon
n-Octyl	α	5.10, d (3.5)	← 4.80–5.20, m →		5.55, t	← 3.35–3.85, m →		3.95–4.10	2.00–2.13, 4s	0.90 (3H, t, CH_3) 1.33 (12H, bs, 6 × CH_2) 4.20 (2H, t, OCH_2)
cis-3-Hexenyl	β	4.60, d (7.0)	← 4.95–5.35, m →			← 3.40–4.00, m →			2.00–2.10, 4s	1.00 (3H, t, CH_3) 1.95–2.60 (4H, m, 2 × CH_2)
Eugenyl	α	5.20, bs	← 4.90–5.10, m →		5.60–5.90, m	← 4.10–4.60, m →			2.01–2.02, 4s	3.30–3.40 (2H, d, $ArCH_2$) 4.30 (2H, t, OCH_2)
n-Propylthio	α	5.65, d (5.7)	5.37, t	← 4.98–5.10, m →		4.41–4.47, m	4.30, dd (4.7, 12.3)	4.08, d (11.7)	2.02–2.09, 4s	0.97 (3H, t, CH_3) 1.58–1.67 (2H, m, CH_2) 2.44–2.59 (2H, m, SCH_2)
n-Propylthio	β	4.48, d (10.0)	5.22,t	5.09–5.12, t	5.00–5.04, t	3.67–3.74, m	4.25, dd (4.9, 12.3)	4.13, dd (2.4, 12,3)	2.01–2.09, 4s	
sec-Butylthio	α	5.74, d (5.7)	5.30–5.36, m	← 4.94–5.08, m →		4.40–4.50, m	4.26–4.34, m	4.04–4.10, m	2.02–2.08, 4s	0.96 (3H, t, CH_3) 1.30 (3H, d, CH_3) 1.59 (2H, m, CH_2) 2.85–2.99 (1H, m, SCH)
sec-Butylthio	β	4.58, dd (3.2, 10.1)	5.26, t	← 4.95–5.11, m →		3.66–3.73, m	4.22, dd (0.6, 12.2)	4.12, dd (2.5, 12.3)	2.01–2.08, 4s	

In parenthesis, coupling constants in Hz.

2,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranosides were combined and crystallized from MeOH. Their optical rotations and mp are given in Tables 2 and 3. Spectral data of newly prepared per-*O*-acetyl-D-glucopyranosides are given in Table 4. The conventional Zemplén deacetylation [15] yielded the 1-*O*/*S*-alkyl/aryl D-glucopyranosides.

*Preparation of methyl tetra-*O*-acetyl-β-D-glucopyranoside.*—Aceto-bromoglucose (4.11 g, 10 mmol) dissolved in dry MeOH (50 mL), was refluxed with ZnO (0.6 g, 7.4 mmol) for 2 h on a water bath. The reaction mixture was filtered and the filtrate concentrated. The residue was taken in $CHCl_3$ (50 mL), washed with water (15 mL × 3), dried over anhydrous Na_2SO_4 and concentrated. The crude product crystallized from absolute MeOH as needles, yield 3.10 g (85%). Its mp and specific rotation are given in Table 2.

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