α-Glucosylation of Phenols with Tetra-*O*-benzyl-α-D-glucose

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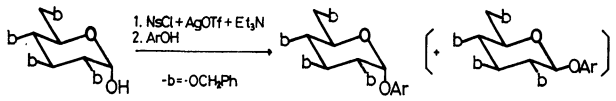
(Received October 8, 1980)

Synopsis. An α-glucosylation of phenols with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose is described. This uses a mixture of *p*-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate and triethylamine in dichloromethane in a two-stage treatment.

Continuing our study of glucosylation using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**),[1] we have found a novel α-glucosylation of phenols in two stages, as shown by Eq. 1. Although there have been several procedures reported for α-glucosylation of phenols,[2] the recommended one seems to give the product only in low yields.[3]



Eq. 1

When **1** was pre-treated with an equimolar mixture of *p*-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate, and triethylamine in dichloromethane

Table 1. Results of glucosylation of 2-methylphenol[a]

Run	Reaction time/h[b]	Yield/%	
		α-Anomer	β-Anomer
23	0.1	21	7
24	0.5	42	14
2	3.0	47	16
25	5.0	46	17
26[c]	3.0	46	19
27[d]	3.0	14	17

a) The first stage was conducted at −10 °C for 0.5 h. b) Reaction time for the second stage. c) An excess amount (5.0 equiv.) of the phenol was used. d) An equimolar mixture of the phenol and triethylamine in dichloromethane was used.

Table 2. Yields and physical data of aryl tetra-*O*-benzyl-α-D-glucopyranosides

Run	Phenol	Code	Yield/%	Solv.[a]	Mp/°C[b]	$[\alpha]_D(c)$[c]	δ of C-1[d]/ppm
1	Phenol[e]	**2**	63[h]	HI	—	+82°(2.0)	95.4
2	2-Methylphenol[g]	**3**	47[i]	HC	69—70(n)	+84°(0.5)	96.1
3	2-Ethylphenol[g]	**4**	38	HC	55—56(n)	+78°(0.8)	95.9
4	2-Isopropylphenol[g]	**5**	44	HC	—	+73°(0.6)	96.1
5	2-*t*-Butylphenol[g]	**6**	28	HC	—	+71°(1.4)	95.0
6	2-Methoxyphenol[g]	**7**	50	BB	86—87(n)	+74°(0.6)	97.0
7	3-Methoxyphenol[g]	**8**	47	HC	—	+77°(0.7)	95.4
8	4-Methoxyphenol[f]	**9**	52	HC	—	+92°(1.0)	96.3
9	2-Ethoxyphenol[g]	**10**	35	BB	78—79(n)	+71°(0.4)	96.9
10	2-Fluorophenol[g]	**11**	43	BB	75—76(p)	+67°(0.3)	97.6
11	2-Phenylphenol[e]	**12**	48	BB	—	+58°(2.1)	96.5
12	3-(Methoxycarbonyl)phenol[f]	**13**	48	BB	87—88(n)	+95°(1.0)	95.5
13	4-(Methoxycarbonyl)phenol[f]	**14**	40	HC	—	+107°(1.0)	95.2
14	4-(Dodecyloxycarbonyl)phenol[f]	**15**	51	BB	—	+71°(0.8)	95.1
15	4-(Benzyloxycarbonyl)phenol[f]	**16**	45	BB	—	+83°(1.8)	95.2
16	4-(Phenoxycarbonyl)phenol[e]	**17**	46	HC	—	+102°(0.8)	95.8
17	3-Nitrophenol[e]	**18**	38	HC	—	+90°(0.8)	95.9
18	4-Nitrophenol[e]	**19**	32	BB	98—99(n)	+131°(0.4)	95.6
19	2,6-Dimethylphenol[e]	**20**	14[j]	HI	—	+46°(0.8)	99.5
20	2,6-Dimethoxyphenol[e]	**21**	30	BB	74—75(l)	+84°(1.4)	97.9
21	1-Naphthol[f]	**22**	50	HC	92—93(p)	+72°(0.8)	96.3
22	2-Naphthol[e]	**23**	66	HC	70—71(n)	+98°(1.3)	95.3

a) Solvent systems for chromatography: BB=benzene–butanone, HC=hexane–chloroform, HI=hexane–diisopropyl ether. b) n=Needles, p=prisms, l=leaves. c) At 20 °C in $CHCl_3$. d) In $CDCl_3$ with TMS. e) A supersaturated solution of the phenol in a small amount of the solvent was injected into the vessel. f) The phenol was added into the vessel during the short time the stopper was removed. g) The phenol was injected into the vessel. h) The β-anomer (**2β**), 21%: mp 84.5—86 °C; $[\alpha]_D$ −9° (*c* 1.0, $CHCl_3$); δ 101.6 (C-1) (Found: C, 77.70; H, 6.50 %). i) The β-anomer (**3β**), 16%: mp 106—107 °C; $[\alpha]_D$ −7° (*c* 0.7, $CHCl_3$); δ 101.2 (C-1) (Found: C, 77.70; H, 6.66%). j) The β-anomer (**20β**), 17%: mp 140—141 °C; $[\alpha]_D$ +25° (*c* 1.0, $CHCl_3$); δ 104.1 (C-1) (Found: C, 78.19; H, 6.86%)

Table 3. Analysis of aryl tetra-*O*-benzyl-α-D-glucopyranosides

Code	Mole formula	Found (%)		Calcd (%)	
		C	H	C	H
2	$C_{40}H_{40}O_6$	77.29	6.53	77.90	6.54
3	$C_{41}H_{42}O_6$	77.94	6.70	78.07	6.71
4	$C_{42}H_{44}O_6$	78.01	6.87	78.23	6.88
5	$C_{43}H_{46}O_6$	78.05	7.06	78.39	7.04
6	$C_{44}H_{48}O_6$	77.60	7.41	78.54	7.19
7	$C_{41}H_{42}O_7$	75.57	6.23	76.14	6.55
8	$C_{41}H_{42}O_7$	75.66	6.64	76.14	6.55
9	$C_{41}H_{42}O_7$	75.38	6.60	76.14	6.55
10	$C_{42}H_{44}O_7$	76.18	6.69	76.34	6.17
11	$C_{40}H_{39}FO_6$	75.42	6.18	75.69	6.19
12	$C_{46}H_{44}O_6$	79.50	6.64	79.74	6.40
13	$C_{42}H_{42}O_8$	74.71	6.21	74.76	6.27
14	$C_{42}H_{42}O_8$	74.15	6.40	74.76	6.27
15	$C_{53}H_{64}O_8$	76.59	7.75	76.78	7.78
16	$C_{48}H_{46}O_8$	76.34	6.39	76.78	6.17
17	$C_{47}H_{44}O_8$	76.06	6.32	76.61	6.02
18	$C_{40}H_{39}NO_8$	72.17	6.00	72.60	5.94
19	$C_{40}H_{39}NO_8$	72.33	6.24	72.60	5.94
20	$C_{42}H_{44}O_6$	77.43	7.06	78.23	6.88
21	$C_{42}H_{44}O_8$	74.46	6.75	74.53	6.55
22	$C_{44}H_{42}O_6$	79.18	6.25	79.25	6.35
23	$C_{44}H_{42}O_6$	79.07	6.30	79.25	6.35

at −10 °C[1a] and then reacted with phenol, we found that phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**2**) was formed predominantly. This is in contrast with the fact that a similar glucosylation of alkanol with **1** gave β-anomer preferentially.[1a,b] The ratio of anomers measured by ^{1}H NMR spectroscopy in the case of 2-methylphenol was constant throughout the reaction (Table 1). Various phenols were glucosylated with **1** in a similar way (Table 2). Except for 2,6-dimethylphenol, α-glucosides were formed prepondantly. But in the reaction of **1** with triethylammonium 2-methylphenolate, the β-glucoside was formed in a significant yield.

Our procedure is useful for preparing a compound such as 4-phenoxylcarbonylphenyl α-D-glucopyranoside (**25**), which was prepared through glucosylation of the phenol with **1** and subsequent catalytic hydrogenolysis to remove benzyl groups.

Experimental

Specific rotations were measured at 20 °C in a 1-dm cell. Column chromatography was carried out on silica gel (Kanto Kagaku). Silica gel (Merck, No. 7731) was used for TLC.

General Procedure for Glucosylation. To a mixture of **1** (270 mg, 0.5 mmol), *p*-nitrobenzenesulfonyl chloride (122 mg, 0.55 mmol), and silver trifluoromethanesulfonate (141 mg, 0.55 mmol) in dichloromethane (2.7 ml), triethylamine (77 μl, 0.55 mmol) was added at −10 °C. After stirring for 0.5 h, a phenol (0.65 mmol) was added to the mixture, which was then stirred for 3 h at 0 °C. After filtration the reaction mixture was chromatographed using appropriate solvent systems (Table 2) to give aryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside. Usually, the β-anomer was isolated as a by-product.

*Anomeric Phenyl 2,3,4,6-Tetra-O-acetyl-α- and β-D-glucopyranosides **24** and **24β**.* An anomeric mixture (70 mg) of **2** and **2β** (Run 1) was hydrogenated in acetic acid (3 ml) containing water (1 ml), methanol (3 ml), and palladium black (80 mg, Wako) at 340 kPa, acetylated with acetic anhydride and pyridine, and then chromatographed using benzene containing butanone (gradient) to give first **24** (35 mg): mp 113—114 °C; $[\alpha]_D$ +165° (*c* 1, $CHCl_3$) [lit,[4] mp 115 °C; $[\alpha]_D^{20}$ +169.7° (*c* 2, $CHCl_3$)], and then **24β** (8 mg): mp 124.5—125.5 °C; $[\alpha]_D$ −21° (*c* 0.6, $CHCl_3$) lit,[4] mp 125—126 °C; $[\alpha]_D^{20}$ −22.5° (*c* 2, $CHCl_3$).

*4-(Phenoxycarbonyl)phenyl α-D-Glucopyranoside (**25**).* Compound **17** (60 mg, 0.8 mmol) was hydrogenated in acetic acid (3.7 ml) containing methanol (3.5 ml), water (1.2 ml), and palladium black (60 mg) at 340 kPa overnight, purified chromatographically using chloroform containing methanol (20%), and crystallized from ethanol to give **25** (26 mg, 84%): 155—157 °C; $[\alpha]_D$ +151° (*c* 0.7, MeOH). Found: C, 60.04; H, 5.38%. Calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36%.

*Alternative Synthesis of **2** and **2β**.* A mixture of phenyl α-D-glucopyranoside (60 mg, 0.23 mmol), benzyl bromide (Tokyo Kasei 0.86 ml), barium oxide (1.08 g), and barium hydroxide octahydrate (0.42 g) in *N,N*-dimethylformamide (1.2 ml)[5] was stirred at 25 °C overnight, filtered, and evaporated *in vacuo*. The residue was chromatographed using benzene containing butanone (2%) to give **2** (53 mg, 56%), $[\alpha]_D$ +83° (*c* 3.0, $CHCl_3$).

Phenyl β-D-glucopyranoside[4] (0.54 g, 2.1 mmol) was converted in a similar way into **2β** (0.44 g, 34%): mp 83.5—85 °C; $[\alpha]_D$ −13° (*c* 0.4 EtOH), −12° (*c* 1.0, $CHCl_3$) [lit,[6] mp 82 °C; $[\alpha]_D^{18}$ −13.5° (EtOH)].

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