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Stereoselectivity of Reactions at the Glycoside Center of Carbohydrates: VII.[1] Synthesis of Aryl α- and -β-D-Glucopyranosides by Helferich, Catalyzed by Boron Trifluoride Etherate

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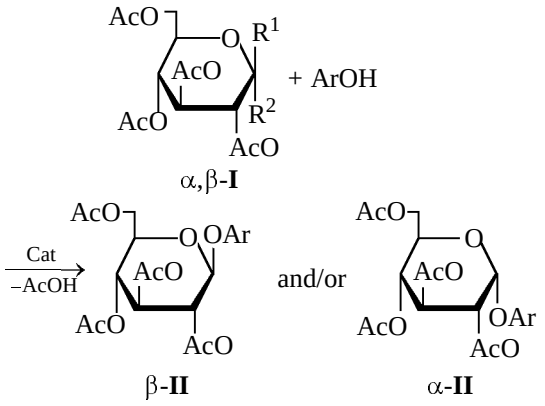
Abstract — ^{13}C NMR spectroscopy was used to study the stereoselectivity of glycosylation of phenols with the α and β anomers of penta-*O*-acetyl-D-glucopyranose, penta-*O*-trifluoroacetyl-D-glucopyranose, and 2,3,4,6-tetra-*O*-acetyl-1-*O*-trifluoroacetyl-D-glucopyranose in the presence of boron trifluoride etherate at varied temperature, time, and catalyst amount. The boron trifluoride etherate–catalyzed reaction of penta-*O*-acetyl-β-D-glucopyranose and 2,3,4,6-tetra-*O*-acetyl-1-*O*-trifluoroacetyl-β-D-glucopyranose with phenols occurs with a high stereocontrol to give, depending on conditions, predominantly 1,2-*cis*- or 1,2-*trans*-aryl-glycosides. This reaction can be used for preparative synthesis of the α- and β-anomeric forms of glycosides of a wide range of phenols.

Phenol glycosides are conveniently prepared by the Helferich method that involves the acid-catalyzed reaction of full saccharide acetates with phenols [2], yielding a mixture of 1,2-*trans*- and 1,2-*cis*-glycosides (β and α anomers), which is separated by fractional crystallization or chromatographic methods.



R^1 = H, R^2 = OAc (α-**I**); R^1 = OAc, R^2 = H (β-**I**).

The reaction can be accomplished by melting the reagents in a 4–6-fold excess of phenols at 110–140°C using as catalysts *p*-toluenesulfonic acid or zinc chloride [3], sulfuric acid [4], aluminum chloride [5], polyphosphoric acid or its ethyl ester [6], anhydrous orthophosphoric acid [7], etc. The excess of phenols can be much cut down by boiling the reagents in an inert solvent in the presence of phosphorus oxychloride [8], anisole–boron trifluoride complex [9], or tin chloride [10] as catalysts.

We earlier studied the stereoselectivity of glycosylation of phenols with full D-glucopyranoside acetates in various conditions [11]. By spectral data we determined the contents and ratios of the α and β anomers of arylglycosides in the reaction products and formulated principal regularities. In the present work we studied the boron trifluoride etherate–catalyzed glycosylation of phenols with the α and β anomers of penta-*O*-acetyl-D-glucopyranose α- and β-**I**, penta-*O*-trifluoroacetyl-D-glucopyranose α- and β-**III**, and 2,3,4,6-tetra-*O*-acetyl-1-*O*-trifluoroacetyl-D-glucopyranose α- and β-**IV**.

The conversions of starting materials and the compositions of arylglycosides were determined by the intensities of signals of anomeric carbon atoms in the ^{13}C NMR spectra as described in [11].

Preliminary experiments with varied reagent concentrations and ratios, catalysts, and reaction temperatures and times showed that phenol is easily glycosylated with acetate β-**I** in an inert organic solvent, such as benzene or methylene chloride, even at room temperature in the presence of a small excess of phenol and a catalyst (0.1–0.2 mol) to give predominantly phenyl tetra-*O*-acetyl-β-D-glucopyranoside

[1] For communication VI, see [1].

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Table 1. Stereoisomeric composition of products of boron trifluoride etherate-catalyzed glycosylation of phenols with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (β-**I**)[a]

Exp. no.	Compound	Catalyst amount, mol	Reaction time, h	Conversion of acetate (β-**I**), %	Total content of α- and β-glycosides (**II**), %	Ratio of α- and β-glycosides (**II**) in reaction products, %	Content of other components, %
1	Phenol	0.1	2	25	25	0/100	β-**I**, 75
2		0.1	24	46	46	0/100	β-**I**, 54
3		0.1	48	53	53	0/100	β-**I**, 47
4		0.1	70	86	86	0/100	β-**I**, 14
5		0.1	115	89	89	0/100	β-**I**, 11
6		0.2	144[b]	92	92	5/95	β-**I**, 8
7		0.2	190	93	93	8/92	β-**I**, 7
8	4-Methylphenol	0.1	48	92	82	8/92	α-**I**, 14; β-**I**, 4
9		0.1	96	98	82	15/85	α-**I**, 16; β-**I**, 2
10		0.1	120	100	82	22/78	α-**I**, 18
11	2-Methoxyphenol	0.1	48	68	68	0/100	β-**I**, 32
12	4-Methoxyphenol	0.1	48	100	100	8/92	—
13	4-Hexyloxyphenol	0.1	48	92	92	9/91	β-**I**, 8
14	3-Methylphenol	0.1	48	96	76	15/85	α-**I**, 20; β-**I**, 4
15		0.1	96	96	76	24/76	α-**I**, 20; β-**I**, 4
16	3,4-Dimethylphenol	0.1	48	87	87	13/87	β-**I**, 13
17	3-Diethylaminophenol	0.1	48	0	0	—	β-**I**, 100
18	3-Chlorophenol	0.1	48	68	68	0/100	β-**I**, 32
19		0.5	48	97	71	16/84	α-**I**, 24; β-**I**, 3
20		0.5	96	97	74	32/68	α-**I**, 27; β-**I**, 3
21		0.5	190	100	83	42/58	α-**I**, 17
22	4-Nitrophenol	0.1	48	27	3	0/100	α-**I**, 24; β-**I**, 3
23		0.2	190[b]	33	4	0/100	α-**I**, 29; β-**I**, 7
24		0.2	285	36	6	0/100	α-**I**, 30; β-**I**, 4
25	Phenol	1	0.167	100	94	75/25	6[c]
26		1	0.5	100	100	89/11	—
27		1	1	100	93	88/12	7[c]
28	4-Methoxyphenol	1	0.25	100	75	54/46	α-**I**, 12; 13[c]
29		1	0.5	100	92	85/15	α-**I**, 8
30		1	1	100	94	83/17	α-**I**, 6
31		1	1.5	100	100	85/15	—
32	4-Methylphenol	1	0.5	100	74	83/17	α-**I**, 26
33		1	1	100	81	88/12	α-**I**, 6; 13[c]
34		1	1.5	100	84	86/14	α-**I**, 4; 12[c]
35	3-Chlorophenol	1	0.5	100	66	29/71	α-**I**, 34
36		1	1	100	95	63/37	α-**I**, 5
37	4-Nitrophenol	1	1	100	18	100/0	α-**I**, 82

[a] Exp. nos. 1–24 were performed at room temperature and with excess phenol (0.1 mol); exp. nos. 25–37 were performed by boiling reactants in benzene with excess phenol (2 mol). [b] Additional amount of catalyst was added. [c] Unidentified admixtures.

(β-**II**). According to spectral data, the conversion of β-**I** increases with increasing reaction time and reaches 86% after 70 h (Table 1, exp. nos. 1–4). The reaction occurs stereoselectively with exclusive formation of β-**II**. The product was isolated individual in an yield of ~70% by fractional crystallization from ethanol. Longer reaction times (115, 144, and 190 h) and double catalyst concetration increased the conversion of acetate β-**I** by only 3–6% (exp. nos. 5–7). The above reagent : catalyst ratio appears to be close to

Table 2. Ratios of the α and β forms of acetylated aryl glucopyranosides α- and β-**II** in products of anomerization of aryl tetra-*O*-acetyl-β-D-glucopyranosides β-**II** in the presence of boron trifluoride etherate at various reaction times (%/%)

Initial glycoside	α/β Ratio				
	5 min	15 min	0.5 h	1 h	1.5 h
Phenyl tetra-*O*-acetyl-β-D-glucopyranoside	12/88	29/71	30/70	72/28	89/11
4-Methylphenyl-tetra-*O*-acetyl-β-D-glucopyranoside	25/75	–	45/55	–	75/25
4-Chlorophenyl-tetra-*O*-acetyl-β-D-glucopyranoside	6/94	–	30/70	–	64/36

optimum, since using 0.5 mol of boron trifluoride etherate per 1 mol of acetate β-**I** increases the fraction of glycoside α-**II**, apparently because of anomerization of the primarily formed β-arylglycoside β-**II** (exp. nos. 6 and 7). Increased reaction temperature and time produce the same effect.

Unlike acetate β-**I**, penta-*O*-acetyl-α-D-glucopyranose (α-**I**) failed to react with phenol under these conditions and was almost completely recovered from the reaction mixture.

Analysis of the ^{13}C NMR spectra of the reaction mixtures obtained by glycosylation of substituted phenols with pentaacetate β-**I** showed that electron-donor substituents in the aromatic ring accelerate the reaction, and the conversion of the starting acetate β-**I** reaches 76–100% already within 48 h (exp. nos. 8–16). Unlike the other phenols with electron-donor substituents, 3-diethylaminophenol fails to enter the glycosylation reaction, and from the reaction mixture we quantitatively recovered the starting pentaacetate β-**I** (exp. no. 17).

The example of the reaction of 2-methoxyphenol with acetate β-**I** was used to show that *ortho* substituents in the aromatic ring decrease the conversion of acetate β-**I**, probably, by steric reasons (exp. no. 11).

Electron-acceptor substituents in the aromatic ring adversely affect the activity of phenols in the glycosylation reaction and increase the fractions of glycoside α-**II** and acetate α-**I**. 4-Nitrophenol is poorly reactive, the conversion of pentaacetate β-**I** into glycosides **II** is as low as 6% even after 285 h, while most pentaacetate β-**I** undergoes anomerization to α-**I** (exp. nos. 22–24).

If glycosylation of phenols with pentaacetate β-**I** is performed with an equimolar catalyst amount under reflux in benzene, the starting acetate almost completely converts into glycosides α-**II** and β-**II** already within 15–30 min (exp. nos. 25–37). Therewith, the fraction of α-**II** increases with increasing reaction time. Table 2 lists the the ratios of the α and β anomers obtained by anomerization of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, 4-methylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, and 4-chlorophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside under reflux in benzene at a glycoside–phenol–etherate ratio of 1 : 1.1 : 1. These data provide evidence showing that boron trifluoride etherate induces anomerization, and this property can be used for preparative synthesis of aryl tetra-*O*-acetyl-α-D-glucopyranosides from corresponding β isomers.

As known, the stereisomeric composition of glycosylation products is much dependent on the type of protective groups in the carbohydrate moiety of the molecule. Therewith, protective groups that take no part in the reaction are considered to favor 1,2-*cis*-glycoside formation [12]. We studied the stereoisomeric composition of products of phenol glycosylation with 1-*O*-trifluoroacetyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (β-**IV**) and of 4-metoxyphenol with 1,2,3,4,6-penta-*O*-trifluoroacetyl-β-D-glucopyranose (β-**III**). At room temperature in the presence of catalytic amounts of boron trifluoride etherate, the conversions of β-**IV** and β-**III** into α and β glycosides after 48 h were as low as 11 and 8%, respectively (Table 3, exp. nos. 1–2), while the most part of the starting acetates converted into the poorly reactive α anomers (α-**IV** and α-**III**) which, according to our experimental findings, fail to enter the phenol glycosylation reaction.

If the reaction of trifluoroacetate β-**IV** with phenol is performed at the boiling point of the solvent with a stoichiometric amount of the catalyst, complete conversion of β-**IV** into α- and β-glycosides occurs within 5 min; therewith, the fraction of α-**II** increases with increasing reaction time (exp. nos. 3–8). Under these conditions, both α-**IV** and α-**III** fail to react with phenol.

Pentaacetate β-**I** and its 1-*O*-trifluroacetyl derivative β-**IV** similarly react with phenols containing electron-donor substituents. The major products of these reactions are 1,2-*cis*-arylglycosides whose fractions in the reaction mixtures attain 85% and more (Table 1, exp. nos. 28–34, Table 3, exp. nos. 9–11).

Table 3. Stereoisomeric composition of products of boron trifluoride etherate–catalyzed glycosylation of phenols with 1-*O*-trifluoroacetyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (β-**IV**) and 1,2,3,4,6-penta-*O*-trifluoroacetyl-β-D-glucopyranose (β-**III**)[a]

Exp. no.	Starting trifluoroacetate	Compound	Catalyst amount, mol	Reaction time, h	Conversion of acetate β-**I**, %	Total content of α- and β-glycosides, %	Ratio of α- and β-glycosides in reaction products, %	Content of other components, %
1	β-**IV**	Phenol	0.1	48	86	11	100/0	α-**IV**, 75
2	β-**III**	4-Methoxyphenol	0.1	48	66	8	100/0	α-**III**, 58
3	β-**IV**	Phenol	0.2	1	100	63	12/88	37[b]
4	β-**IV**		1	0.08	100	100	26/74	–
5	β-**IV**		1	0.25	100	100	47/53	–
6	β-**IV**		1	0.5	100	100	59/41	–
7	β-**IV**		1	1	100	100	93/7	–
8	β-**IV**		1	1.5	100	100	100/0	–
9	β-**IV**	4-Methylphenol	1	1	100	100	85/15	–
10	β-**IV**	3-Methylphenol	1	1	100	100	89/11	–
11	β-**IV**	4-Methoxyphenol	1	1	100	100	89/11	–
12	β-**IV**	4-Chlorophenol	1	1	100	100	75/25	–
13	β-**IV**	4-Nitrophenol	1	1	100	100	65/35	–

[a] Exp. nos. 1 and 2 were performed at room temperature and with excess phenol (0.1 mol); exp. nos. 3–13 were performed by boiling reactants in benzene with excess phenol (2 mol). [b] Unidentified admixtures.

With 4-chlorophenol, the fraction of a 1,2-*cis*-arylglycoside in the reaction products is much reduced (Table 1, exp. nos. 35–36, Table 3, exp. no. 12). The greatest difference in the reactivity of pentaacetate β-**I** and trifluoroacetate β-**IV** is observed in the glycosylation of 4-nitrophenol. Unlike pentaacetate β-**I**, trifluoroacetate β-**IV** readily reacts with 4-nitrophenol in similar conditions, and the fraction of a 1,2-*cis*-glycoside in the reaction mixture attains 65% (Table 3, exp. no. 13).

The results obtained for phenol glycosylation with compounds β-**I** and β-**IV** were used to prepare a series of aryl tetra-*O*-acetyl-α- and -β-glucopyranosides in good yields (Table 4). The purity and structure of the resulting compounds were confirmed by their elemental analyses, optical rotations, and ^{13}C NMR spectra (Tables 4, 5).

Table 4. Aryl tetra-*O*-acetyl-α- and -β-D-glucopyranosides α- and β-**II**

Compound	Method of synthesis[a], reaction time, h	Yield, %	mp, °C (ethanol)	$[\alpha]_D^{20}$, deg (*c* 1, $CHCl_3$)	Found, %		Formula	Calculated, %	
					C	H		C	H
Phenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IIa**)	A, 115	70	125–126	–22	56.40	5.59	$C_{20}H_{24}O_{10}$	56.60	5.70
3-Methylphenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IIb**)	A, 48	62	136–136	–20	57.80	5.75	$C_{21}H_{26}O_{10}$	57.53	5.97
4-Methylphenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IIc**)	A, 48	54	95–97	–10	57.40	5.77	$C_{21}H_{26}O_{10}$	57.53	5.97
4-Methoxyphenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IId**)	A, 48	68	90–92	–14	55.38	5.54	$C_{21}H_{26}O_{11}$	55.50	5.76

Table 4. (Contd.)

Compound	Method of synthesis[a], reaction time, h	Yield, %	mp, °C (ethanol)	$[\alpha]_D^{20}$, deg (*c* 1, $CHCl_3$)	Found, %		Formula	Calculated, %	
					C	H		C	H
2-Methoxyphenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IIe**)	A, 48	58	154–155	–21	55.20	5.59	$C_{21}H_{26}O_{11}$	55.50	5.76
3-Chlorophenyl tetra-*O*-acetyl-β-D-glucopyranoside (β-**IIf**)	A, 48	58	133–134	–25	51.92	5.15	$C_{20}H_{23}ClO_{10}$	52.35	5.05
Phenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IIa**)	B, 1 C, 1	70 76	112–114	+170	55.70	5.00	$C_{20}H_{24}O_{10}$	56.60	5.70
3-Methylphenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IIb**)	C, 1	63	158–160	+178	58.00	6.10	$C_{21}H_{26}O_{10}$	57.53	5.97
4-Methylphenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IIc**)	C, 1	60	188–190	+182	57.60	6.00	$C_{21}H_{26}O_{10}$	57.53	5.97
4-Methoxyphenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IId**)	B, 1 C, 1	68 64	144–145	+159	55.90	5.90	$C_{21}H_{26}O_{11}$	55.50	5.76
4-Chlorophenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IIg**)	C, 1	50	100–102	+169	53.18	5.86	$C_{20}H_{23}ClO_{10}$	52.35	5.05
4-Nitrophenyl tetra-*O*-acetyl-α-D-glucopyranoside (α-**IIh**)	C, 1	43	108–110	+170	52.18	4.94	$C_{20}H_{23}NO_{12}$	51.17	4.93

[a] (A) Reaction of pentaacetate β-**I** with phenols at room temperature; (B) boiling of pentaacetate β-**I** with phenols in a benzene solution; and (C) boiling of 1-*O*-trifluoroacetate β-**IV** with phenols in a benzene solution.

Table 5. ^{13}C NMR spectra of aryl tetra-*O*-acetyl-α- and -β-D-glucopyranosides, δ_C, ppm

Compound no.	Carbohydrate component						Other carbon atoms
	C^1	C^2	C^3	C^4	C^5	C^6	
β-**IIa**	98.9	71.0	71.8	68.2	72.5	61.8	156.7, 116.8, 129.3, 123.1, 129.3, 116.8 (Ar[a]); 20.3 (CH_3CO); 168.9, 169.1, 169.8, 170.1 (CO)
β-**IIb**	99.0	71.1	71.8	68.3	72.7	62.0	156.8, 117.7, 139.3, 124.0, 129.5, 113.7 (Ar); 21.3 (CH_3); 20.4 (CH_3CO); 169.2, 169.3, 170.1, 170.4 (CO)
β-**IIc**	99.5	71.2	71.9	68.3	72.7	61.9	154.8, 117.0, 129.9, 132.8, 129.9, 117.0 (Ar); 20.4 (CH_3); 20.4 (CH_3CO); 169.2, 170.1, 170.5 (CO)
β-**IIe**	100.6	71.2	71.8	68.4	72.6	61.9	146.1, 150.6, 112.9, 124.5, 120.7, 120.1 (Ar); 55.9 (CH_3O); 20.4 (CH_3CO); 169.1, 169.2, 169.8, 170.1, 170.3 (CO)
α-**IIa**	94.2	68.3	70.4	67.9	70.0	61.5	156.0, 116.6, 129.5, 123.0, 129.5, 116.6 (Ar); 20.4 (CH_3CO); 169.4, 169.9, 170.3 (CO)

[a] Signals of phenyl C^1, C^2, C^3, C^4, C^5, and C^6, respectively.

EXPERIMENTAL

The ^{13}C NMR spectra of acetylated and trifluoroacetylated derivatives were recorded for 50% solutions in $CDCl_3$ on a Varian CFT-20 spectrometer against internal TMS. The rotation angles of arylglycosides in chloroform were measured on an SU-3 universal saccharimeter at 20°C.

Glycosylation of phenols. *a*. To a solution of 30 mmol of penta-*O*-acetyl-α- or -β-D-glucopyranoses **I**, their 1-*O*-trifluoroacetyl derivatives α- or β-**IV**, or penta-*O*-trifluoroacetates α- or β-**III** in 100 ml of dry benzene we added 33 mmol of corresponding phenol, 0.4 ml of boron trifluoride etherate (~3 mmol), and the reaction mixture was left to stand at room temperature. After a time, the reaction was terminated by dilution of the reaction mixture with 100 ml of benzene. The benzene solution was washed with water (1 × 100 ml), 1 N sodium hydroxide (2 × 50 ml), and water to neutral washings, dried with sodium sulfate, and evaporated in a vacuum at a bath temperature not higher than 50°C. The syrup-like residue was analyzed by ^{13}C NMR spectroscopy.

In a preparative experiment, aryl tetra-*O*-acetyl-β-D-glucopyranosides β-**II** were isolated by crystallization of the syrup-like residue from hot ethanol and dried in a vacuum at 75–80°C.

b. To a solution of 30 mol of penta-*O*-acetyl-α- or -β-D-glucopyranosides α- or β-**I**, 1-*O*-trifluoroacetate α- or β-**IV**, or penta-*O*-trifluoroacetate α- or β-**III** in 70 ml of dry benzene we added 33 ml (~30 mmol) of corresponding phenol. The reaction mixture was refluxed for 1 h in moisture-proof conditions and then treated as described above.

Anomerization of acetylated aryl β-D-glucopyranosides. A solution of 10 mmol of aryl tetra-*O*-acetyl-β-D-glucopyranoside β-**II**, 1.1 mmol of corresponding phenol, and 1.3 ml of boron trifluoride etherate in 25 ml of dry benzene in moisture-proof conditions. After a time, the solution was cooled, diluted with benzene, treated as described above, and the residue was analyzed by ^{13}C NMR spectroscopy.

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