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Note

Phase-transfer-catalyzed synthesis of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosides

HENRY P. KLEINE, DAVID V. WEINBERG, ROBERT J. KAUFMAN, AND RAVINDER S. SIDHU*
Monsanto Agricultural Products Co., 800 N. Lindbergh Boulevard, St. Louis, Missouri 63167 (U.S.A.)
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During the past decade, phase-transfer catalysis has become a valuable tool in the varied repertoire of techniques employed by synthetic chemists. The burgeoning popularity of the method residues in the fact that it affords a mild, catalytic route to compounds previously accessible by methods necessitating such harsh and undesirable reaction conditions as high temperatures and dipolar aprotic solvents.

Recent applications of this methodology in the carbohydrate field have involved the synthesis of *C*-heteroaryl derivatives by the Wittig reaction[1]; selective esterification of primary hydroxyl groups[2]; synthesis of glycosyl dithiocarbonates[3]; partial *O*-substitution of D-mannose derivatives[4]; and benzylation[5], acylation[6], and methylenation[7] of carbohydrate derivatives. Amongst the alkylation methods, those having applications directed toward the stereospecific synthesis of glycosides appear to hold the most promise as general and high-yielding routes to these compounds. In this regard, two recent literature reports described the use of solid phase-transfer catalysts as mediators of the synthesis of nitrophenyl β-D-glycopyranosides[8] and aryl 1-thio-β-D-glycopyranosides[9].

Although these methods appear to work well for the particular cases reported, the scope and generality of this technique has not been fully explored. Initial preparation of the resin-bound phenoxide or thioxide is required, and this may limit the ease and scale-up of the solid-phase procedure. Solution phase-transfer for the preparation of aryl glycosides appears to be a more general technique, as evidenced by the synthesis[10] of a series of aryl β-D-glucopyranosides by reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with the appropriate, substituted phenol prepared, followed by deprotection. However, these workers[10] were unable to convert acetylated glycosyl halides into aryl glycosides successfully under the same conditions.

In direct contrast to these findings, our initial communication[11] in the area reported the expeditious conversion of commercially available, per-*O*-acetylated

*To whom correspondence should be addressed.

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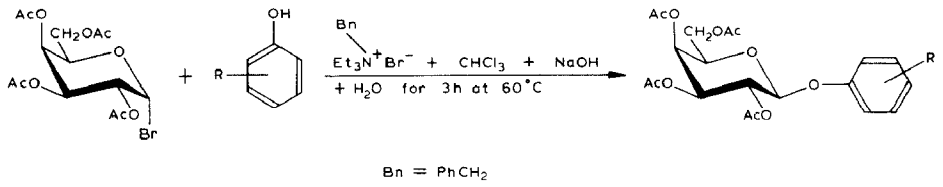
TABLE I

ARYL 2,3,4,6-TETRA-*O*-ACETYL-β-D-GALACTOPYRANOSIDES

Compound	*Aryl substituent*	*Yield (%)*	*M.p. (°)*		$[\alpha]_D^{22}$ *(deg)*[a]		*Elemental analysis (%)*										*Purification method*[c]	*References*
			Found	*Reported*	*Found*	*Reported*	*Calc.*					*Found*						
							C	*H*	*X*[b]	*N*	*S*	*C*	*H*	*X*[b]	*N*	*S*		
1	4-NO_2	70	143–145	145–146	−10	−11						known					A	8
2	3-NO_2	73	105–106	110–112	−8	−9						known					A	8
3	2,4-di-NO_2	67	175–178		+65.3		46.70	4.31		5.45		46.71	4.32		5.42		C	
4	2-NO_2, 4-Cl	86	195–197	199–200	+56.1	+55.9						known					A	12
5	4-OCH_3	56	98–100	102–103	+2.7	+2.9						known					A	12
6	3-OCH_3	50	86–88	87–88	+1.5	+0.3						known					D	12
7	3,5-di-OCH_3	61	syrup		+1.61		54.54	5.83				54.33	5.60				D	
8	4-OEt	60	80–82	82–83	+3.55	+3.6						known					A	12
9	4-OBu	50	71–74		+4.29		58.06	6.50				57.82	6.45				D	
10	4-OCH_2Ph	56	85–88		+5.26		61.13	5.70				61.49	5.71				A	
11	4-OPh	47	foam		+8.85		60.46	5.46				60.73	5.56				D	
12	4-(4-NO_2-PhO-)	69	foam		+12.10		55.62	4.85		2.49		55.65	4.56		2.50		D	
13	3,4-methylenedioxy	56	foam		+2.71		53.85	5.16				53.44	4.81				D	
14	4-Br	67	98–100	102–103	+4.8	+4.4						known					A	12
15	3-Br	70	89–91	90–91	+1.2	+1.2						known					A	12
16	2,4,6-tri-Br	80	133–135	136–137	−12.03	−12.4						known					A	12
17	4-Cl	63	97–99	97–99	+3.0	+7.6						known					A	13
18	3-Cl	51	74–78	70–71	−4.1[d]	−8.3[d]						known					A	12
19	2,4-di-Cl	79	125–127	130–131	−24.1	−25.4						known					A	12
20	3,5-di-Cl	52	99–102		−3.1		48.70	4.50	14.37			48.69	4.51	14.37			A	
21	3,4-di-Cl	65	76–78	81–82	+1.2	+0.7						known					A	12
22	4-Cl, 2-CHO	69	167–169		−8.82		51.43	4.81	7.23			51.14	4.92	6.88			A	
23	4-I	59	85–88		+8.52		43.65	4.21	23.06			43.68	4.25	23.05			A	
24	4-F	65	100–103		−2.93[e]		54.30	5.24				53.86	5.16				A	
25	3-F	66	96–99		−3.85		54.30	5.24				54.54	5.07				B	
26	4-CN	64	foam		−0.7		56.12	5.16		3.12		56.17	5.20		3.10		D	
27	4-N=N-Ph	53	125–132		+28.66		59.09	5.34		5.30		59.22	5.39		5.50		A	

28	4-SCH_3	65	114–115		+10.3		53.61	5.57		6.81	53.64	5.59		6.80	A		
29[f]	4-NH_2	87	foam		+5.83		54.67	5.73	3.19		54.44	5.79	3.17		—		
30	H	64	120–122	123–124	−27.6	−26.4					known				A		14
31	4-CH_3	58	98–100	99–100	+3.9	+4.2					known				A		13
32	3-CH_3	45	71–74		+1.9		57.53	5.98			57.57	6.01			B		
33	3-CH_3, 4-Cl	52	67–72		+4.0		53.34	5.33	7.50		53.34	5.34	7.48		A		
34	4-CH_2CH_3	56	93–95	98–99	+4.77	+4.7					known				A		12
35	2,4,6-tri-CH_3	30	138–141	144–145	−9.82	−11.6					known				A		12
36	4-$CH(CH_3)_2$	53	95–97		+5.99		59.22	6.48			59.45	6.43			A		
37	4-*sec*-butyl	33	70–73		+5.32		59.99	6.71			60.41	6.59			B		
38	4-$(CH_2)_{11}CH_3$	30	syrup		+8.73		63.87	8.21			63.53	8.01			D		
39	3,5-di-$C(CH_3)_3$	29	147–150		+6.66		62.67	7.51			62.98	7.48			A		
40	4-CH_2Ph	45	109–111		+5.58		63.03	5.88			62.99	5.91			A		
41	4-*trans*-CH=CH-Ph	55	159–163		+20.37		63.87	5.74			63.83	5.77			C		
42	2-allyl, 4-CH_3	47	133–135		−6.4		60.24	6.32			60.29	6.35			A		
43	4-trityl	47	foam		+11.7		68.42	5.84			68.82	5.77			D		
44	4-phenyl	58	122–125		+12.76		62.39	5.64			62.77	5.92			A		

[a]Specific rotations reported for 2% solutions in chloroform. [b]Cl, Br, or I. [c]Purification methods: A, crystallized from ethanol; B, crystallized from ethanol–water; C, trituration. [d]$[\alpha]^{22}_{Hg\,436}$. [e]$[\alpha]^{22}_{Hg\,407}$. [f]Prepared by reduction of compound **1**.



Bn = $PhCH_2$

α-D-glycopyranosyl bromides into their respective aryl glycosides under phase-transfer conditions. Initial results from this study[11] demonstrated that acetylated aryl D-galactopyranosides could be produced in superior yields relative to their D-glucose counterparts, presumably due to less β-elimination in the *galacto* series.

To explore the scope and limitations of the method further, a comprehensive evaluation of the reaction of different aryl aglycons with tetra-*O*-acetyl-α-D-galactopyranosyl bromide was launched, and the results of this investigation are summarized in Table I. A perusal of the data demonstrates the wide variety of substituents that can be accommodated by the phase-transfer glycosylation method, including such sensitive functional groups as nitrile and aldehyde. Of the many phenols evaluated by this technique, only four were found to be unreactive, namely, 4-acetamidophenol, 4,4′-dihydroxystilbene, 4,4′-dihydroxydihydrostilbene, and hydroquinone. Presumably, the monoanions of these phenols are too polar to be transferred across the chloroform–alkali interface, resulting in low levels of phenolic reactant in the organic layer and, consequently, essentially no reaction.

In summary, phase-transfer glycosylation with tetra-*O*-acetyl-α-D-galactopyranosyl bromide provides a facile, stereospecific, and general entry to aryl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosides. The ease of preparation of these compounds makes them particularly valuable in biochemical studies as substrates in the assay of glycosidases, and as ligands in affinity chromatography.

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were recorded at 60 MHz with Varian T-60 and EM-360 spectrometers. Melting points were determined in a Laboratory Devices Mel-temp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. L.c. was conducted in a Waters Prep-500A instrument, and elemental analyses were performed by Atlantic Microlabs, Inc. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide was obtained from the Sigma Chemical Co., St. Louis, MO, and all phenols were purchased from the Aldrich Chemical Co., Milwaukee, WI.

Aryl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosides. — A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (10 g, 24 mmol) in chloroform (100 mL) was vigorously stirred, by means of an overhead, mechanical stirrer, at reflux (60°) with a solution of the appropriate phenol (48 mmol) and benzyltriethylammonium bromide (5.53 g, 20 mmol) in 1.25M aqueous sodium hydroxide (35

mL, 44 mmol). After 3 h, the mixture was cooled, and diluted with water (100 mL). The two phases were separated, and the organic layer was washed with 1.25M sodium hydroxide (2 × 50 mL), dried (anhydrous magnesium sulfate), and evaporated *in vacuo*. The crude product was then purified by one of the four procedures listed in Table I. All compounds were characterized by ^{1}H-n.m.r. spectroscopy. Chemical-shift values obtained for compound **1** are typical: δ 8.30–8.05 (m, AA', 2 H, H_{Ar}), 7.25–6.95 (m, BB', 2 H, H_{Ar}), 5.70–5.0 (m, 4 H, H-1–4), 4.30–4.04 (m, 3 H, H-5,6,6), 2.20 (s, 3 H), 2.05 (s, 6 H), and 2.00 (s, 3 H).

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