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Note

Direct one-pot conversion of acylated carbohydrates into their alkylated derivatives under heterogeneous reaction conditions using solid NaOH and a phase transfer catalyst☆

Soni Kamlesh Madhusudan, Geetanjali Agnihotri, Devendra S. Negi† and Anup Kumar Misra*

Medicinal and Process Chemistry Division, Central Drug Research Institute (CDRI), Chattar Manzil Palace, Lucknow 226 001, UP, India

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Abstract—A convenient one-pot protocol for the direct conversion of acyl-protected carbohydrates into their alkylated counterparts has been developed by using alkyl halides in the presence of solid sodium hydroxide and a phase transfer catalyst. These economically convenient, mild, two-phase reaction conditions allow the preparation of a variety of monosaccharide intermediates for use in the synthesis of complex oligosaccharides.

Keywords: Alkylation; Heterogeneous reaction conditions; Carbohydrates; Sodium hydroxide; One-pot

The protection and deprotection of hydroxyl groups are at the heart of multi-step oligosaccharide syntheses.[1–8] In connection with the synthesis of oligosaccharides related to some bacterial polysaccharides, we had a need to prepare several benzylated monosaccharide intermediates. Generally, alkyl ether protected sugars are prepared from their acylated derivatives via a two-step sequence consisting of deacylation by alkaline hydrolysis followed by alkylation in the presence of a base.[9,10] Although acetyl-, benzoyl-, and pivaloyl-protecting groups are removed via alkaline hydrolysis under homogeneous reaction condition,[11–14] a recent report described heterogeneous reaction conditions for the removal of acyl protecting groups from simple alcohols and phenols using solid sodium hydroxide in the presence of a phase transfer catalyst.[15]

To make oligosaccharide synthesis simpler, one-pot methodologies for conducting several steps are always desirable. To this end, we have developed, and report here, convenient one-pot reaction conditions for the preparation of alkylated carbohydrate derivatives directly from their acylated counterparts using an alkyl halide and solid sodium hydroxide in the presence of a phase transfer catalyst (Scheme 1). In an earlier report, alkylation of carbohydrates has been carried out using alkyl halide in DMSO in the presence of 50% aq NaOH.[16] Although the protocol is straightforward, it requires pre-generation of the hydroxyl groups by saponification of acetyl groups following established protocols, which increases the number of reaction steps. Moreover, the use of high boiling, malodorous DMSO makes the final workup procedure tedious. Conventionally, acylated sugar derivatives are treated with sodium methoxide followed by a cation exchange resin to provide unprotected sugars, which upon subsequent treatment with benzyl bromide in the presence of sodium hydride or sodium hydroxide under anhydrous conditions furnishes benzylated sugar derivatives. To the best of our knowledge, a heterogeneous solid–liquid one-pot

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* Corresponding author. Fax: +91 0522 223938; e-mail: akmisra69@rediffmail.com

† Department of Chemistry, H.N.B. Garhwal University, Srinagar (Garhwal), Uttaranchal 246174, India.

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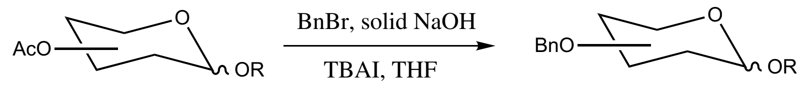

Scheme 1. Direct conversion of acyl-protected sugars into alkyl-protected sugar derivatives.

reaction protocol for this purpose has not been described, despite its advantages such as ease of application, simple workup, and use of inexpensive and relatively safe reagents.

In a first set of experiments, a well-stirred solution of tri-*O*-acetyl-D-glucal (1.0 mmol) in THF (5.0 mL) was treated with benzyl bromide (4.0 equiv) and powdered NaOH (10 equiv) at room temperature in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI), a phase transfer catalyst. The reaction was monitored by TLC and after stirring for 3.0 h at room temperature, the clean formation of a product with higher R_f value was observed. After some experimentation, it was found that the use of 1.5 equiv of benzyl bromide and 2.0 equiv of solid NaOH per acetyl group of the acetylated sugars in the presence of TBAI (0.1 equiv with respect to the sugar derivative) in THF were the best conditions. A number of solvents have been recommended in the literature for use in alkylation reactions and these were evaluated. It was found that THF and 1,4-dioxane offered almost equal efficacy and were the best solvents for this reaction. The use of a phase transfer catalyst is essential because the reaction does not go to the completion in the absence of the catalyst, even at prolonged reaction times. Other commonly used phase transfer catalysts such as tetrabutylammonium hydrogen sulfate and tetrabutylammonium bromide were also tested and both were found to be as effective as TBAI. Under the same reaction conditions, a number of acylated monosaccharide derivatives have been alkylated in excellent yield by using various alkyl halides (Table 1).

In conclusion, high yielding, one-pot heterogeneous reaction conditions have been devised for the direct conversion of acyl-protected sugars into the corresponding alkylated sugar derivatives, thus avoiding the conventional two-step procedure of deacylation and alkylation. A large number of protecting groups on the sugar residue were unaffected under these conditions. This protocol should be attractive to synthetic carbohydrate chemists as it is operationally simple, economically convenient, less toxic to the environment, and reduces the number of reaction steps.

1. Experimental

1.1. General methods

All reactions were monitored by thin layer chromatography on silica gel coated plates; spots were visualized by warming ceric sulfate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates on a hot plate or in an oven at ~100 °C. Silica gel 230–400 mesh was used for column chromatography. FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon/Xenon (6 kV, 10 MA) as the FAB gas. ^{1}H and ^{13}C NMR spectra were recorded on Brüker Advance DPX 200 MHz using TMS as the internal reference. Chemical shift values are expressed in ppm. Elemental analysis was carried out on a Carlo ERBA-1108 analyzer. Commercially available grades of organic solvents of adequate purity are used; THF was distilled from sodium-benzophenone prior to use. Products of all known compounds gave acceptable ^{1}H NMR and ^{13}C NMR data that matched that reported in the references cited in Table 1.

1.2. Typical experimental protocol

Preparation of 3,4,6-tri-O-benzyl-D-glucal: To a solution of 3,4,6-tri-*O*-acetyl-D-glucal (2.8 g, 10.3 mmol) in THF (10 mL) were added powdered NaOH (2.5 g, 62.5 mmol), TBAI (100 mg, 0.27 mmol), and benzyl bromide (5.5 mL, 46.24 mmol) successively and the reaction mixture was allowed to stir briskly for 3 h at room temperature. After completion as monitored by TLC, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness. The crude reaction product was purified over SiO_2 using hexane–EtOAc as the eluant to furnish pure 2,4,6-tri-*O*-benzyl-D-glucal (4.1 g, 95%). IR (liquid film): 3031, 2896, 1647, 1591, 1452, 1097, 1047, 734, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34–7.22 (m, 15H, aromatic), 6.42 (dd, 1H, J = 6.1, 1.0 Hz, H-1), 4.87 (dd, 1H, J = 6.3, 2.7 Hz, H-2), 4.18–4.21 (m, 1H, H-3), 4.07–4.01 (m, 1H, H-4), 3.89–3.81 (m, 1H, H-5), 3.79–3.74 (m, 2H, H-$6_{a,b}$); ^{13}C NMR ($CDCl_3$): δ 145.1, 128.8–128.0 (aromatic), 100.4, 77.2, 76.2, 74.9, 74.2, 73.9, 70.9, 69.0.

1.3. Isopropyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (2h)

Yellow oil; IR (liquid film): 3032, 2866, 2374, 1455, 1372, 1308, 1095, 1026, 737, 697 cm^{-1}; $[\alpha]_D^{25}$ +92.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 7.40–7.00 (m, 10H, aromatic), 6.09–6.02 (m, 1H, H-2), 5.83–5.73 (dt, 1H, J = 2.5, 2.5 Hz, H-3), 5.11 (br s, 1H, H-1), 4.83–4.77 (d, 1H, J = 11.7 Hz, PhCH_2), 4.67–4.40 (m, 3H, PhCH_2), 4.20–4.14 (dd, 1H, J = 9.4, 1.3 Hz, H-4), 4.02–3.93 (m, 1H, H-5), 3.80–3.64 (m, 3H, H-$6_{a,b}$,

Table 1. Direct conversion of acylated sugars to their alkylated derivatives using alkyl halides and solid NaOH in the presence of catalytic TBAI

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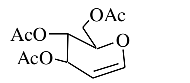
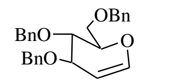
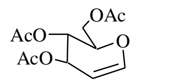
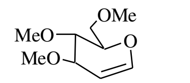
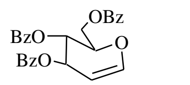
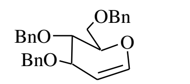
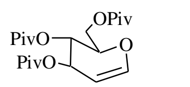
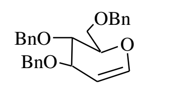
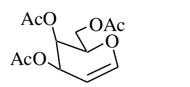
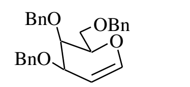
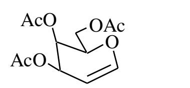
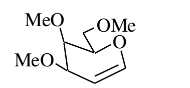
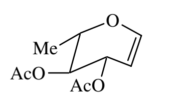
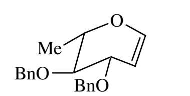
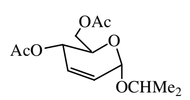
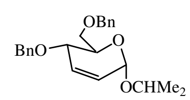
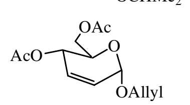
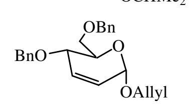
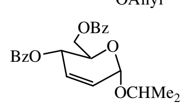
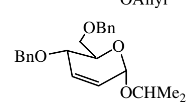
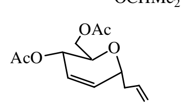
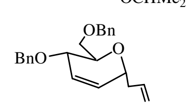
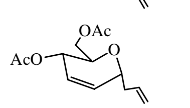
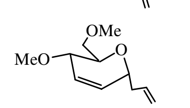
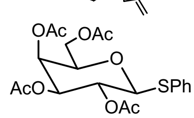
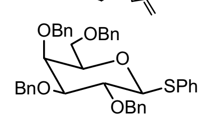
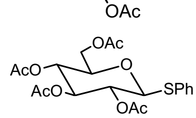
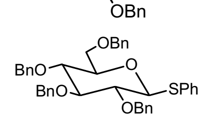
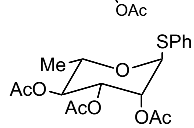
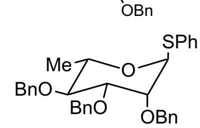
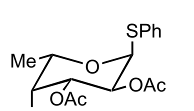
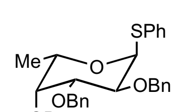
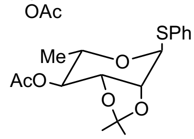
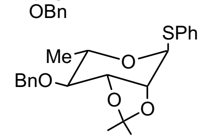
a		Benzyl bromide		95	17
b		Methyl iodide		85	18
c		Benzyl bromide		90	17
d		Benzyl bromide		92	17
e		Benzyl bromide		92	19
f		Methyl iodide		90	19
g		Benzyl bromide		82	20
h		Benzyl bromide		90	—
i		Benzyl bromide		92	21
j		Benzyl bromide		85	—
k		Benzyl bromide		90	22
l		Methyl iodide		90	23
m		Benzyl bromide		95	24
n		Benzyl bromide		92	25
o		Benzyl bromide		87	26
p		Benzyl bromide		90	27
q		Benzyl bromide		95	28

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Table 1 (*continued*)

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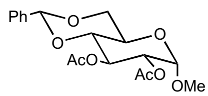
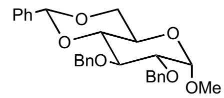
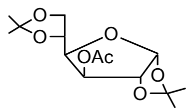
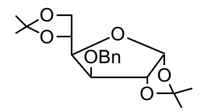
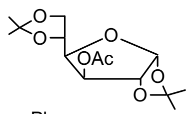
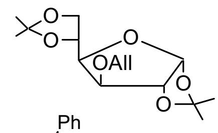
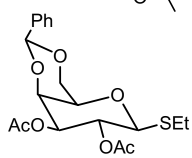
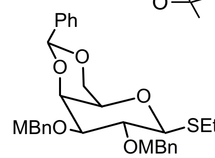
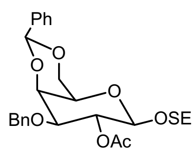
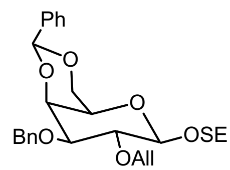
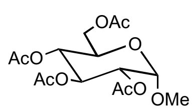
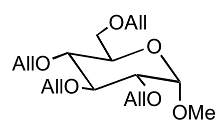
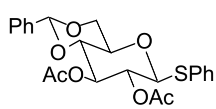
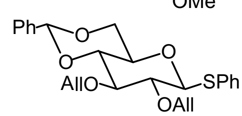
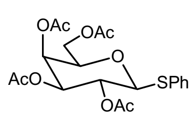
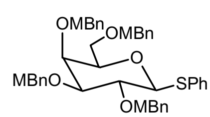
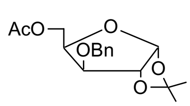
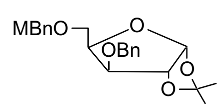
r		Benzyl bromide		92	29
s		Benzyl bromide		97	30
t		Allyl bromide		95	31
u		4-Methoxybenzyl chloride		90	32
v		Allyl bromide		88	—
w		Allyl bromide		90	16
x		Allyl bromide		92	33
y		4-Methoxybenzyl chloride		85	34
z		4-Methoxybenzyl chloride		95	35

C*H*(CH_3)$_2$), 1.22 (d, 3H, CH(C*H*$_3$)$_2$), 1.16 (d, 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$): 138.7, 138.5, 131.3, 128.8–127.0 (aromatic, C-2, C-3), 94.7, 73.8, 71.5, 70.9, 70.4, 69.8, 69.4, 24.1, 22.3; MS (FAB): *m*/*z* 369 [M+1]; Anal. Calcd for $C_{23}H_{28}O_4$ (368): C, 74.97; H, 7.66. Found: C, 74.82; H, 7.74.

1.4. 2-(Trimethylsilyl)ethyl 2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (2v)

Yellow oil; $[\alpha]_D^{25}$ +7.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.08 (m, 10H, aromatic), 6.02–5.80 (m, 1H, CH_2–C*H*=CH_2), 5.31 (s, 1H, PhC*H*), 5.16–4.97 (m, 2H, CH_2CH=C*H*$_2$), 4.52–4.46 (dd, 2H, J = 12.5, 12.5 Hz, PhC*H*$_2$), 4.25 (dd, 1H, J = 12.3, 5.7 Hz, H-6$_a$), 4.16 (d, 1H, J = 7.8 Hz, H-1), 4.11 (dd, 1H, J = 12.4, 5.9 Hz, H-6$_b$), 3.91 (d, 1H, J = 3.4 Hz, H-4), 3.53 (dd, 1H, J = 9.6, 7.8 Hz, H-2), 3.30 (1H, dd, J = 9.6, 3.6 Hz, H-3), 3.12 (br s, 1H, H-5), 3.87–3.80 (m, 2H, OC*H*$_2$CH$_2$-SiMe$_3$), 0.85 (m, 2H, OCH$_2$C*H*$_2$SiMe$_3$), −0.15 (s, 9H, Si*Me*$_3$); ^{13}C NMR ($CDCl_3$): δ 138.4–126.5 (aromatic), 135.3, 116.4, 103.1, 101.3, 78.9, 78.0, 74.1, 73.9, 72.0, 69.1, 67.2, 66.2, 18.2, −1.5 (3C); MS (FAB): *m*/*z* 499 [M+1]; Anal. Calcd for $C_{28}H_{38}O_6Si$ (498): C, 67.44; H, 7.68. Found: C, 67.25; H, 7.90.

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