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ACYLATED 2-OXOGLYCOSYL BROMIDES : EXPLORATION OF THEIR REACTION POTENTIAL

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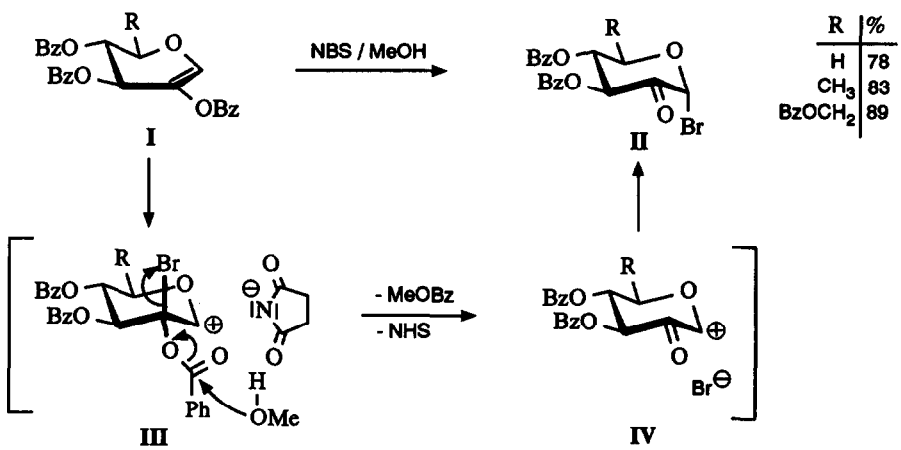
Abstract: Acylated glycos-2-ulosyl bromides give a variety of useful ensuing reactions, preparatively most relevant being their smooth α- and β-selective glycosidation, their reduction to glucosyl bromides with a free 2-OH, and their C-homologation to higher-carbon sugars.

Acylated 2-oxoglycosyl bromides of type II may efficiently be generated from hydroxyglycal esters by either of two ways, i.e. a high-yield, three-step procedure involving hydroxylaminolysis[1], deoximation[2], and photobromination[3], or, alternately, by a one-step process, simply consisting of exposure of I, in dichloromethane solution, to NBS or bromine in the presence of methanol[4]. Mechanistically, the direct conversion I → II is thought to proceed via initial attack of a brominium ion to a 2-bromobenzoxonium salt intermediate of type III[5a], in which the 2-*O*-benzoyl group is captured by methanol; the resulting formation of methyl benzoate leaves ion pair IV that combines to II. The ease with which this conversion can be effected (30 min, room temperature) is as remarkable as the yields attainable (80-90 %) and the applicability to disaccharide-derived hydroxyglycal esters[6]. Accordingly, glycos-2-ulosyl bromides of type II are nearly as well accessible from basic monosaccharides as the standard acylated glycosyl halides, which, in turn, necessitated a detailed exploration of their reaction potential. This is provided herein, with the 3,4,6-tri-*O*-benzoyl-α-D-*arabino*-hexosulosyl bromide (**1**) as the model compound.

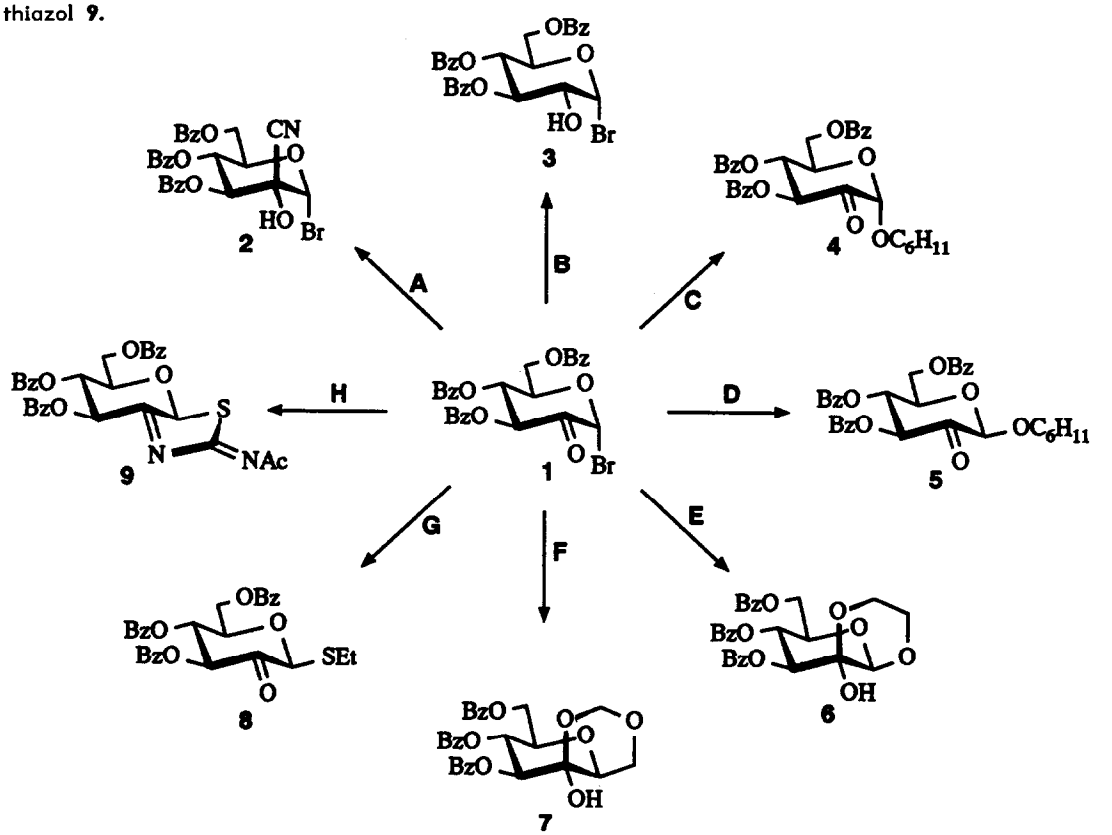


R	%
H	78
CH_3	83
$BzOCH_2$	89

Ulosyl bromide **1** is a stable, crystalline compound, storable for weeks without decomposition, its comparatively low anomeric reactivity — as compared to benzobromoglucose for example — being demonstrated by its recovery from methanol solution at ambient temperature, methanolysis occuring on heating only. Exposure of **1** to trimethylsilylcyanide/boron trifluoride gives an instantaneous reaction,

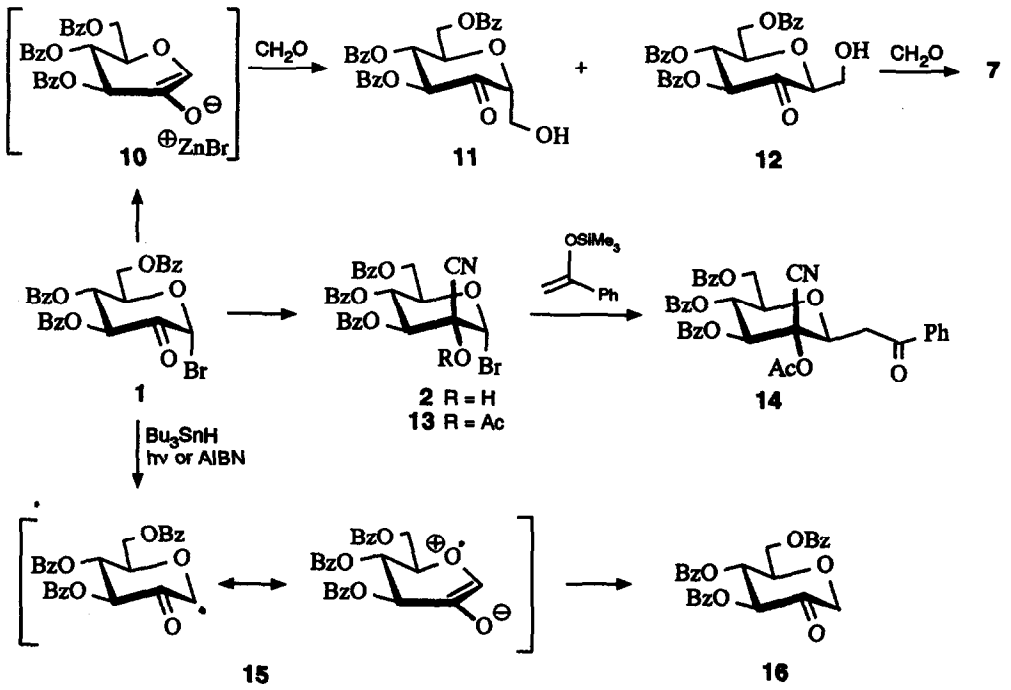
yet not the anomeric bromine is replaced by cyanide, but the cyanohydrin **2**[7] is generated. The anomeric bromine even survives saturation of the carbonyl function : acid-catalyzed reduction with sodium cyanohydridoborate results in exclusive axial attack of the hydride to afford the glycosyl bromide **3**[7] in high yield[8], none of the 2-epimeric *manno*-isomer being detectable (^{1}H-NMR) in the reaction mixture.

Of the several procedures evaluated for α-selective alcoholysis of **1**, best if moderate results gave Lemieux's in situ anomerization procedure, an approximate 4:1 mixture of **4** and **5** being formed on Et_4NBr-promoted reaction with cyclohexanol. In contrast, β-selective glycosidation is most efficiently achieved under standard Koenigs-Knorr conditions, e.g. with cyclohexanol (**1** → **5**) or glycol (**1** → **6**), in the latter case alcoholysis being followed by intramolecular acetalization to the pyrano-dioxane **6**. On silver carbonate-induced reaction with ethanethiol, the β-ethylthio glycosidulose **8** is readily formed; when reacted with thiourea, **1** quantitatively generates a β-thioamidinium bromide (m.p. 174–175 °C, $[\alpha]_D^{20}$ -4.6°, acetone), which under standard acetylation conditions undergoes cyclization to the pyrano-thiazol **9**.



Key A : $TMSCN/BF_3$, CH_2Cl_2, r.t., 10 min; 87 %
B : $NaBH_3CN/H^+$ (resin), CH_2Cl_2, r.t., 10 h; 79 %
C : $C_6H_{11}OH/Et_4NBr$, CH_2Cl_2, r.t., 2 d; 53 %
D : $C_6H_{11}OH/Ag_2CO_3$, CH_2Cl_2, r.t., 1 h; 79 %
E : glycol/Ag_2CO_3, CH_2Cl_2, r.t., 1.5 h; 92 %
F : Zn/CH_2O, THF, -35 → -10 °C, 2 h; 29 %
G : $EtSH/(Me_2N)_2CO$, CH_2Cl_2, r.t., 6 h; 75 %
H : thiourea in acetone, r.t., then Ac_2O/pyr., 0 °C; 86 %

Anomeric C-homologation can be effected by applying Reformatsky conditions : exposure of **1** to copper-activated zinc in THF smoothly generates zinc enediolate **10**, its nucleophilic anomeric center reacting with aldehydes to α/β-mixtures of hydroxyalkylation products. With formaldehyde the hydroxymethyl compounds **11** and **12**, i.e. 2,6-anhydro-hept-3-uloses of D-*gluco*- and D-*manno*-configuration, are formed in nearly equal amounts, of which **12** reacts with another formaldehyde to give the 1,3-*O*-methylene-bridged cycloacetal **7**, isomeric to **6**. Acetaldehyde as the electrophile yields a 2:1-mixture α- and β- (2-hydroxyethyl)-compounds, i.e. 3,7-anhydro-oct-4-ulose tribenzoates, of which one, after reduction and benzydilenation could be characterized as a pyrano-dioxane linked octitol[5b].



An alternate approach to anomeric C-extension of ulosyl bromides makes use of their carbonyl-protected derivatives, as, e.g., the cyanohydrin **2**. After acetylation to **13**, a silver triflate-promoted reaction with the trimethylsilyl-enol ether of acetophenone cleanly gives the β-phenacyl derivative **14** (71 %, syrup, $[\alpha]_D^{20}$ - 41°, $CHCl_3$).

Attempts to evoke a radical-induced coupling with acrylates or acrylonitrileunder a variety of conditions failed; the capto-dative radical, generated by $Bu_3SnH/h\nu$ or AIBN is quantitatively trapped by hydrogen even in acrylonitrile as the solvent, to afford the known[2] 1,5-anhydro-D-fructose tribenzoate **16**. Thus, the tributyltin hydride-induced radical coupling of halogenoses with alkenes, which in the propitious case acetobromoglucose/acrylonitrile gives C-extension and bromine exchange by hydrogen in a ratio of 2.9 : 1 only[9], appears to be limited in its preparative utility as well as scope.

In summary, acylated glycos-2-ulosyl bromides are shown to undergo a variety of synthetically useful reactions, of which their reduction to glucosyl bromides with a free 2-OH group, their α- and β-selective glycosidation, their cycloacetalization to pyrano-dioxan systems and their C-homologation to higher carbon sugars appear to most important.

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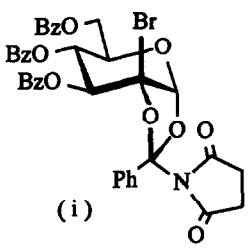
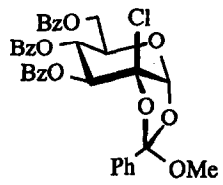
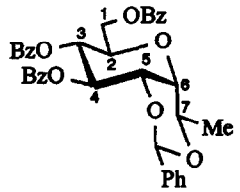
5. 5a) On reaction of I (R = CH_2OBz) with NBS in the absence of methanol, the orthoester amide intermediate (i) can be isolated (12 %, amorph, $[\alpha]_D^{20}$ -18.3° in $CHCl_3$), its ^{1}H-NMR data, most notably the small $J_{3,4}$-value of 0.8 Hz, closely corresponding to those found (I. Lundt, C. Pedersen, *Acta Chem. Scand.* **B29** (1975) 70) for orthoester (ii).



(i)



(ii)



(iii)

5b) The 2,6-anhydro-1,3,4-tri-*O*-benzoyl-5,7-*O*-benzylidene-8-deoxy-D-*erythro*-L-*gulo*-octitol (iii), obtained from **1** by zinc-mediated addition to acetaldehyde, hydride reduction ($NaBH_3CN$), and acetalization with benzaldehyde dimethylacetal (38 % yield for the 3 steps), had m.p. 170-171 °C and $[\alpha]_D^{20}$ + 15.2° ($CHCl_3$); ^{1}H-NMR (2 D at 300 MHz, $CDCl_3$): δ = 1.47 (d, 8-H_3), 4.07 (dd, 6-H), 4.27 (ddd, 2-H), 4.41 and 4.56 (2 dd, 1-H_2), 4.52 (dd, 5-H), 4.59 (dd, 7-H), $J_{1,2}$ = 2.9 and 5.8, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 10.0, $J_{5,6}$ = 6.5, $J_{6,7}$ = 10.6 Hz. The configurational assignments were ascertained by NOE experiments (S. Schwidetzky, *Dissertation*, Technische Hochschule Darmstadt, 1988).

6. F.W. Lichtenthaler, E. Kaji, S. Weprek, *J. Org. Chem.* **50** (1985) 3503.
7. Selected physical data (m.p., $[\alpha]_D^{20}$ at c = 0.7-1.2 in $CHCl_3$, ^{1}H-NMR at 300 MHz in $CDCl_3$) of
   - **2** : 178-180 °C; +81.4°; δ = 4.49 (dd, 6-H), 4.66 (3H-m, 5-H, 6-H', OH), 5.94 (d, 3-H), 6.08 (t, 4-H), 6.64 (s, 1-H), $J_{3,4}$ = $J_{4,5}$ = 9.7 Hz.
   - **3** : 153-155 °C; +128.5°; δ = 2.72 (d, OH), 3.92 (m, 2-H), 5.78 (2H-m, 3-H+4-H), 6.64 (d, 1-H), $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.3 Hz. — Lit.[8]: 157-158 °C; +126.8°.
   - **4** : 165-166 °C; +40.7°; δ = 4.86 (ddd, 5-H), 5.14 (s, 1-H), 5.86 (dd, 4-H), 6.17 (d, 3-H), $J_{3,4}$ = $J_{4,5}$ = 10.2 Hz.
   - **5** : 134-135 °C; -49.1°; δ = 4.52 (ddd, 5-H), 5.25 (s, 1-H), 5.91 (dd, 4-H), 5.96 (d, 3-H), $J_{3,4}$ = 10.2, $J_{4,5}$ = 8.2 Hz.
   - **6** : 181-182 °C; -7.1°; δ = 4.10 (ddd, 5-H, 4.50 and 4.67 (2 dd, 6-H_2), 4.85 (s, 1-H), 5.24 (d, 3-H), 5.86 (dd, 4-H), $J_{3,4}$ = $J_{4,5}$ = 10.0, $J_{5,6}$ = 2.9 and 5.0 Hz (hexose numbering).
   - **7** : 139-140 °C; -47.8°; δ = 3.51 (dd, 2-H), 4.10 and 4.25 (2 dd, 1-H_2), 4.54 and 4.64 (2 dd, 7-H_2), 5.11 (d, 4-H), 5.78 (s, OH), 5.90 (dd, 5-H).
   - **8** : 112-113 °C, -79.2°; δ = 4.51 (m, 5-H), 4.57 and 4.71 (2dd, 6-H_2), 5.42 (s, 1-H), 5.95 (m, 3-H+4-H), $J_{5,6}$ = 2.9 and 5.7 Hz.
   - **9** : 108-109 °C, +16.0°; δ = 4.16 (ddd, 5-H), 4.44 and 4.56 (2dd, 6-H_2), 5.31 (s, 1-H), 5.50 (dd, 4-H), 5.89 (d, 3-H), $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.6 Hz.
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