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Versatile Behavior of *O*-Stannylated D-Glucal Towards Halogens

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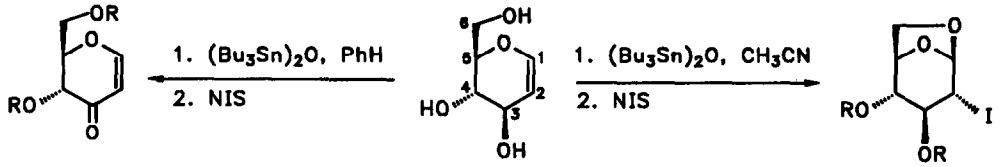
Abstract: *O-Tributylstannyl-D-glucal undergoes allylic oxidation when treated with N-iodosucinimide (NIS) in benzene, whereas oxidative 1,6-halocyclization occurs with NIS in acetonitrile or molecular halogens in various solvents.*

Tributylstannyl ethers[1] in benzene or toluene solution were reported to be monomeric species with a tetrahedral tin atom geometry[2]. Their reactivity towards various electrophiles can be enhanced by solvents having high dielectric constants (DMF, CH_3CN...)[3], catalytic amounts of quaternary ammonium halides[4], *N*-methylimidazole[5], or fluoride ions[3]. Complexation of tin atoms with these Lewis bases increases the nucleophilicity of the related alcoholic functions. We now report that similar complexation in *O*-stannyl derivatives of D-glucal[6] induces deep conformational changes which dramatically influence their reactivity towards positive halogens.

When D-glucal (1) was *O*-stannylated in benzene, then reacted with *N*-iodosuccinimide (NIS) in the same solvent, oxidation at the allylic position was principally observed[7] leading to the enone 2 isolated in 60% yield[8] together with small amounts of an iodocyclization product 3[9] (Scheme 1). Whereas tri-*O*-acetyl-D-glucal in solution was reported[10] to be a 3:2 mixture of half-chair $^4H_5$ and $^5H_4$ (D) conformers with the latter being favored by the vinylogous anomeric effect, *O*-tributylstannyl-D-glucal with electron-donating substituents will generally adopt an $^4H_5$ conformation in benzene solution. The pseudo-axial orientation of H-3 facilitates its transfer as hydride to an iodine cation since the developing electron-deficient orbital at C-3 will be stabilized by the β-effect of tin[11] and the overlap with the adjacent π orbital of the double bond as well (Scheme 2).



2 R = H
2a R = Ac

1

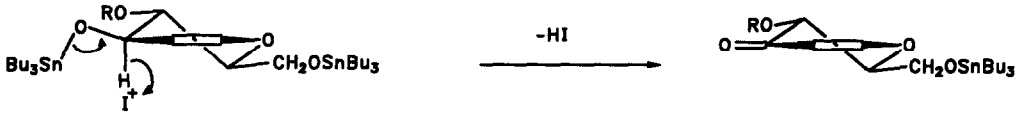
3 R = H
3a R = Ac

Scheme 1

When *O*-stannylation of 1 was performed in acetonitrile, then followed by treatment with NIS, the iodocyclized product 3 was isolated in 70% yield with only traces of 2[12].

Oxidative coupling of protected glycals with alcohols is a well-known reaction[14] usually triggered by a halogen cation which gives a cyclic halonium ion by electrophilic addition to the double bond. Regiospecific attack at C-1 by the alcohol is then assisted by an electron lone pair of the pyranose ring

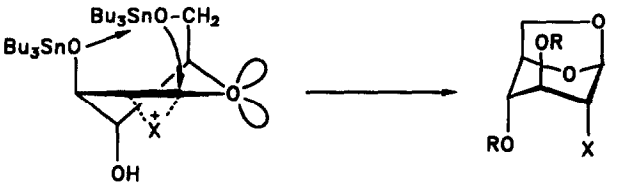
oxygen atom.



$^4H_5$ (D) R = H or $SnBu_3$

Scheme 2

O-Tributylstannyl ethers have been successfully used in such "haloglycosylation" reactions[15]. Here we postulate the formation of an intermediate cyclic iodonium cation in a $^5H_4$ (D) conformation stabilized by coordination of tin atoms to acetonitrile and intramolecular chelation of pseudo-axial O-3 with the tin atom at O-6 (Scheme 3).



$^5H_4$ (D) **3** X = I, R = H **3b** X = Br, R = H **3a** X = I, R = Ac **3c** X = Br, R = Ac

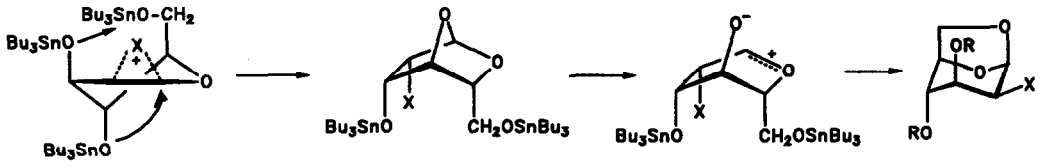
Scheme 3

The *gluco* configuration of **3** reflects an exclusive attack of I^+ from below the plane of the double bond, an orientation favored by the inverse anomeric effect[16]. D-Glucal (**1**) itself without *O*-stannyl residues gives only very small amounts of **3**[17], whereas 3,4-di-*O*-acyl-glycals were recently reported[13] to cyclize efficiently in the presence of an I^+ donor. The vinylogous anomeric effect[10] which is much less effective in D-glucal (and also in 3,4-di-*O*-benzyl-glycals)[13] could explain these results.

We have also found that molecular bromine and iodine give *only* halocyclization products when reacted with *O*-stannylated D-glucal, whatever be the solvent ($CHCl_3$, PhH, CH_3CN). A 9:1 mixture of 1,6-anhydro-2-bromo-2-deoxy-β-D-*gluco* (**3b**) and -*manno* pyranose (**4**) was isolated in 56% yield from the reaction with bromine in chloroform[18]. A similar result was obtained with iodine in acetonitrile[19].

The charge-transfer complex which is formed when the halogen molecule approaches the π system of the enol ether must collapse to a cyclic halonium cation with the help of some tributyltin species (in an inter- or intramolecular way) acting as Lewis acids for coordination of the halide ion. Such a complexation facilitates the formation of the halonium transition state as a locked $^5H_4$ conformer. In spite of inverse anomeric effect and severe steric hindrance, approach of the halogen molecule from above the plane of the double bond occurs at 10% extent and leads to the cyclized product **4** through a mechanism which could be reminiscent of the conversion of phenyl β-D-*manno*-pyranoside to 1,6-anhydro-β-D-*manno*-pyranose[20]. A highly-strained 1,4-anhydro compound **5**[21] resulting from nucleophilic attack of O-4 (which must be stannylated to some extent) rearranges to the 1,6-anhydro product **4** by a nonconcerted process involving an oxocarbenium ion[22] (Scheme 4).

In conclusion, application of the tin methodology[1] to glycals affords a convenient access to useful [3.2.1] bicyclic compounds usually accessible in several steps by conventional methods[23].



5

$B_{1,4}$ (D)

4 X = Br, R = H
4a X = Br, R = Ac

Scheme 4

Acknowledgment: We thank Dr. J.-M. Valery for NMR measurements.

References and Notes

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6. D-Glucal (1) was prepared by deacetylation of commercial tri-*O*-acetyl-D-glucal with 10:10:1 methanol-water-triethylamine for 5 h at room temperature, followed by evaporation, then drying under vacuum. *O*-Stannylation was systematically conducted by refluxing in various solvents with $(Bu_3Sn)_2O$ (1.5 molar equiv.) and powdered 3 Å molecular sieves (4 g/100 mL). A mixture of 3,6-di- and 3,4,6-tri-*O*-tributylstannyl ethers is thus expected. For a ^{119}Sn and ^{13}C NMR study of stannylated polyhydroxyl compounds, see Ref. 2 and 5.
7. Tributylstannyl ethers undergo oxidation to carbonyl compounds with Br_2; a) Saigo, K.; Morikawa, A.; Mukayama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1656-1658; or NBS; b) Ogawa, T.; Matsui, M. *J. Am. Chem. Soc.* **1976**, *98*, 1629-1630.
8. Enone 2 has already been prepared by regioselective oxidation of 1 with Fetizon's reagent; a) Tronchet, J.M.J.; Tronchet, J.; Birkhauser, A. *Helv. Chimica Acta* **1970**, *53*, 1489-1490; or with pyridinium dichromate; b) Czernecki, S.; Vijayakumaran, K.; Ville, G. *J. Org. Chem.* **1986**, *51*, 5472-5475.
9. NIS (1.2 equiv.) was added to a freshly prepared solution of *O*-stannylated D-glucal in benzene at 5°C under argon. The temperature was raised to 20°C and the reaction monitored by TLC (1:1, toluene-acetone). Complete disappearance of **1** (R_F 0.14) was only achieved when propylene oxide (10% v/v) was present as a scavenger of HI. Compound **2** (R_F 0.31) was separated from traces of **3** (R_F 0.45) by *O*-acetylation, then flash chromatography. Compound **2a** was identical (TLC, IR, ^1H-NMR) to a sample prepared according to Ref. 8b.
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12. Reaction of NIS (1.2 equiv.) with *O*-stannylated D-glucal in acetonitrile was conducted as in Ref. 9. Compound **3a** was isolated as a crystalline material, m.p. 95°C (lit.[13], 95°C).

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18. Br_2 (1.5 equiv.) in $CHCl_3$ was added dropwise at room temperature under argon to freshly prepared *O*-stannylated D-glucal in $CHCl_3$ in the presence of powdered 3 Å molecular sieves. After usual workup and acetylation, a 9:1 mixture of **3c** and **4a** was isolated. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 5.62 (s, 0.9 H, H-1 Glc), 5.53 (bd, 0.1 H, H-1 Man), 5.25 (m, 0.1 H, H-3 Man), 5.11 (m, 0.9 H, H-3 Glc), 4.80 (m, 0.1 H, H-4 Man), 4.70 (bds, 0.9 H, H-4 Glc), 4.66 (m, 1 H, H-5 Glc and Man), 4.26 (dd, 0.1 H, $J_{6,6'}$ 8.5 Hz, H-6 endo Man), 4.19 (m, 1 H, $J_{6,6'}$ 7.7 Hz, H-6 endo Glc and H-2 Man), 3.84 (m, 1 H, $J_{5,6'}$ 5.7 Hz, H-6 exo Glc and Man), 3.79 (bds, 0.9 H, H-2 Glc), 2.19 and 2.13 (2 s, 5.4 H, 2 OAc Glc), 2.17 and 2.16 (2 s, 0.6 H, 2 OAc Man),. Compound **4a** is known; Bock, K.; Lundt, I. Pedersen, C.; Pedersen, H. *Acta Chem. Scand., Ser. B* **1988,** *42,* 640-645.
19. Compound **3** was easily separated from the *manno* isomer by crystallization from ethanol-hexane, m.p. 101-103°, $[\alpha]_D^{20}$ +10° (*c* 1, MeOH); ^{1}H-NMR (250 MHz, DMSO d_6): δ 5.61 (s, 1 H, H-1), 5.52 and 5.20 (2 d, 2 H, *J* 4 Hz, 2 OH), 4.42 (m, 1 H, H-5), 4.01 (d, 1 H, $J_{6,6'}$ 6.9 Hz, H-6 endo), 3.94 and 3.83 (2 m, 2 H, H-3,4), 3.52 (dd, 1 H, $J_{5,6'}$ 6.4 Hz, H-6 exo), 3.45 (m, 1 H, H-2).
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22. We found that stannylation of 4-*O*-benzyl-D-glucal in acetonitrile, followed by reaction with I_2, only gave the 1,6-anhydro-*gluco* compound in good yield, whereas extensive *O*-stannylation (2 molar equiv. of tin oxide, 24 h reflux) of D-glucal, followed by reaction with I_2, increased the proportion of the *manno*-compound
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