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Radical Oxygenation of 2-Deoxy-2-Iodo Hexopyranosides with Molecular Oxygen

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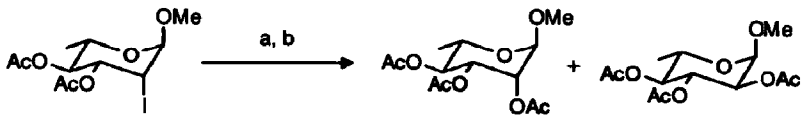
Abstract: 2-Deoxy-2-iodo hexopyranosides react with molecular oxygen and tributylstannane to give the epimeric C-2 alcohols in high yield and moderate selectivity.

In recent years, the application of highly efficient radical chain reactions has been a major development of organic synthesis, allowing group interconversion and carbon-carbon bond formation.[1,2] Despite its biradical nature and high affinity for carbon centered radicals,[3] molecular oxygen has been scarcely used for radical mediated oxygenation in synthetic organic chemistry. Notable exceptions are the autoxidation of organoboranes[4], the reduction of organomercurials in presence of oxygen[5], the synthesis of *nor*-alcohols from thiohydroxamic esters[6] and the cobalt-mediated oxygenation of olefins.[7] Direct radical transformation of a carbon-halogen bond to a carbon-oxygen bond is possible with 2,2,6,6-tetramethylpiperidinyloxy radical, (TEMPO),[8] or molecular oxygen.[9] These methods of radical substitution could complement the more classical nucleophilic substitution of halogens,[10] provided that some stereocontrol of the reaction could be achieved. We report that radical oxygenation of 2-deoxy-2-iodo hexopyranosides to the C-2 alcohols proceeds in high yield and with moderate selectivity.

The starting materials were obtained from the corresponding protected glycals (L-rhamnal,[11] D-glucal and D-galactal[12]), by N-iodosuccinimide promoted iodo glycosylation with the appropriate alcohol in acetonitrile.[13,14] When methyl-3,4-diacetyl-2,6-dideoxy-2-iodo-α-L-*manno*-hexopyranoside **1a** in toluene was treated at 60°C with tributylstannane (3 equivalents) and AIBN (1 equivalent) under aerobic conditions (dry air bubbled through the solution), it was smoothly transformed within 3 hours into a 2/1 mixture of the L-*manno* and L-*gluco* alcohols, characterized as their triacetates **1b** and **1c**, in 82% isolated yield. (Scheme 1).

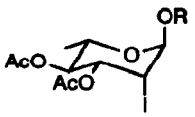
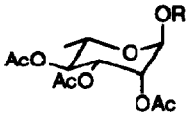
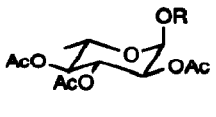
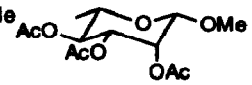
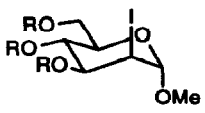
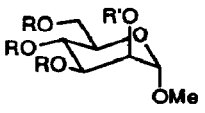
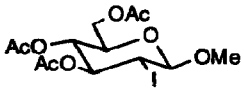
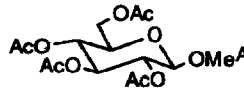
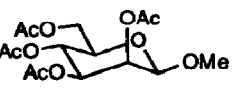
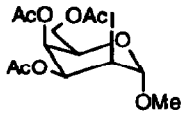
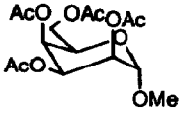
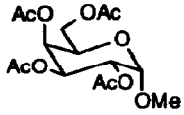
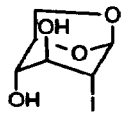
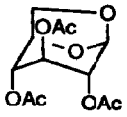
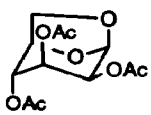


1a **1b** **1c**

a: Bu_3SnH, AIBN, air, toluene, 60°C, 3hrs; b: Ac_2O, pyridine.

Scheme 1

Table 1

Entry	Substrate	Products		Yield[a]	Selectivity[b]
					
1	**1a** R = Me	**1b**	**1c**	82%	2/1
2	**2a** R = tBu	**2b**	**2c**	78%	2/1
					
3	**3a**	**3b**	**3c**	88%	4/1
					
4	**4a** R = Ac, R' = Ac	**4b**	**4c**	76%	1.5/1
5	**5a** R = Bn, R' = H	**5b**	**5c**	58%	1.5/1
6	**6a** R = TBS, R' = H	**6b**	**6c**	84%	4/1
					
7	**7a**	**7b**	**7c**	78%	4/1
					
8	**8a**	**8b**	**8c**	76%	1.3/1
					
9	**9a**	**9b**	**9c**	63%	20/1

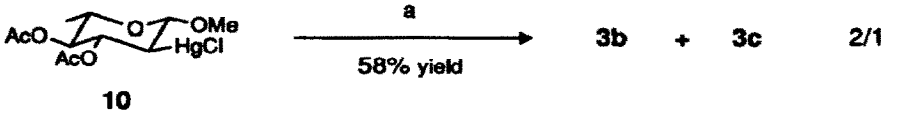
a: Yields are for isolated products after acetylation except for entries 5 and 6.

b: Selectivity was determined by ^{1}H-NMR on the mixture of isomers.

The reaction is general and tolerates the classical protecting groups used in carbohydrate chemistry. It can be run on the deprotected sugar as well (entry 9), the only limitation seemed to be the solubility of polyhydroxylated compounds in toluene. The main by-product is the 2-deoxy glycoside,[15] and its formation could be easily minimized by slow addition of the tin hydride to the reaction mixture. In the case of acetylated substrates, acetate migration was sometimes observed[16] and the mixture of alcohols was acetylated before purification and analysis. Selectivity was determined by ^1H NMR in $CDCl_3$ on the purified mixture of the alcohols or the peracetylated products.[17] Our results are summarized in Table 1.

In every case, the major diastereoisomer is the 1,2 *trans* product, obtained with low to moderate selectivity. 2-Deoxy pyranosyl radicals have been shown to exist in the $^4C_1$(D) conformation[18] and give predominantly equatorial products when they add to carbon-carbon double bonds.[19] On the other hand, Bu_3SnH gave preferential axial hydride transfer on these radicals.[20] These results have been interpreted by a combination of steric and torsional effects.[21] Molecular oxygen is less sensitive to steric effects than the more bulky reagent Bu_3SnH. Oxygenation of the *tert*-butylglycoside **2a** gave the same ratio of *manno* to *gluco* isomers as the methyl analog **1a**, while with Bu_3SnD quench, the ratio of axial to equatorial products rose from 4/1 with **1a** to 20/1 with **2a**.[20] The influence of the C-4 configuration of the sugar is also very small. (compare entries 4 and 8). Surprisingly, quenching of the radical derived from **5a** with TEMPO (TEMPO, $(Bu_3Sn)_2$, hv, benzene, 40°C)[8b] gave a 2/1 ratio of D-*manno* **5b** to D-*gluco* **5c** products after hydroxylamine reduction, which is very close to that achieved with molecular oxygen despite the different bulkiness of the quenching agent (entry 5). The very high selectivity observed for compound **9a** is related to the rigid nature of the 1,6-anhydro glucopyranose framework and efficient shielding of the β face of the intermediate radical. Conformational effects are important: introduction of three *tert*-butyldimethylsilyl ether groups on the 2-deoxy-2-iodo-α -D-*manno*-pyranoside **6a** resulted in a distorsion of the $^4C_1$(D) conformation of the ring and had a pronounced effect on the selectivity with an increase of the D-*manno* product **6b**.

For the purpose of comparison, we carried out two experiments: first, oxygenation of **1a** under Nakamura's conditions,[9] (Bu_3SnH, room temp.) afforded a very low yield of alcohols (10%) but with the same 2/1 *manno/gluco* ratio. The reaction did not proceed to completion even after one day and we obtained the 2-deoxy-glycoside as the major product. Second, the chloromercuric compound **10**[22] was reduced with sodium borohydride in DMF under oxygen[5] and gave the expected products **3b** and **3c**, in 58% yield after acetylation (Scheme 2).



10

a: $NaBH_4$, O_2, DMF, room temperature, then Ac_2O, pyridine.

Scheme 2

However, the ratio **3b/3c** was only 2/1, compared to 4/1 with our system (entry 3). **3a** and **10** should give the same intermediate radical which then should react with oxygen to yield the products. Whether this difference is related to the reaction conditions (solvent and temperature) or to a subtle change in the structure of the intermediate is not known at the moment.[23]

In conclusion, molecular oxygen is very efficient for the radical substitution of iodine in carbohydrate

derivatives. Yields are high and the selectivity is moderate. Application of this oxygenation procedure to more complex cases and experiments aimed to clarify the factors influencing the selectivity are currently under way.

References and notes

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16. 1,2-Acyl migration in pyranosyl radicals had been described.[25] Analysis of the reaction products of the oxygenation of **1a** before acetylation showed a complex mixture of alcohols. Acetylation of this mixture gave **1b** and **1c** as the only isolated products in high yield. This result and the considerable rate difference reported for the oxygen quench[3] and the 1,2-migration[25b] favor acetate migration on hydroxyl compounds.
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