Radical Substitution of 2-Deoxy-2-Iodo Pyranosides using 2,2,6,6-Tetramethylpiperidinoxy (TEMPO) Free Radical

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Methyl 2-hydroxy-α-D-pyranosides were formed *via* photolytic radical substitution of methyl 2-deoxy-2-iodo-α-D-pyranosides with 2,2,6,6-tetramethylpiperidinoxy (TEMPO) free radical followed by zinc reduction.

Recently, during a synthesis of sucrose, we encountered difficulties effecting the S_N2 substitution of iodide **1** by oxygen-centred nucleophiles.[1] However, radical-mediated substitution (Scheme 1)[2] under photolytic conditions with TEMPO free radical **4** provided hydroxylamine **2**. Global deprotection *via* dissolving metal reduction gave sucrose which was isolated as the octacetate **3**. We speculated that this method would also be applicable to iodoethers derived from glycals. Glycals are useful intermediates for the elaboration of glycosides, *via* epoxidation or iodoetherification *etc.*,[3] and this methodology has recently been applied by Friesen and Danishefsky[3] in oligosaccharide assembly. Herein, we report a method for the radical substitution of 2-deoxy-2-iodo-α-D-pyranosides with TEMPO to provide glycosides.

Methyl 2-deoxy-2-iodo-α-D-pyranosides (**5**,[4] **7** and **9**) were synthesised from 3,4,6-tri-*O*-benzyl-D-glucal,[5] -allal,[6] and -galactal[7] respectively *via* oxidative coupling with methanol {MeOH, [Ag(*sym*-collidine)$_2$]ClO_4, I_2, 4 Å molecules sieves, CH_2Cl_2, 0 °C}.[3] Subsequent photolysis [>200 nm, $(Bu_3Sn)_2$, 40 °C] in the presence of TEMPO (2.5 equiv.) afforded the hydroxylamine derivatives **6**, **8** and **10** (Scheme 2).† Despite proceeding through a radical manifold, moderate diastereoselectivity was observed for each substrate. For example, the mannopyranoside **5** yielded a mixture of diastereoisomers‡ favouring the mannopyranoside **6a** over the glucopyranoside **6b** (2.0:1). This modest selectivity is consistent with approach of the bulky TEMPO reagent from the less sterically congested face[8] of the radical intermediate. Radical substitution of the altropyranoside **7** favoured the corresponding altropyranoside **8a** over the allopyranoside **8b** (4.5:1). In contrast, photolysis of iodide **9** in the presence of TEMPO (**4**) and hexabutyldistannane gave rise predominately to the *cis*-glycoside (**10a**:**10b** = 2.2:1). Again both these selectivities are consistent with steric approach control. Unfortunately, efforts to increase the diastereoselectivities of these radical substitution reactions by lowering the temperature served only to slow the process. Dissolving metal reduction (activated Zn dust, 10% HOAc–EtOH–EtOAc 3:1:1, sonication) of **6a**, **8a** and **10a** resulted in cleavage of the hydroxylamine nitrogen–oxygen bond affording the hydroxy pyranosides **11**[9] (81%), **12** (78%) and **13**[10] (93%) respectively.†§

In conclusion a mild method for stereoselective radical substitution of iodine with oxygen functionality has been demonstrated on several 2-deoxy-2-iodo pyranosides. The diastereoselectivity of reaction is consistent with steric approach control of the TEMPO free radical. Recently, Nakamura *et al.*[11] have described an alternative method for the radical substitution of alkyl iodides using tributylstannane and oxygen.

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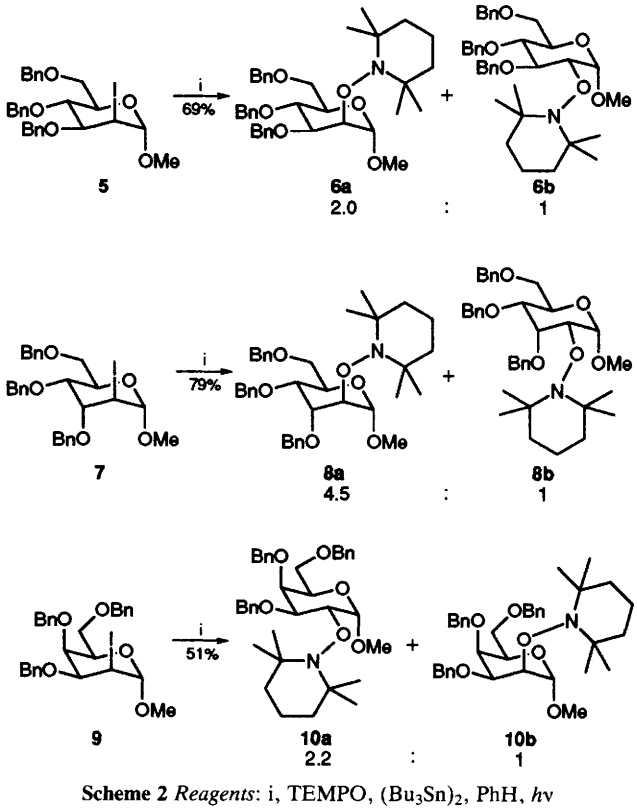
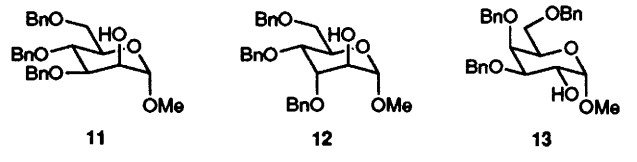
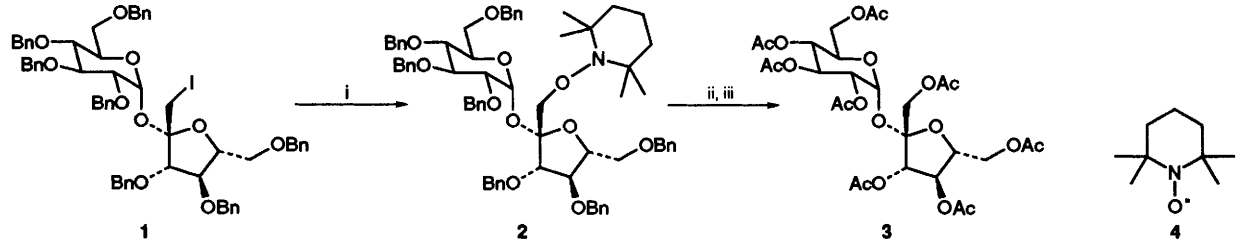


Scheme 2 *Reagents*: i, TEMPO, $(Bu_3Sn)_2$, PhH, *hv*





Scheme 1 *Reagents*: 4, Bu_3SnH, PhH, *hv*; ii, Na, NH_3, THF; iii, Ac_2O, pyridine, bn = benzyl

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Footnotes

† Pyranosides **6a**, **7**, **8a**, **9**, **10a** and **12** were fully characterised by spectroscopic data and microanalyses. The minor diastereoisomers **6b** and **10b** were characterised by ^{1}H NMR, ^{13}C NMR and MS only. The minor diastereoisomer **8b** could not be completely purified and its structural assignment is tentative.

‡ The preparation of hydroxylamines (**6a/6b**) is representative: iodide **5** (51.6 mg, 90.0 μmol) was dissolved in benzene (1.5 ml) in a quartz reaction vessel. TEMPO **4** (37.4 mg, 0.239 mmol) and $(Bu_3Sn)_2$ (67 μl, 0.175 mmol) were added and the mixture was irradiated (>200 nm) for 2 h at 40 °C with a 450 W mercury immersion lamp equipped with a quartz cooling jacket. EtOAc (5 ml) was added and the solution washed with 10% aqueous KF (2 × 10 ml). The aqueous layers were combined and extracted with EtOAc (3 × 10 ml), and the extracts dried (Na_2SO_4), evaporated, and chromatographed on silica (eluant hexanes–Et_2O 3:1) to yield **6a** (25 mg, 46%) and **6b** (12.6 mg, 23%) both as oils.

§ The preparation of pyranoside **11** is representative: to a solution of **6a** (42.6 mg, 71.0 μmol) in 10% aqueous AcOH–EtOH–EtOAc (7 ml, 3:1:1) was added activated zinc dust (220 mg, 3.36 mmol). The mixture was sonicated for 14 h, extracted with EtOAc (3 × 5 ml), dried Na_2SO_4) and evaporated. Chromatography on silica (eluant hexanes–EtOAc 7:3) yielded **11** (27 mg, 81%) as a clear oil.

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