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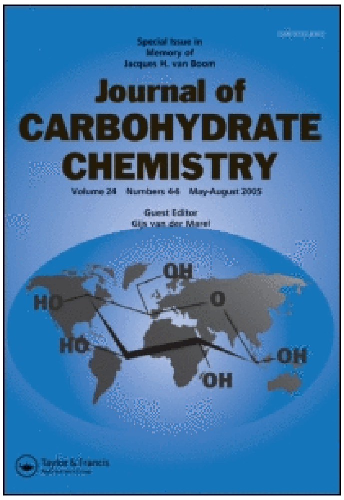

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COMMUNICATION

THE REDUCTIVE COUPLING OF CARBOHYDRATE RADICALS WITH DIAZONIUM IONS: A NEW ACCESS TO 2-AMINO-2-DEOXY GLYCOSIDES

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The oxidative coupling of glycals with alcohols is an efficient procedure for creating an α-glycosidic bond. It can be triggered by an "I^+"-reagent (iodonium di-*sym*-collidine perchlorate[1] or *N*-iodosuccinimide[2]) and occurs in a 1,2-diaxial fashion through a presumed 1,2-iodonium ion intermediate leading to 2-deoxy-2-iodo-α-glycosides. This iodoglycosylation allows the preparation of 2-deoxy-α-glycosides by reductive deiodination with tributylstannane[3] or nickel boride.[4] Considering the behavior of good leaving groups at C-2 of α-D-mannopyranosides,[5] the displacement of iodine by oxygen or nitrogen functions through S_N2-type reactions would be difficult or impossible, unless performed with internal nucleophiles.[6] In contrast, a C-2 radical can be easily trapped by electron-deficient olefins[7] or nitrogen monoxide[8] giving access to C-2 branched carbohydrates and oximes, respectively. Nucleophilic radicals have also been trapped by aryldiazonium ions in a reversible manner to give azo radical cations.[9] In the presence of a reducing agent (Ti^{3+}, Fe^{2+}, Cr^{2+}, V^{2+}), the equilibrium is shifted towards the azo compound:

$$R^{\bullet} + N{\equiv}\overset{+}{N}\text{-Ar} \rightleftharpoons R\text{-}\overset{+\bullet}{N}{=}N\text{-Ar} \xrightarrow{e^-} R\text{-}N{=}N\text{-Ar}$$

Carbohydrate radicals are nucleophilic and we report here their coupling with aryldiazonium ions in the presence of tributyltin species. It is already known that aryldiazonium tetrafluoroborates in acetonitrile solution are reduced by tin hydrides to the corresponding arenes.[10] Aryl radicals are generated by electron transfers[11] from Bu_3SnH and $Bu_3Sn^\bullet$ to the diazonium ion through a transient diazenyl radical $ArN_2^\bullet$:

$$(1)\ ArN_2^+ + Bu_3SnH \longrightarrow Ar^\bullet + N_2 + H^+ + Bu_3Sn^\bullet$$

$$(2)\ ArN_2^+ + Bu_3Sn^\bullet \longrightarrow Ar^\bullet + N_2 + Bu_3Sn^+$$

$$(3)\ Bu_3Sn^+ + BF_4^- \longrightarrow Bu_3SnF + BF_3$$

Reaction (1) occurs spontaneously at 0 °C and can be considered as the initiation step of a free-radical chain process.[12] If an alkyl iodide is present in the reaction mixture, alkyl radicals will be generated either by:

$$(4)\ RI + Bu_3Sn^\bullet \longrightarrow R^\bullet + Bu_3SnI\ (k = 4.3 \times 10^9\ M^{-1}s^{-1}, \text{for } R = CH_3)^{13}$$

or by selective iodine transfer to the aryl radical.

$$(5)\ RI + Ar^\bullet \longrightarrow R^\bullet + ArI\ (k > 10^9\ M^{-1}s^{-1})^9$$

With an excess of diazonium salt, the azo-coupling reaction occurs as follows:

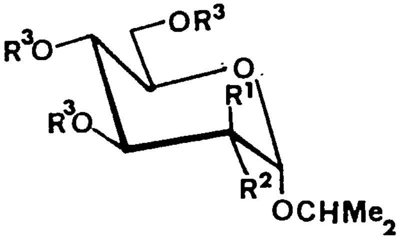
$$(6)\ R^\bullet + ArN_2^+ \longrightarrow R\text{-}N\overset{+\bullet}{=}N\text{-}Ar$$

And the azo radical cation is reduced by Bu_3SnH:

$$(7)\ R\text{-}N\overset{+\bullet}{=}N\text{-}Ar + Bu_3SnH \longrightarrow R\text{-}N{=}N\text{-}Ar + H^+ + Bu_3Sn^\bullet$$

Reduction of the alkyl radical by Bu_3SnH (or by acetonitrile to give $^\bullet CH_2CN$) may become significant if the concentration of the diazonium ions is not high enough.

$$(8)\ R^\bullet + Bu_3SnH \longrightarrow RH + Bu_3Sn^\bullet$$



1 $R^1 = I, R^2 = R^3 = H$ **4** $R^1 = R^2 = R^3 = H$

2 $R^1 = R^3 = H, R^2 = N{:}NC_6H_4Cl(p) \xrightarrow{i,\ ii}$ **5** $R^1 = H, R^2 = NHAc, R^3 = Ac$

3 $R^1 = N{:}NC_6H_4Cl(p), R^2 = R^3 = H \xrightarrow{i,\ ii}$ **6** $R^1 = NHAc, R^2 = H, R^3 = Ac$

i, H_2-Pd/C; *ii*, Ac_2O-py

Isopropyl 2-deoxy-2-iodo-α-D-mannopyranoside (**1**)[14] was treated with *p*-chlorophenyldiazonium tetrafluoroborate[15] (3 equiv) and Bu_3SnH (3-4 equiv) in deaerated acetonitrile at 0 °C under argon. After neutralization, isopropyl 2-deoxy-2-*p*-chlorophenylazo-α-D-*gluco* (**2**, 25%) and -*manno* (**3**, 12%) pyranosides were isolated by column chromatography.[16] Large amounts of isopropyl 2-deoxy-α-D-*arabino*-hexopyranoside (**4**)[17] (30-50%) were also isolated.

In order to minimize hydrogen abstraction by the C-2 radical, other trialkyltin species were investigated. $Bu_3SnSnBu_3$ is known to operate as a two-electron donor with good electron acceptors.[18] Initiation of the reaction requires heating and compounds **2** and **3**, although formed in small amounts at room temperature, were not stable under the refluxing conditions.

So far, the highest yields in the azo-coupling reaction were obtained with tri-butylstannyl(pyridine)cobaloxime, a crystalline derivative of bis(dimethylglyoximato) cobalt (III) with a covalent Sn-Co bond, soluble in most organic solvents and air-sensitive.[19] This complex was found to reduce spontaneously diazonium salts in acetonitrile at 0 °C according to an electron-transfer step:

$$(9)\ Bu_3SnCo^{III}(dmgH)_2py + ArN_2^+ BF_4^- \longrightarrow Bu_3SnCo^{IV}(dmgH)_2py^+ BF_4^- + Ar^{\bullet} + N_2$$

followed by fragmentation of a cobalt (IV) species:

$$(10)\ Bu_3SnCo^{IV}(dmgH)_2py^+BF_4^- \longrightarrow Bu_3Sn^{\bullet} + Co^{III}(dmgH)_2py^+BF_4^-$$

a mechanism which is consistent with the oxidation of alkyl cobalt (III) complexes at $\simeq$0.4V anodic potentials.[20]

A 60% yield of azo compounds (**2**:**3** $\simeq$2:1) was obtained[21] together with small amounts of **4** generated by hydrogen abstraction from acetonitrile. BF_3 is known[22] to react readily with the two OH...O groups of cobaloximes to afford stable $O\text{-}BF_2\text{-}O$ bridges and HF, and the labile pyridine ligand may also help in neutralizing the acidity of the reaction mixture (observed pH $\simeq$ 4-5).

Hydrogen bonding between OH-3 and the nitrogen atom β to the pyranose ring[23] in compounds **2** and **3** may contribute to the success of the reaction, since the tri-*O*-acetyl derivative of **1** gave intractable mixtures.

Hydrogenation of **2** and **3** (Pd/C, room temperature, atmospheric pressure) in ethanol readily gave the 2-amino-2-deoxy-glycosides which were characterized as their *N,O*-acetylated derivatives **5** and **6**.[24] The rate of hydrogenolytic cleavage of the N=N bond was certainly increased by the presence of the HCl liberated during fast hydrogenolysis of the C-Cl bond, since hydrogenation of phenylazo compounds usually requires more drastic conditions.[23,25]

Thus the azo-coupling reaction appears as a valuable way to convert the products of iodoglycosylation reactions into biologically important aminoglycosides, and more generally, to transfer nitrogen to nucleophilic radicals.

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14. Compound 1 was prepared by reaction of triacetyl-D-glucal with isopropanol and *N*-iodosuccinimide in acetonitrile, followed by deacetylation; syrup, $[\alpha]_D^{20} + 61°$ (*c* 1.57, methanol); ^{1}H NMR (D_2O): δ 5.36 (d, 1 H, $J_{1,2} < 1$ Hz, H-1); 4.43 (dd, 1 H, $J_{2,3} = 4.2$ Hz, H-2); 3.98 (m, 1 H, C*H*Me$_2$); 3.86-3.65 (m, 4 H); 3.19 (dd, 1 H, $J_{3,4} = 8.4$ Hz, H-3); 1.18 and 1.14 (2 d, each 3 H, $J = 6.2$ Hz, CMe_2).
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16. **2**, Yellow, R_F 0.27 (1:1, toluene-acetone), ^{1}H NMR (CD_3OD): δ 7.79-7.73 and 7.58-7.49 (2 m, each 2 H, 4 H arom.); 5.04 (d, 1 H, $J_{1,2}$ = 4 Hz, H-1); 4.73 (dd, 1 H, $J_{2,3}$ = 10, $J_{3,4}$ = 9 Hz, H-3); 4.02-3.77 (m, 4 H); 3.73 (dd, 1 H, H-2); 3.53 (dd, 1 H, $J_{4,5}$ = 9.7 Hz, H-4); 1.27 and 1.01 (2 d, each 3 H, J = 6 Hz, CMe_2); mass spectrum: m/z 345 (M + 1), 285 (M-$OCHMe_2$).

    3, Yellow, R_F 0.39 (1:1, toluene-acetone), after exposure to daylight gives a 4:1 mixture of two isomeric forms (possibly E and Z azo isomers); ^{1}H NMR (CD_3OD): δ 7.80-7.74 and 7.57-7.47 (2 m, each 2 H, 4 H arom.); 4.89 (d, 0.8 H, $J_{1,2}$ = 1.7 Hz, H-1); 4.75 (d, 0.2 H, $J_{1,2}$ = 1.4 Hz, H-1); 1.31 and 1.20 (2 d, 4.8 H, J = 6 Hz, CMe_2); 1.22 and 1.05 (2 d, 1.2 H, J = 6 Hz, CMe_2); mass spectrum: m/z 345 (M + 1), 285 (M - $OCHMe_2$) .

17. **4**, mp 100 °C (ethyl acetate); lit.[26]: mp 103-104 °C, ^{1}H NMR (CD_3OD): δ 5.06 (dd, 1 H, $J_{1,2ax}$ = 3.6, $J_{1,2eq}$ = 1.2 Hz, H-1); 3.96 (m, 1 H, C*H*Me_2); 3.87 (ddd, 1 H, $J_{2ax,3}$ = 12, $J_{2eq,3}$ = 5, $J_{3,4}$ = 9 Hz, H-3); 3.62 (m, 1 H, H-5); 3.26 (dd, 1 H, $J_{4,5}$ = 9 Hz, H-4); 2.01 (ddd, 1 H, $J_{2ax,2eq}$ = 13 Hz, H-2eq); 1.64 (ddd, 1 H, H-2ax); 1.23 and 1.17 (2 d, each 3 H, J = 6 Hz, CMe_2).

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21. *Typical experimental procedure:* Solid $Bu_3SnCo(dmgH)_2py$ (2 mmol) was added portionwise to a solution of **1** (1 mmol) and *p*-chlorophenyldiazonium tetrafluoroborate (3 mmol) in dry deaerated acetonitrile (30 mL) at 0 °C under argon. After disappearance of **1**, as checked by TLC (1:1, toluene-acetone), the mixture was concentrated, the residue extracted with ethyl acetate, and the extract filtered over silica gel to remove tin and cobalt by-products. The eluate was then chromatographed on silica gel (17:3, ethyl acetate-hexane).

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24. Isopropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside (**5**), mp 90 °C (ether-hexane); lit.[27] mp 94 °C; ^{1}H NMR ($CDCl_3$): δ 5.56 (d, 1 H, J = 9.5 Hz, N*H*); 5.14 (dd, 1 H, $J_{2,3}$ = 10, $J_{3,4}$ = 9.5 Hz, H-3); 5.04 (dd, 1 H, $J_{4,5}$ = 9.5 Hz, H-4); 4.86 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1); 4.25 (ddd, 1 H, H-2); 4.16 (dd, 1 H, $J_{5,6a}$ = 4.5, $J_{6a,6b}$ = 12.1 Hz, H-6a); 4.02 (dd, 1 H, $J_{5,6b}$ = 2.4 Hz, H-6b); 3.96 (m, 1 H, H-5); 3.83 (m, 1 H, C*H*Me_2); 2.02, 1.97, 1.96 and 1.88 (4 s, each 3 H, 4 Ac); 1.18 and 1.09 (2 d, each 3 H, CMe_2); mass spectrum: m/z 407 (M + 18), 390 (M + 1), 330 (M - $OCHMe_2$) .

    Isopropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*manno*-pyranoside (**6**), ^{1}H NMR ($CDCl_3$): δ 5.65 (d, 1 H, J = 9.4 Hz, N*H*); 5.32 (dd, 1

H, $J_{2,3}$ = 4.5, $J_{3,4}$ 10.2 Hz, H-3); 5.04 (dd, 1 H, $J_{4,5}$ = 10 Hz, H-4); 4.88 (d, 1 H, $J_{1,2}$ = 1.5 Hz, H-1); 4.52 (ddd, 1 H, H-2); 4.24 (m, 1 H, H-6a); 4.08-4.01 (m, 2 H, H-5,6b); 3.85 (m, 1 H, C*H*Me_2); 2.08, 2.03 and 1.96 (12 H, 4 Ac); 1.21 and 1.15 (2 d, each 3 H, CMe_2); mass spectrum: m/z 407 (M + 18), 390 (M + 1), 330 (M - $OCHMe_2$).

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