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Intramolecular carbene and nitrene insertions at C-2 of diacetone-D-glucose

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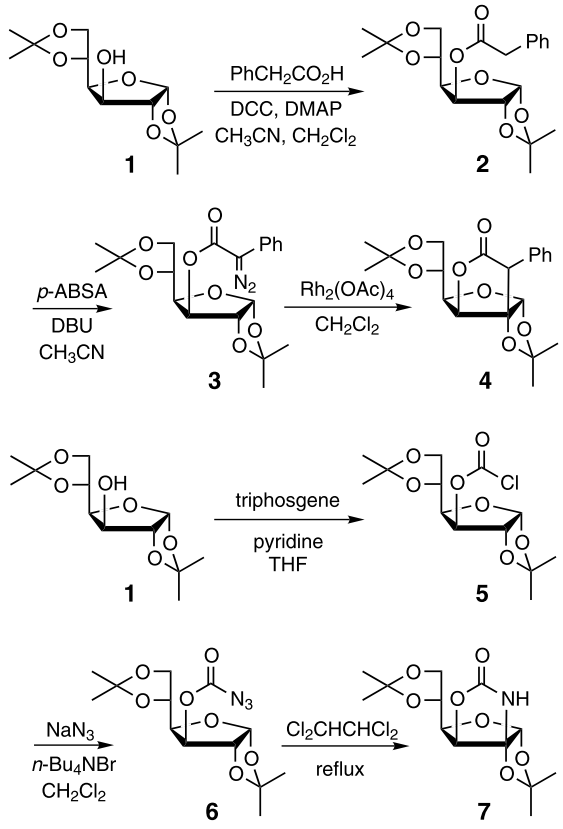
Abstract—Decomposition of a diazoester and an azidoformate attached at O-3 of 1,2;5,6-di-*O*-isopropylidene-D-glucofuranose ('diacetone-D-glucose') leads to intramolecular insertion into the C-2–H bond as the major process in both cases.

The functionalization of carbohydrates by the direct insertion of carbenes (or carbenoids) to produce branched sugars, and nitrene species to produce aminosugars, has received little attention considering the potential for such chemistry to provide rapid access to products that might otherwise be difficult to prepare.[1] Despite recent progress in metal-catalyzed diazo decomposition chemistry,[2] the use of carbenic methods for branched-chain sugar synthesis has been limited to the cyclopropanation of various glycals.[3] Similarly, insertion of nitrenes into glycals produces aziridines, which are subsequently opened by alcohols to provide an interesting glycosylation strategy.[4] Nitrene insertion into C–H bonds on sugars has produced enantiomerically pure 1,3-oxazin-2-ones that have then been employed as auxiliaries in asymmetric synthesis;[5] however, intramolecular nitrene insertions as applied to aminosugar synthesis have been rare.[6]

Our interest lies in developing both carbenic and nitrenic insertions on simple carbohydrates as a potential method for producing branched-chain sugars and aminosugars, respectively, and herein we disclose results using diazoester and azidoformate derivatives of readily available diacetone-D-glucose (**1**). The fairly rigid furanose structure of **1** was expected to limit the possible reaction pathways open to a carbene or nitrene species attached at O-3, with insertion into either the C-1–H or C-2–H bonds being the most likely events. The former pathway would provide a novel route to ketose derivatives, whereas the latter process would afford C-2 branched-chain analogues of D-glucose.

Thus, conversion of **1** to phenacyl ester **2** (Scheme 1) was effected in 90% yield using conventional DCC–DMAP coupling conditions and conversion of **2** to the diazoester **3** was accomplished using *p*-acetamidoben-



Scheme 1.

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zenesulfonyl azide (*p*-ABSA) and DBU to furnish **3** as a yellow syrup in 93% yield after flash column chromatography. Decomposition of the diazoester using $Rh_2(OAc)_4$ as catalyst was then studied with the cleanest reaction mixtures resulting from slow addition of a CH_2Cl_2 solution of **3** to a suspension of the catalyst in CH_2Cl_2. After resolution of the reaction mixture by MPLC, the major product proved to be compound **4**,[7] the result of insertion of an intermediate carbenoid into the C-2–H bond. Branched-chain sugar **4**, isolated in 47% yield as a colorless syrup, was identified primarily from its mass and NMR spectra; however, the configuration of the new stereogenic carbon α- to the ester is as yet unknown.

In addition to the appearance of M^+ ($+H_2O$) in the mass spectrum, the ^1H NMR spectrum if **4** revealed a 1H singlet at 5.83 ppm that was assigned to H-1 of the furanose ring. In the precursors **1**–**3** the signal for H-1 appears as a doublet between 5.80 and 5.92 ppm, with J_{H1-H2} typically 3.7 Hz, indicating a coupling with H-2.[8] Additionally the ^{13}C NMR spectrum of **4** shows signals for three acetal carbons, two of which have no protons attached with the carbon at 110.9 ppm (C-1) having one H attached as seen from an APT experiment. The observation that the major insertion process occurred to form a five-membered ring rather than to form a six-membered ring mirrors the studies of Adams and co-workers who showed a similar preference in non-carbohydrate systems[9] and used C–H insertion chemistry as the key step in the synthesis of several natural products.[10] It is of interest here to note that insertion into the C-1–H bond at the anomeric carbon, which is activated by two oxygen atoms, is not the major process and that five-membered ring formation is favored.

To study the insertion preferences of a nitrene attached at O-3 of diacetone-D-glucose, **1** was treated with triphosgene to afford the chloroformate **5** in 79% yield (Scheme 1), which was then reacted with NaN_3 to provide the azidoformate **6**, isolated as a colorless syrup in 78% yield. Decomposition of **6** in refluxing 1,1,2,2-tetrachloroethane gave a major product in 44% yield that was identified as **7**,[11] the result of nitrene insertion into the C-2–H bond of the furanose ring. In 2addition to the mass spectrum of **7** ($M^+ + H^+ = 302.16$), the ^1H spectrum of this material showed a 1H singlet at 5.63 ppm corresponding to H-1 of the furanose ring, as well as a broad N–H signal at 7.73 ppm. The ^{13}C spectrum of **7** showed four signals between 101–112 ppm (C-1, C-2 and $2\times CMe_2$) of which three had no hydrogens attached and one (C-1) with one H attached as seen from an APT experiment.

In conclusion, decomposition of a diazoester and an azido-formate linked at O-3 of diacetone-D-glucose both result in the insertion of the thus generated intermediate into the C-2–H bond of the furanose ring. We are presently expanding the scope of these reactions to other carbohydrates.

Acknowledgements

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7. Characterization data for compound **4** (syrup): $[\alpha]_D^{20}$ −80.5° (*c* 3.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 3.99 (s, 1H), 4.07 (dd, 1H, J=4.4, 8.8 Hz), 4.17 (dd, 1H, J=6.0, 8.7 Hz), 4.28 (dd, 1H, J=2.7, 8.4 Hz), 4.42 (ddd, 1H, J=4.6, 6.0, 10.1 Hz), 4.91 (d, 1H, J=2.7 Hz), 5.83 (s, 1H); 7.21–7.62 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 26.7, 27.0, 27.7, 52.9, 67.1, 72.4, 81.1, 85.1, 109.7, 110.9, 113.3, 128.1, 128.6 (double intensity), 128.9 (double intensity), 129.9, 132.2, 173.2; MS (EI pos) calcd for $C_{20}H_{24}O_7$ ($M+H^+ + H_2O$) 393.15, found 393.16.
8. Due to their essentially orthogonal relationship, the signal for H-3 in compound **4** at 4.91 ppm would likely not be affected by the loss of H-2 if carbene insertion had indeed occurred at that position.
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11. Characterization data for compound **7** (syrup): $[\alpha]_D^{20}$ −16.0° (*c* 2.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.45 (s, 6H), 1.52 (s, 3H), 4.02 (dd, 1H, J=4.2, 8.8 Hz), 4.13 (dd, 1H, J=5.5, 8.6 Hz), 4.31 (m, 1H), 4.36 (d, 1H, J=3.3 Hz), 4.75 (d, 1H, J=3.5 Hz), 5.63 (s, 1H), 7.73 (s, 1H, N-H); ^{13}C NMR (100 MHz) δ 25.1, 26.9, 27.0, 27.1, 66.7, 72.0, 81.1, 84.7, 101.6, 106.9, 109.7, 112.3, 156.9; MS (APCI pos) calcd for $C_{13}H_{19}NO_7$ ($M+H^+$) 302.12, found 302.16.