Free Radical Acylation Approach of Carbohydrate Derivatives[§]

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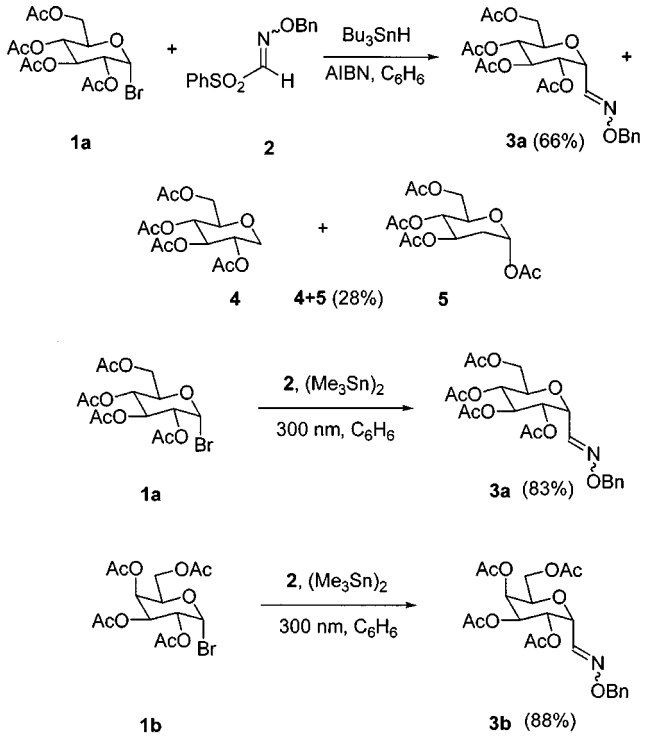
C-Glycosides have been the subject of considerable interest in carbohydrate chemistry because many carbohydrate derivatives exhibit very interesting biological activities such as antitumor activity and inhibitors of metabolic processes.[1] Thus, a modification of carbohydrates *via* carbon-carbon bond formation receives increasing attention among synthetic organic chemists and also provides valuable synthons suitable for the synthesis of complex molecules since carbohydrate derivatives contain a large number of chiral centers and functional groups.[2] In view of the synthetic importance of carbohydrate derivatives, a variety of synthetic methods for the preparation of various carbohydrate derivatives have been reported.[3]

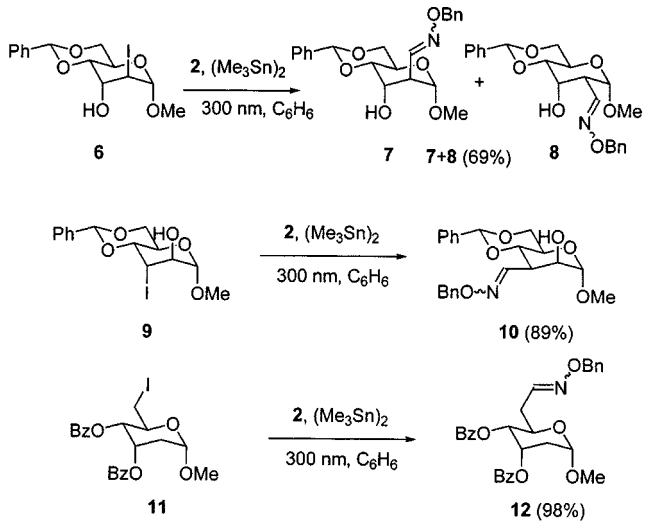
Free radical addition to multiple bonds is recognized as a powerful means for carbon-carbon bond formation.[4] Radical-mediated approaches have special advantages for the synthesis of carbohydrate derivatives due to mild reaction conditions and tolerance of a wide range of functional groups. However, as compared with radical cyclizations, intermolecular addition reactions have rather limited use due to the relatively slow rate of the addition and several competing reactions. Thus, highly efficient radical acceptors are normally required and two approaches involving additions to activated olefins and fragmentation reactions are generally useful. Giese utilized addition of glycosyl radical to activated olefins,[5] whereas Keck employed reliable radical allylation reactions for the synthesis of C-glycosides.[6] Recently, vinylphosphonates were also employed for the diastereoselective synthesis of *C*-glycosylphosphonates.[7] Furthermore, free radical-mediated glycosylations generally involve three-carbon extensions and only two reports appeared for radical-mediated one-carbon extensions.[8]

We reported highly efficient radical acylation approaches of alkyl iodides using sulfonyl oxime ether derivatives.[9] Since this approach is very useful to introduce not only acyl groups but also amino-alkyl groups,[10] we have studied radical acylation reactions of several carbohydrate derivatives. First, *C*-glycosylation of α-D-glycopyranosyl bromides (**1a**, **1b**) was briefly examined with phenylsulfonyl oxime ether **2**. Treatment of **1a** with **2** (2.0 equiv) and Bu_3SnH (1.5 equiv) using AIBN as initiator in refluxing benzene for 6 h under a high diluted condition afforded the axial C-glycopyranoside **3a** in 66% yield along with a mixture of the direct reduction product **4** and the rearranged product **5**, apparently resulting from the 1,2-acyloxyl migration in pyranoyl radicals.[11] In order to prevent the direct reduction by Bu_3SnH, the reaction was carried out with hexamethylditin in benzene at 300 nm for 8 h. Under photochemically initiated conditions (300 nm), much better results were obtained, yielding **3a** ($J_{1,2}$ = 6.2 Hz) in 83% yield.[12] A similar result was also obtained with **1b** under the similar conditions, yielding **3b** ($J_{1,2}$ = 5.7 Hz)[13] in 88% yield. The preference for the formation of α-linked C-glycopyranosides has been well known and is attributed to better stability and higher nucleophilicity of the axial σ-radical over the equatorial σ-radical in glucose derivatives.[14]



We next studied the synthesis of several *C*-branched glycosides and prepared methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**6**), methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-altropyranoside, (**9**) and methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-6-iodo-a-D-altropyranoside (**11**) by

[§]Dedicated to the late Prof. Sang Chul Shim for his outstanding contributions to organic chemistry.



the known procedures.[15] When **6** was treated with **2** and hexamethylditin in benzene at 300 nm for 4 h, a 2 : 1 mixture of *C*(2)-branched glycoside **7**[16] and **8**[17] was obtained in 69% yield. The ratio of two isomers was determined by ^{1}H NMR spectral data ($J_{1,2}$ = 0.74 Hz for **7**, $J_{1,2}$ = 3.92 Hz for **8**). The stereochemical course of the reaction was governed by steric effects of the vicinal substituents, indicating that the axial attack was somewhat favored over the equatorial attack by sulfonyl oxime ether **2**. Reaction of **9** with **2** under the same conditions provided *C*(3)-branched glycoside **10** in 89% yield without the formation of the direct reduction product. The reaction was clean and stereoselective, yielding the equatorial isomer, probably due to 1,3-diaxial interaction for the axial isomer. For the synthesis of *C*(6) chain-extended glycoside derivative, when **11** was subjected to the standard conditions, **12** was isolated in 98% yield.

In conclusion, we have developed a highly efficient method for one carbon extended diastereoselective glycosidation of glycopyranosides. The present method is also applicable to the synthesis of *C*-branched glycosides.

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12. A benzene (1 mL) solution of **1a** (95 mg, 0.23 mmol), **2** (127 mg, 0.46 mmol), and hexamethylditin (90 μL, 0.27 mmol) in quartz tube was degassed with nitrogen gas for 20 min. The solution was irradiated at 300 nm in Rayonet photochemical reactor for 8 h. The reaction mixture was diluted with ethyl acetate and quenched with potassium fluoride and a few drops of water. The mixture was stirred at room temperature for 1 h and then filtered over silica gel. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel using n-hexane:ethyl acetate = 3:1 solution as eluent to give **3a** (89 mg, 83 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 3.86-3.90 (ddd, 1H, H-5, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 4.5 Hz), 4.01 (dd, 1H, H-6, $J_{5,6a}$ = 2.3 Hz, $J_{6a,6b}$ = 12.4 Hz), 4.15 (dd, 1H, H-6, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 12.4 Hz), 4.82 (dd, 1H, H-1, $J_{1,2}$ = 6.2 Hz, J = 6.2 Hz), 5.00 (dd, 1H, H-4, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 9.6 Hz), 5.09 (dd, 1H, H-2, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 9.6 Hz), 5.12 (s, 2H), 5.42 (dd, 1H, H-3, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.6 Hz), 7.26-7.36 (m, 5H), 7.55 (d, 1H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.43, 20.55, 20.60, 20.65, 61.84, 68.46, 69.48, 70.09, 70.54 (2C), 76.57, 128.04, 128.40, 128.58, 137.01, 143.62, 169.39, 169.58, 169.93, 170.56; IR (NaCl) 3065, 3032, 2956, 2365, 2344, 1752, 1654, 1497, 1455, 1436, 1369, 1228, 1098, 1038, 957, 909, 741, 701, 648, 601, 561, 516, 484 cm^{-1}
13. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (s, 3H), 1.94 (s, 3H), 1.97 (s, 3H), 2.07 (s, 3H), 4.02 (m, 2H, H-6), 4.06-4.10 (ddd, 1H, H-5, $J_{4,5}$ = 1.7 Hz, $J_{5,6a}$ = 5.7 Hz, $J_{5,6b}$ = 7.0 Hz), 4.84 (dd, 1H, H-1, $J_{1,2}$ = 5.7 Hz, J = 5.7 Hz), 5.07 (s, 2H), 5.23 (dd, 1H, H-3, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.2 Hz), 5.29 (dd, 1H, H-2, $J_{1,2}$ = 5.7 Hz, $J_{2,3}$ = 10.4 Hz), 5.35 (dd, 1H, H-4, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.7 Hz), 7.24-7.31 (m, 5H), 7.50 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.48, 20.53, 20.56, 20.61, 61.51, 67.05, 67.67, 68.16, 69.51, 70.28, 76.50, 128.03, 128.39, 128.49, 137.01, 143.84, 169.75, 169.80, 170.02, 170.31; IR (NaCl) 3063, 3031, 2937, 2434, 1750, 1496, 1455, 1434, 1371, 1227, 1054, 1170, 1119, 1054, 943, 909, 825, 738, 700, 603, 553, 473 cm^{-1}
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16. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.03-3.09 (m, 2H), 3.42 (s, 3H), 3.61-3.73 (m, 2H), 4.14-4.32 (m, 3H), 4.81 (s, 1H), 5.09 (s, 2H), 5.50 (s, 1H), 7.30-7.38 (m, 8H), 7.42 (d, 1H, J = 5.16 Hz), 7.45-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.3, 55.7, 58.2, 67.4, 69.2, 76.2, 76.4, 76.7, 78.2, 99.8, 102.2, 126.2, 128.0, 128.1, 128.3, 128.4, 128.5, 129.1, 137.2, 137.3, 146.8
17. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.75-2.82 (m, 1H), 2.92 (d, 1H, J = 6.85 Hz), 3.39 (s, 3H), 3.57 (dd, 1H, J = 2.79 Hz, J = 9.49 Hz), 3.77 (t, 1H, J = 9.89 Hz), 4.15-4.22 (m 2H), 4.27-4.38 (m, 1H), 4.70 (d, 1H, J = 3.76 Hz), 5.08 (s, 2H), 5.59 (s, 1H), 7.27-7.36 (m, 8H), 7.44-7.50 (m, 2H), 7.65 (d, 1H, J = 7.74 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.8, 44.5, 56.1, 57.8, 57.9, 66.6, 67.9, 69.2, 75.9, 76.3, 77.2, 79.0, 79.2, 98.6, 100.5, 102.10, 102.11, 126.2, 126.3, 127.0, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 137.1, 137.4, 137.5, 146.7, 148.2 (*E*, *Z* isomer mixture).