CHEMISTRY LETTERS, pp. 1469-1472, 1992.

An Efficient Deoxysugar Synthesis using Bu_4NBH_4 via an S_N2 Reduction

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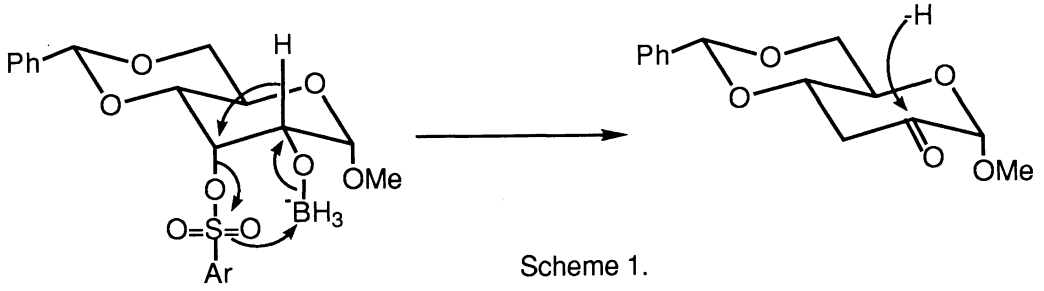
Deoxysugar derivatives were prepared from the corresponding triflate, tosylate, halogen, and epoxide derivatives. Employing the tetrabutylammonium tetrahydroborate reagent, the deoxygenation proceeds via an S_N2 type displacement in good yield.

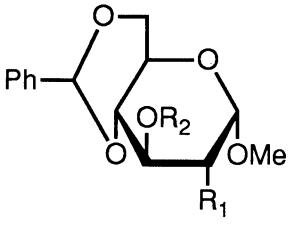
The preparation of deoxysugars is important in natural products chemistry where deoxysugars are frequently encountered as constituents of these materials. Hitherto most of the established deoxygenation methods involve a free radical promoted reduction mechanism, although this type of reduction can be quite stereoselective.[1] Deoxygenation via an S_N2 reaction by hydride reagents, which would not be subject to the above disadvantages, has been of little use in sugar chemistry, because most metal hydride reagents such as lithium aluminum hydride (LAH) which are required for the displacement, are limited to the overall conversion of primary hydroxyls to methyl groups. Furthermore, the reduction of sulfonyloxy groups by the use of LAH usually requires a long reaction time and careful handling. Although LAH and lithium triethyl hydroborate (LTBH) [2] react with carbohydrates containing sulfonyloxy groups or halogens to give the corresponding deoxy compounds, activated secondary sugar hydroxyls are too unreactive to be displaced by their hydride reagents but rather suffer O-S cleavage, molecular rearrangement,[2a,2b] and reduction of other functional groups such as epoxy, azido, acyl, in general.

In our previous synthetic studies [3] on the synthesis of 6-deoxy derivatives, hydrogenation of the easily available 6-bromo-6-deoxy- and 6-O-p-tolylsulfonylhexopyranosides with sodium tetrahydroborate ($NaBH_4$) in dimethyl sulfoxide (DMSO) and sodium cyanotrihydroborate ($Na[BH_3CN]$) in hexamethylphosphoric triamide (HMPT) were examined. Although $NaBH_4$ is not a very reactive hydride transfer agent, it is capable of reducing some primary and unhindered secondary sulfonyloxy, halogen, ester, azido, and epoxy groups in DMSO at 80 °C. On the other hand, $Na[BH_3CN]$ in HMPT [3,4] gave selectively, the corresponding 6-deoxysugars in good yield without reacting with other functional groups as mentioned above. The latter method may be of considerable utility in the preparation of functionalized 6-deoxypyranosides. In connection with the deoxygenation at a secondary position, in 1984, Barrette and Goodman reported[5] a convenient and stereospecific synthesis of deoxysugars by the reductive displacement of trifluoromethanesulfonates with $NaBH_4$ in acetonitrile at room temperature. They succeeded in obtaining both primary and secondary deoxysugars under extremely mild conditions. However they clarified the limitations of the reduction to certain ester derivatives such as methyl 2,3,4-tri-O-benzoyl-4-O-trifluoromethanesulfonyl-α-D-galactopyranosie (probably as a result of elimination and /or deacylation) and 1,2:5,6-di-O-isopropylidene-3-O-trifluoromethanesulfonyl-α-D-glucofuranose **19** (as a result of the elimination and S-O cleavage).

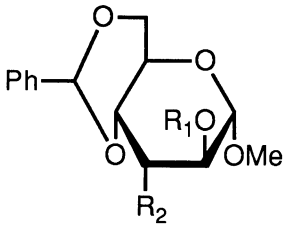
In this paper, we describe a novel reagent tetrabutylammonium tetrahydroborate (Bu_4NBH_4)[6] for the synthesis of deoxysugars as the extension of our previous work. The optimized condition for these reductions were as follows: A mixture of the secondary sugar triflate, primary bromide, primary tosylate or 2,3-anhydro derivative (**1**, **2**, **5**, **6**, **9**, **10**, **13**, **15**, **16**, **19**, **21**, **22**, **25**, **27**, **29**, and **31**) 100 mg and Bu_4NBH_4 (3 equiv.) in dry benzene (2.0 cm^3) was heated at reflux temperature until the starting sugar derivative disappeared on the tlc. Then the mixture was washed with water, dried and evaporated to give the corresponding crude deoxysugar, which was purified on a column of silica gel and recrystallized. Under these conditions, methyl 4,6-O-benzylidene-2-O-trifluoromethanesulfonyl-α-D-glucopyranoside derivative **1** and **2** gave the corresponding 2-deoxy derivative (**3** and **4**) in 87 and 92% yields, respectively. The reduction of methyl 4,6-O-benzylidene-3-O-trifluoromethanesulfonyl-α-D-altropyranoside derivative **5** and **6** gave the corresponding 3-deoxy derivative (**7** and **8**) in 89 and 71% yields, respectively. A similar reduction of methyl 4,6-O-benzylidene-2-O-benzoyl-3-O-p-tolylsulfonyl-α-D-allopyranoside **9** necessitates a longer reaction time and gave the corresponding debenzoylated 3-deoxy derivative, methyl 4,6-O-benzylidene-3-deoxy-ribo-hexopyranoside (**11**) in 43% yield. In contrast to **9**, the corresponding triflate derivative **10** was easily reduced to give the 3-deoxy derivative (**12**) in 91% yield without debenzoylation. It is to be noted that under the reduction condition with $NaBH_4$/DMSO at 80 °C, **9** gave **11** in 65% yield and **10** gave **12** in 81% yield, but the 2-O-methyl derivative of **9** did not react at all. These results may suggest that the reduction of the low reactive secondary p-tolylsulfonyloxy group causes deacylation followed by the hydride shift reaction,[2b] rather than the direct S_N2 reduction (Scheme 1). The Bu_4NH_4 reduction of methyl 4-O-benzyl-2,3-di-O-methyl-6-O-p-tolylsulfonyl-α-D-glucopyranoside **13**, methyl 2,3-di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside **15**, and its 2,3-di-O-benzoyl derivative **16** gave the corresponding 6-deoxy derivative (**14**, **17**, and **18**) in 96, 60, and 87% yields, respectively. The low yield in the case of compound **15** indicates that the acetyl group is too unstable in this reaction condition. As is distinct from the reported result in most hydride reductions,[5,7] the reduction of **19** gave the corresponding 3-deoxy compound, 1,2:5,6-di-O-isopropylidene-3-deoxy-α-D-ribo-hexofuranose (**20**) in 84% yield without O-S cleavage. Attempts to apply the reduction to methyl 4,6-O-benzylidene-2-O-benzoyl-3-O-trifluoromethanesulfonyl-α-D-glucopyranoside **21** were unsuccessful. The reaction gave multiple spots on the tlc plate, which were speculated to be ring contraction and debenzoylation side-products. To gain a further understanding of the reactitivity of this reaction, the reaction of a more stable methyl-blocked sugar **22** was examined which gave the deoxygenated product, methyl 4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-ribo-hexopyranoside (**23**) and the ring contraction product, methyl 5-O-benzyl-3-C-hydroxymethyl-2-O-methyl-α-D-xylo-pentofuranoside (**24**)[8] in 40 and 21% yields, respectively. A proposed mechanism of the ring contraction is showed in Scheme 2.



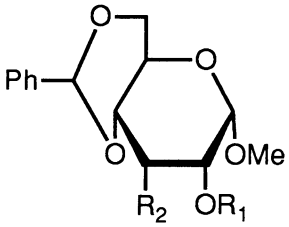
Scheme 1.



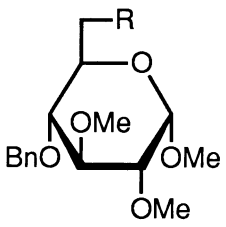
1 R_1=OTf, R_2=Me
2 R_1=OTf, R_2=Bz
3 R_1=H, R_2=Me
4 R_1=H, R_1=Bz



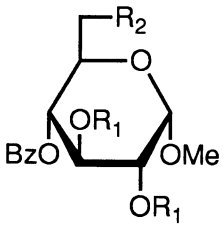
5 R_1=Me, R_2=OTf
6 R_1=Bz, R_2=OTf
7 R_1=Me, R_2=H
8 R_1=Bz, R_2=H



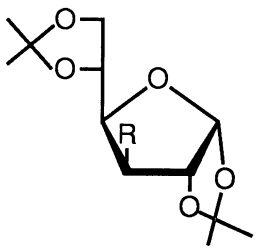
9 R_1=Bz, R_2=OTs
10 R_1=Bz, R_2=OTf
11 R_1=H, R_2=H
12 R_1=Bz, R_2=H



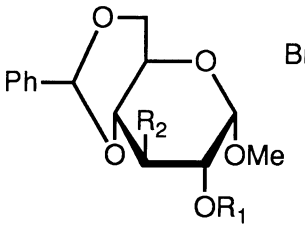
13 R=OTs
14 R=H



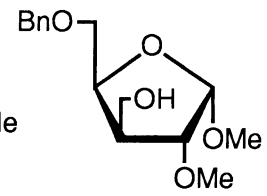
15 R_1=Ac, R_2=Br
16 R_1=Bz, R_2=Br
17 R_1=Ac, R_2=H
18 R_1=Bz, R_2=H



19 R=OTf
20 R=H



21 R_1=Bz, R_2=OTf
22 R_1=Me, R_2=OTf
23 R_1=Me, R_2=H



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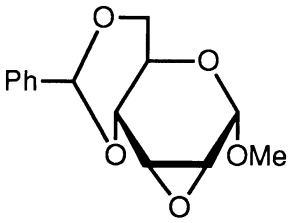

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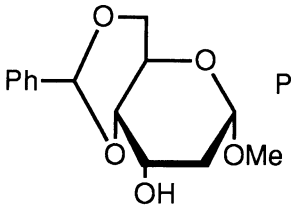

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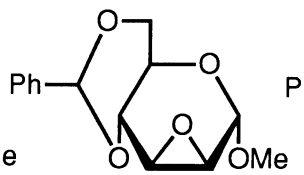

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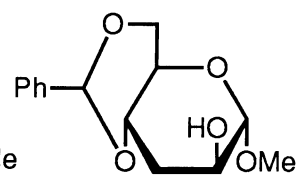
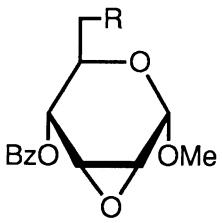
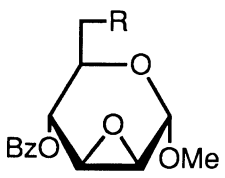


28

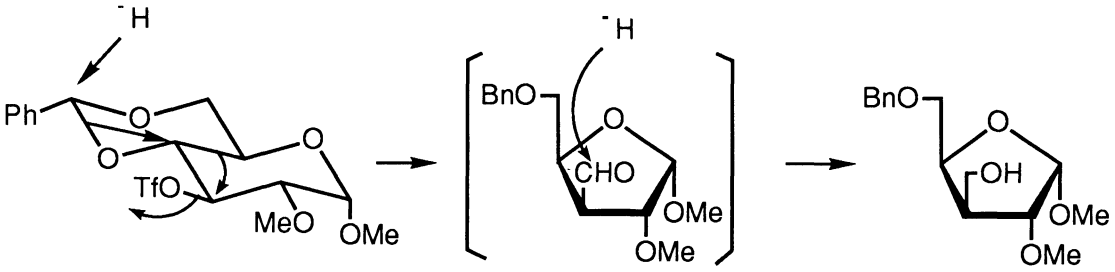


29 R=Br
30 R=H



31 R=Br
32 R=H

Fig. 1.



Scheme 2.

In the case of reductive ring opening of 2,3-anhydro derivatives, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside **25** gave the diaxial ring opening product, methyl 4,6-O- benzylidene-2-deoxy-α-D-ribo-hexopyranoside (**26**) in 91% yield. In the same reduction condition as above, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside **27** did not react at all, but was reduced in toluene at a reflux condition for 18 h to give the corresponding diaxial ring opening 3-deoxy derivative, methyl 4,6-O-benzylidene-3-deoxy-α-D-arabino-hexopyranoside (**28**) in 95% yield. The chemoselectivities of this reagent were examined by the use of methyl 2,3-anhydro-4-O-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside **29** and -mannopyranoside **31**. The reduction of compounds **29** and **31** (100 mg) with Bu_4NBH_4 (3 equiv.) in dry benzene (5 cm^3) at room temperature gave **30** and **32** in 69 and 59% yield, respectively. In summary, the above findings show that this reagent is useful for the hydride reduction via an S_N2 reaction in relatively high yields. The solvent (benzene or toluene) used here may contribute to the results of the high yield of deoxy products and easy isolation, because the similar reduction in DMSO gave unsuccessful results.

References

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8) See Ref. 2. ^1H NMR (JEOL, FX-200) data of the acetyl derivative of compound **24**: δ=7.40-7.25 (5H, m, Ph), 4.99 (1H, d, $J_{1,2}$=4.4 Hz, H-1), 4.54 (2H, s, -CH_2-), 4.40-4.19 (3H, m, H-3'a, H-3'b, and H-4), 3.70 (1H, dd, $J_{2,3}$=9.5 Hz, H-2), 3.63-3.49 (2H, m, H-5a and H-5b), 3.46 and 3.39 (3Hx2, each s, OMex2), 2.75 (1H, dddd, $J_{3,3'a}$=5.9 Hz, $J_{3,3'b}$=$J_{3,4}$=8.9 Hz, H-3), 1.97 (3H, s, OAc).

(Received May 12, 1992)