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N-(4,6-O-BENZYLIDENE-1-O-METHYL-3-OXIMINO-α-D-RIBO-HEXOPYRANOS-2-YL) PYRIDINIUM p-TOLUENESULFONATE. A NOVEL VERSATILE CARBOHYDRATE SUBSTRATE

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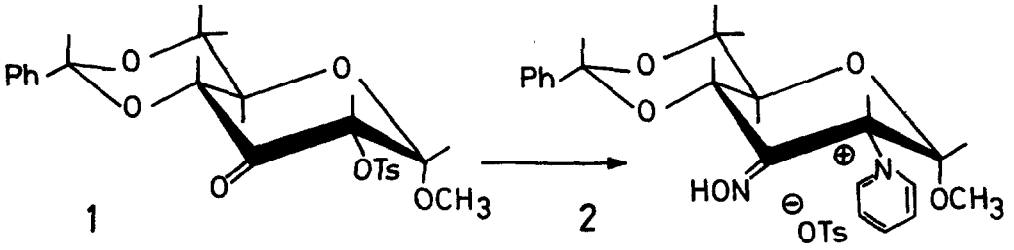
A wide variety of sugars can be prepared by nucleophilic displacement reactions with appropriate carbohydrate derivatives such as sugar sulfonates. The reactions are easiest when the sulfonate group is on a primary hydroxyl, except in cases in which the sulfonyloxymethyl group is adjacent to either a cis-axial substituent on a six-membered ring, as in the 6-sulfonates of galactopyranose derivatives,[1] or adjacent to the anomeric center, as in ketose 1-sulfonates.[2] Displacement is more difficult at secondary positions on a pyranoside ring, and normally requires the use of high boiling aprotic solvents of high dielectric constant. Moreover, these latter reactions depend critically upon the position of the group and upon the stereochemistry and conformation of the molecule. Thus, if a sulfonate is situated at C-2 of a pyranoside, then nucleophilic displacement with charged nucleophiles does not normally occur. It has been suggested[3] that the diminished reactivity is due to the electron-withdrawing effect of the anomeric center and/or unfavorable polar interactions in the transition state. A similar deactivation of a chlorosulfate group at C-2 to nucleophilic substitution by chloride ion has been observed by Jones coworkers.[4]

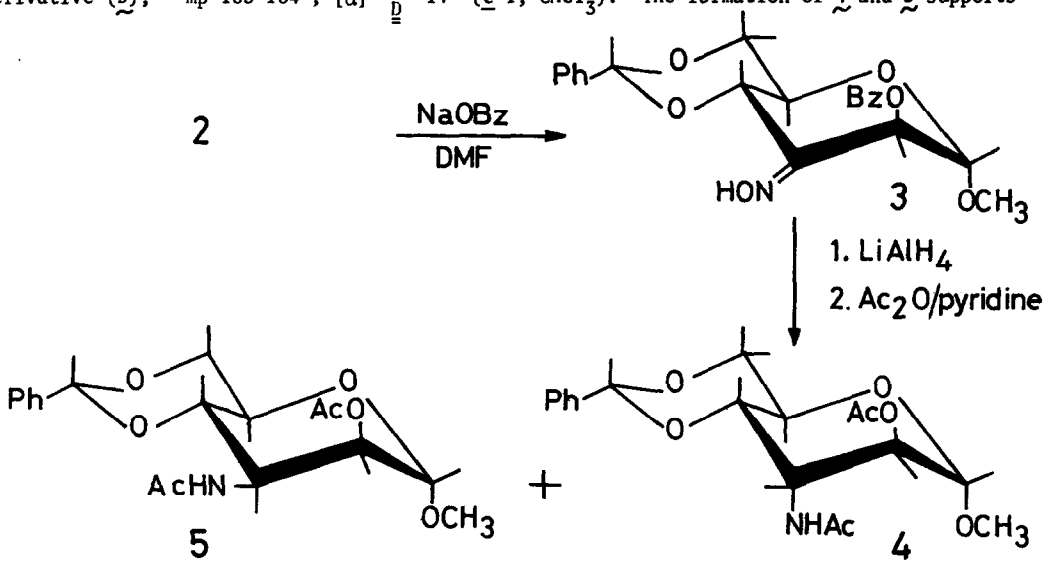
Attempts have been made to achieve nucleophilic displacements of a 2-sulfonate by using a more activated sulfonate as a leaving group as in methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-ribo-hexopyranosid-3-ulose (1). It is known that a carbonyl group adjacent to the reaction center assists bimolecular substitution. The high reactivity can be explained by postulating a stabilization of the transition state by overlap of the π-electrons of the carbonyl group with the p-orbital which is binding the entering and leaving groups at the reaction center.[5] The displacement of the sulfonate group in the α-keto p-toluenesulfonate 1 by azide ion has been attempted[6] under a variety of conditions. A number of products were formed, however, and the pure azido sugar could not be isolated. We report now the preparation from compound 1 of a versatile carbohydrate derivative, N-(4,6-O-benzylidene-1-O-methyl-3-oximino-α-D-ribo-hexopyranos-2-yl)pyridinium p-toluenesulfonate (2), which does permit the

realization of facile displacements at C-2 of a hexopyranoside with charged nucleophiles. The new compound is of considerable interest in synthesis, since, for example, reduction of the oximino group provides a route to amino sugars variously substituted at C-2, or regeneration of the ketone offers a route to branched-chain sugars by way of a Grignard synthesis or other procedures.



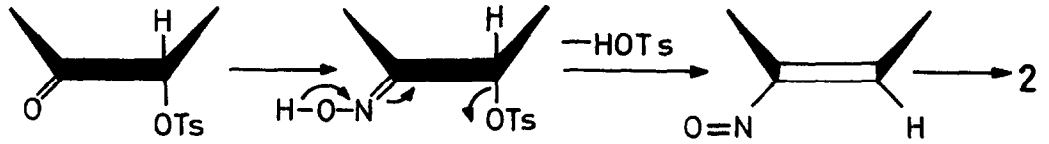
Compound 2 was prepared from the readily available methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-ribo-hexopyranosid-3-ulose (1)[6,7] by treatment with hydroxylamine hydrochloride in 5:1 (v/v) pyridine - water at 50° for 6 days, and was obtained as white needles in 91% yield; mp 199-200° dec, $[\alpha]^{25}_{D}$ -55° (c 2, N,N-dimethylformamide). Anal. Calcd for $C_{26}H_{28}N_2O_8S$: C, 59.1; H, 5.34; N, 5.30; S, 6.07; OCH_3, 5.87. Found: C, 58.9; H, 5.59; N, 5.39; S, 6.01; OCH_3, 5.72. When the reaction was run in pyridine at 90°, extensive decomposition occurred, and after 1 hr the pyridinium salt (2) could be isolated only in 45% yield. The infrared and nuclear magnetic resonance (nmr) spectra of compound 2 are consistent with the assigned structure; the configuration at C-2 has been established by chemical methods. Thus, treatment of a 10% solution of compound 2 in N,N-dimethylformamide with 2 equivalents of sodium benzoate at room temperature for 5 hr afforded crystalline methyl 2-O-benzoyl-4,6-O-benzylidene-3-oximino-α-D-arabino-hexopyranoside (3) in 90% yield; mp 183-184°, $[\alpha]^{25}_{D}$ -32° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.1; H, 5.30; N, 3.51. Found: C, 62.8; H, 5.39; N, 3.64. The nmr spectrum[8] of 3 in chloroform-d showed two 1-proton doublets at τ 5.05 and τ 3.52 attributable to H-1 and H-2, respectively. The splitting of each of the doublets was 0.5 Hz, a value characteristic of the diequatorial arrangement of H-1 and H-2 in methyl 4,6-O-benzylidene-α-D-hexopyranosides.[9] Treatment of compound 3 with lithium aluminum hydride in boiling tetrahydrofuran, followed by acetylation of the resultant product, gave a approximately 1:1 mixture of two compounds, which were separated by chromatography on silic acid. The two compounds were methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside (4), which has been reported previously,[10] and the corresponding D-manno

derivative (5),[11] mp 183-184°, $[\alpha]_D^{25}$ -14° (c 1, $CHCl_3$). The formation of 4 and 5 supports



the assigned stereochemistry at C-2 in the pyridinium salt, since the nucleophilic displacement by benzoate ion would be expected to occur with inversion of configuration. Of particular significance is the ease with which the displacement was accomplished, since, frequently, forcing conditions are necessary to effect direct replacement by nucleophilic reagents of substituents such as sulfonyloxy at secondary carbon atoms of carbohydrates. Compound 2 also readily undergoes substitution reactions with other nucleophiles, including acetate, azide and nitrite ions.

Generally quaternization at an asymmetric carbon atom, by the reaction of organic halides and esters with pyridine bases, takes place with inversion of configuration.[13] A possible mechanism for the formation of compound 2 from the α-keto p-toluenesulfonate 1 with retention of configuration at C-2 is shown below:



The first step is considered to be the formation of the oximino p-toluenesulfonate. Elimination of p-toluenesulfonic acid in the aqueous pyridine medium would give an α-nitrosoolefin. Attack by pyridine could then occur at C-2 to give, after protonation, the more stable product (2).

Acknowledgments

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