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Removal of benzyl protecting groups from controlled pore glass linked sugars

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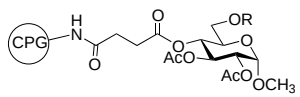
Abstract—Removal of benzyl protecting groups from controlled pore glass bound monosaccharides can be performed with the $NaBrO_3/Na_2S_2O_4$ system in ethyl acetate/water.

The benzyl group is widely employed in synthesis (in particular, of oligosaccharides) for the protection of alcoholic functions due to its stability to a wide range of chemical conditions.[1] Benzyl ethers are typically cleaved under very mild conditions by hydrogenolysis on a heterogeneous catalyst, a procedure which cannot be applied to solid-phase synthesis because of the unpractical separation of the insoluble catalyst from the support. This problem can be circumvented by using modified benzyl protecting groups equipped with 4-acetoxy[2] or 4-azido-3-chloro[3] groups in their aromatic rings, whose removal can also be accomplished on an insoluble resin. Halobenzyl ethers have also been designed as potential transient protecting groups for solid-phase synthesis.[4] However, all these modified benzyl groups require multistep procedures for the preparation of the corresponding benzylating reagent and/or for the deprotection step. Very recently the use of palladium nanoparticles as a removable catalyst for the solid-phase hydrogenolytic cleavage of unsubstituted benzyl groups from Tentagel- and PEGA-bound sugars has been reported.[5]

Recently, we have been investigating the use of CPG (controlled pore glass) in solid-phase glycosidations and its application to the semi automated synthesis of oligomeric saccharo nucleotides.[6] In order to pursue these investigations, several CPG-linked sugars with one free hydroxyl group in various positions needed to be prepared. For this purpose we envisaged that the benzyl protecting group could be advantageously used as a transient protecting group, in view of its easy installation on several positions of saccharidic substrates.[7] The problems related to the solid-phase cleavage of benzyl ethers prompted us to test, on polymer bound sugars, the procedure we have recently described for the debenzylation of protected monoses, which is based on the combined use of $NaBrO_3$ and $Na_2S_2O_4$ under two phase conditions (ethyl acetate and water).[8] This approach proved compatible with a wide variety of protecting groups in solution.[9] In this letter we wish to report on this cheap and experimentally simple alternative approach for the removal of simple benzyl protecting groups from monosaccharides linked to the CPG.



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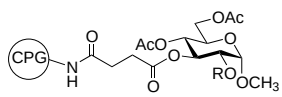
1a R = H



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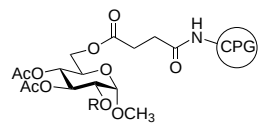
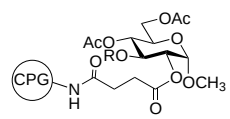


3 R = Bn
3a R = H



4 R = Bn
4a R = H

CPG resin was derivatized through a succinic linker with several saccharidic residues benzylated at one position only (resins **1**–**4**). Small aliquots of these CPG-bound monoses were treated with 32% aq. ammonia in order to test the expected stability of the benzyl protecting groups under conditions typically adopted for the detachment of the sugars from the resin as well as for the removal of acyl protecting groups. In all cases, the

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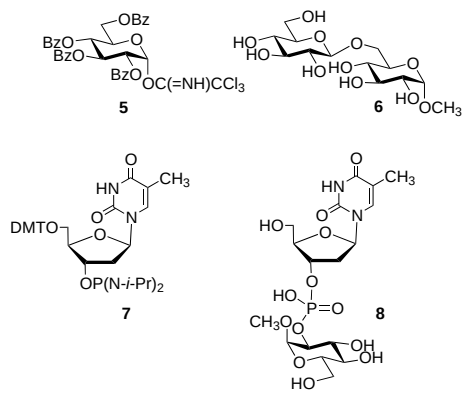
treatment afforded the expected monobenzylated methyl α-glucopyranosides as the sole detectable products (TLC, NMR). Solid-phase debenzylations were then attempted suspending the resins **1**–**4** in the double liquid phase (water and ethyl acetate) in the presence of excess $NaBrO_3$ and $Na_2S_2O_4$. The resulting mixture was kept under vigorous horizontal stirring overnight.[10] Subsequent cleavage with 32% aq. ammonia afforded completely deprotected methyl α-glucopyranoside in all cases. In order to prove the potential of the procedure in oligosaccharide synthesis, the polymer bound acceptor **1a** was glycosylated with imidate **5** under the previously reported conditions[6a] to afford disaccharide **6** in good overall yield (90%) after detachment and deprotection with ammonia. In an initial attempt to link a nucleotide through a secondary hydroxyl of a glucose residue, support **2a** obtained with this procedure was subjected to automated coupling with phosphoramidite **7** under the standard phosphoramidite protocol.[11] Detachment from the resin provided the dimeric conjugate **8** in an unoptimized 56% yield.[12]



In conclusion, we have shown that unmodified benzyl protecting groups can be removed from polymer bound monosaccharides by the two phase $NaBrO_3/Na_2S_2O_4$ method. It should be noted that the procedure described can be successfully applied on the CPG resin, while the application on polystyrene based resins could be limited by the ability of the $NaBrO_3/Na_2S_2O_4$ system to effect radical brominations of benzylic positions. On the other hand, the efficiency of the described solid-phase deprotection despite the use of a double liquid phase is of note.

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10. Typical experimental procedure for the solid-phase debenzylation: a solution of sodium thiosulfate (85%, 56 mg, 0.27 mmol) in water (1.5 mL) was slowly added dropwise to a mixture of CPG resin (200 mg) functionalized with a benzylated sugar (40–60 μmol per g of resin, 8–12 μmol), ethyl acetate (1.5 mL) and a solution of $NaBrO_3$ (48 mg, 0.32 mmol) in water (1.5 mL). The mixture was kept under vigorous horizontal stirring (200 rotations per minute) overnight. The resin was filtered and then washed repeatedly with water, methanol and dichloromethane. The detachment and the simultaneous removal of acetyl groups were performed by treating the support with 32% aq. ammonia for 3 hours at room temperature.
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12. Selected ^1H NMR (D_2O, 300 MHz) data for **8**: 7.44 (1H, s, thymidine H-6), 6.17 (1H, t; $J=6.5$ Hz, thymidine H-1′), 4.81 (1H, d; $J=3.8$ Hz, glucose H-1), 3.23 (3H, s, $-OCH_3$).