# Use of Polymers as Protecting Groups in Organic Synthesis. Preparation of Partially Substituted Derivatives of D-Glucose

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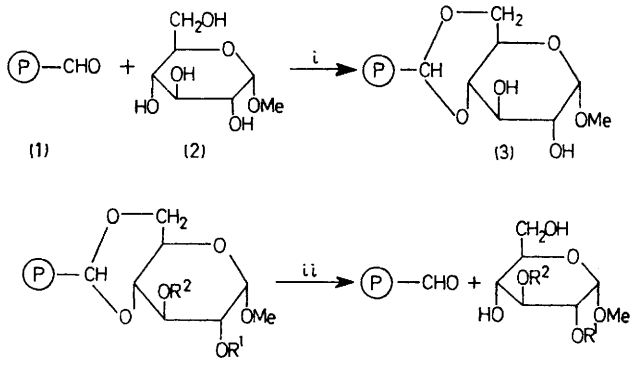
*Summary* Two types of insoluble polystyrene resins bearing vinylbenzaldehyde units have been prepared and used with high efficiency as temporary protecting groups in the synthesis of 2,3 disubstituted derivatives of methyl α-D-glucopyranoside.

INSOLUBLE polymers have recently been used widely as reagents in organic synthesis.[1] Their use has generally resulted in a drastic reduction of the common purification steps, since the excess of reagent and other polymeric reaction products can be removed by simple filtration. When a polymer is used as a protecting group in organic synthesis, the desired product is covalently bound to the polymer while the unchanged material and other soluble by-products can be washed from the polymer. The polymer-protected product then remains attached to its support through one or more synthetic steps, until it is finally removed by action of a suitable reagent, leaving the polymeric by-product in the insoluble phase.[2]

We report here that a polymer containing vinylbenzaldehyde units can be used as a protecting group in the synthesis of partially substituted derivatives of methyl α-D-glucopyranoside. Two types of polymer beads were tested in this study: one was a highly crosslinked macroreticular resin, and the other was a swellable 1% divinylbenzene–styrene copolymer (Bio-bead SM-2 20—50 mesh, and SX-1 200—400 mesh respectively, Bio-Rad Laboratories). While the macroreticular resin could be used in almost any type of solvent since no swelling of the polymer matrix was required prior to reaction, the 1% divinylbenzene–styrene copolymer had to be used in solvents with good swelling properties, such as dioxan, tetrahydrofuran, chloroform, benzene, *etc.* However, when such solvents can be used, the swellable resin does offer some advantages over the macroreticular resin. Thus, it is less fragile and requires less care in handling, and it also reacts faster than the macroreticular resin. For these reasons, most of the results reported here are for reactions in which swellable 1% divinylbenzene–styrene copolymer beads were used. The polymer was prepared as described earlier,[3] by chloromethylation of the divinylbenzene-styrene copolymer[2,4]




(4); $R^1 = R^2 = PhCO$
(5); $R^1 = R^2 = PhCH_2$
(6); $R^1$ or $R^2 = H$; $R^2$ or $R^1 = PhCH_2$
(7); $R^1 = R^2 = PhCO$
(8); $R^1 = R^2 = PhCH_2$
(9); $R^1$ or $R^2 = H$; $R^2$ or $R^1 = PhCH_2$

SCHEME. Reagents: i, *p*-$MeC_6H_4SO_3H$; ii, $CF_3CO_2H$, $H_2O$.

followed by oxidation of the chloromethylated product with $Me_2SO$. The polymer (**1**) exhibited characteristic i.r. absorptions at 5·9 μm and contained 1·15 meq. of functional

group per gram. Condensation of the polymer with methyl α-D-glucopyranoside (**2**) was effected in 89% yield (based on the resin) by refluxing a dioxan suspension of the polymer with a 2—3 fold excess of the glucoside in the presence of a catalytic amount of toluene-*p*-sulphonic acid (20—100 mg for 2 g of resin and 1—1·5 g of methyl α-D-glucopyranoside; 24 h). All the yields reported are based on the resin (**1**) which is the limiting reagent; the excess of glucoside could be recovered after reaction by treatment of the filtrate with an ion exchange resin to remove the acid catalyst. Reactions carried out at room temperature or in the presence of other catalysts such as powdered $ZnCl_2$, $BF_3$–$Et_2O$, or $SnCl_4$, also gave the desired product (**3**) but in lower yields (44—71%). Lower yields were also obtained in the presence of traces of water or when a lower concentration of methyl α-D-glucopyranoside was used.

The toluene-*p*-sulphonic acid-catalysed condensation of (**2**) with macroreticular (**1**) was found to be more sluggish than the reaction on the swellable resin and gave a lower yield of (**3**) (61 *vs.* 89%), although an increase in the reaction time from 1 to 2 days increased the yield to 74%. In every case, the yield of the condensation was estimated from the increase in weight of the polymer; thus, in a typical run, a gain of 362 mg was obtained with 2 g of resin (**1**) for a yield of 89%.

The polymer-protected glucoside (**3**) showed a broad OH i.r. band. Reaction of (**3**) with excess of benzoyl chloride in pyridine at room temperature overnight was accompanied by the disappearance of the OH absorption, while new broad bands appeared in the C=O region (5·8—5·9 μm). The partially benzoylated glucoside (**7**) was removed from the polymer support in 70—80% yield by stirring (**4**) with a 3:1 mixture of dioxan and 90% $CF_3CO_2H$ at room temperature. The cleaved glucoside (**7**) was obtained as a thick oil homogeneous on t.l.c., and had an n.m.r. spectrum consistent with that expected for (**7**) and $[\alpha]_D = +155$ (*c* 1, EtOH) in agreement with earlier data.[5]

The benzylation of (**3**) by reaction with NaH in $Me_2SO$ followed by addition of benzyl chloride at room temperature did not proceed to completion as shown by the i.r. spectrum which showed some remaining OH absorption. Treatment of the benzylated product, (**5**) + (**6**), with 90% $CF_3CO_2H$ in dioxan afforded a complex mixture from which crystalline methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[6] (**8**) could be isolated in 20% yield. Another glucosidic component of the mixture (**9**) isolated in 15% yield contained only one benzyl group and could not be crystallized. Similar benzylation of (**3**) at room temperature with NaH and benzyl chloride in dimethylformamide or $KOBu^t$ and benzyl chloride in tetrahydrofuran produced better yields of (**8**) (30—40%), together with some monobenzylated product (**9**). The increase in yield observed in the last two benzylations is probably due to the better swelling properties of dimethylformamide and tetrahydrofuran as compared to $Me_2SO$. Thus, accessibility of the reactive sites is favoured in the better swelling agents and this results in a more complete benzylation. The fact that a monobenzyl derivative of (**3**) is obtained in the benzylations may reflect the difficulty of preparing anions on some of the less accessible sites of the resin where ion–ion repulsions may become very important, a fact illustrated by the difficulties experienced[3] in the acid–base titrations of resins containing carboxylic acid functional groups.

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