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THE ALLYL ETHER AS A PROTECTING GROUP IN CARBOHYDRATE CHEMISTRY

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The rearrangement of prop-2-enyl (allyl) ethers to cis-prop-1-enyl ethers by base under vigorous conditions has been reported for a variety of compounds (1), and more recently (2) the rearrangement has been shown to be accelerated under milder conditions by the use of potassium t-butoxide in dimethyl-sulphoxide (DMSO). Since allyl ethers are readily prepared from alcohols (e.g. by using allyl bromide and sodium hydroxide) and are stable to acid (see below) and aqueous alkali (3) and the prop-1-enyl ethers are very acid labile (compare vinyl ethers (4)), the facility of this rearrangement suggested that the allyl ether could be used effectively as a protecting group in carbohydrate chemistry which could supplement the use of existing protecting groups (e.g. trityl and benzyl ethers, acetals and ketals) and thus allow the preparation of valuable sugar derivatives which have previously been unavailable.

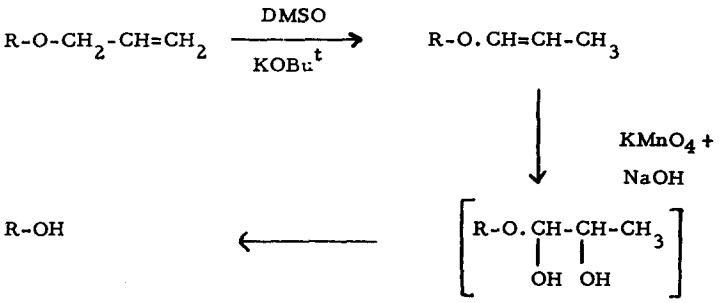
By extension of the method to the rearrangement of allyl glycosides (which are also stable to aqueous alkali (3)) the preparation of benzyl ethers of free sugars in the pyranose form has been facilitated. These compounds, unlike the benzyl ethers of free sugars in the furanose form (5) are not readily available via the methyl glycosides because of the instability of the benzyl ethers to the acidic conditions necessary to break the glycosidic linkage (6, 7).

To test the scope of the method several examples have been investigated. In the case of compounds containing no free hydroxyl groups it has been found that an equimolar quantity of potassium t-butoxide (1, 8) in dry dimethyl sulphoxide (9) (50 mg./ml.) at 100°C results in complete isomerisation within a maximum time of fifteen minutes. The course of the rearrangement could be conveniently followed by removal of portions for direct application to thin layer chromatograms. In all cases investigated the prop-1-enyl ethers had higher Rf values than the allyl ethers. The isomerised material was recovered by pouring the reaction mixture into water and extraction with ether and the presence of the prop-1-enyl ether confirmed by the appearance of a sharp, intense absorption peak at ca. 1660 cm^{-1} in the infra-red spectrum.

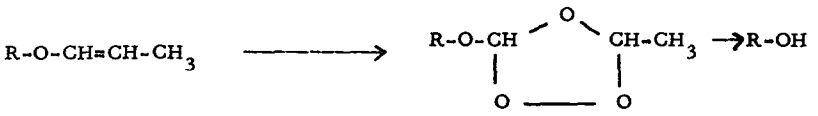
3-O-Allyl-1, 2:5, 6-di-O-isopropylidene-D-glucofuranose (10) and 3-O-allyl-1, 2-O-isopropylidene-glycerol (11) were prepared and isomerised to the corresponding prop-1-enyl ethers, and the effect of acid on these compounds was investigated. The 3-O-prop-1'-enyl-1, 2:5, 6-di-O-isopropylidene-D-glucofuranose (m.p. 56-57° from petrol (40°- 60°)) with dilute acid in aqueous methanol at room temperature gave 1, 2-O-isopropylidene-D-glucofuranose and the 3-O-prop-1'-enyl-1, 2-O-isopropylidene glycerol (b.p. 44°/0.8 mm.) gave glycerol showing that the prop-1-enyl ethers have the same order of acid lability as the readily hydrolysed isopropylidene groups in these compounds. A similar result has been obtained with 3-O-vinyl-1, 2:5, 6-di-C-isopropylidene-D-glucofuranose (4).

A more convenient method of removing the allyl ether under completely basic conditions was devised for compounds containing other acid labile groups. 3-O-Prop-1'-enyl-1, 2:5, 6-di-O-isopropylidene-D-glucofuranose was dissolved in 0.5 N methanolic sodium hydroxide and a 4% aqueous solution of potassium permanganate added slowly with stirring at 10°C until a small excess was present. (The hydroxylation of the double bond is rapid and the hemiacetal formed breaks down immediately). The solution was filtered to remove

manganese dioxide and on evaporation gave 1, 2:5, 6-di-O-isopropylidene-D-glucofuranose (m.p. 108-110° from cyclohexane) in quantitative yield.



A further decomposition of the prop-1-enyl ether, under non-acidic conditions, was effected by ozonolysis and decomposition of the ozonide and intermediate formate ester by alkali in aqueous ethanol.



The stability of the allyl ether to benzylation conditions using powdered sodium hydroxide and benzyl chloride at 100°C during six hours was shown by the conversion of 1-O-allyl-glycerol (11) to 1-O-allyl-2, 3-di-O-benzyl glycerol (b.p. 148°/0.015 mm.) without evidence of rearrangement. After rearrangement with potassium t-butoxide in DMSO the 1-O-prop-1'-enyl-2, 3-di-O-benzyl glycerol was hydrolysed with 0.1 N HCl in 90% aq. acetone at reflux for 15 minutes to give 1, 2-di-O-benzyl glycerol (b.p. 150°/0.05 mm.) (12).

Hydrolysis of 3-O-allyl-1, 2:5, 6-di-O-isopropylidene-D-glucofuranose with 0.1 N HCl in aq. methanol at room temperature gave 3-O-allyl-1, 2-O-isopropylidene-D-glucofuranose as a syrup (diacetate m.p. 85-86° from petrol (60°-80°)). This was converted to the dibenzyl ether (short path distillation, bath temp. 195°/0.015 mm.) as above. Isomerisation to the prop-1-enyl ether and hydrolysis with 0.1 N HCl in aq. methanol at room temperature (or removal by the permanganate

method) gave 5,6-di-O-benzyl-1,2-O-isopropylidene-D-glucofuranose as a syrup (acetate m.p. 57-59° from petrol (40°-60°)) and hydrolysis of this gave 5,6-di-O-benzyl-D-glucofuranose as a syrup, $[\alpha]_D^{24}$ - 15° (C, 1.5 in $CHCl_3$) Rf 0.56. (Thin layer chromatography (T.L.C.) on silica gel with ether/ethyl acetate 1/1 as solvent).

To test the stability of the trityl ether to these conditions, the 1-O-allyl ether of glycerol was converted to 1-O-allyl-3-O-trityl glycerol (m.p. 78-80° from cyclohexane) and this was benzylated to give 1-O-allyl-2-O-benzyl-3-O-trityl glycerol Rf 0.7 (T.L.C. on silica gel with petrol (40°-60°)/ether 4/1 as solvent). This was isomerised without decomposition to the 1-O-prop-1'-enyl-2-O-benzyl-3-O-trityl glycerol, which gave 2-O-benzyl glycerol (m.p. 38°-39°) on hydrolysis with dilute acid.

In the case of compounds containing free hydroxyl groups the rearrangement of allyl to prop-1-enyl ethers is slower, but if an extra molar proportion of potassium t-butoxide is added for each hydroxyl group the rearrangement proceeds at a reasonable rate.

With 1-O-allyl glycerol and three moles of potassium t-butoxide in DMSO the isomerisation was completed within one hour at 100°C. Addition of water and solid carbon dioxide and removal of the DMSO under reduced pressure followed by extraction with chloroform gave 1-O-prop-1'-enyl glycerol (b.p. 96°/1.5 mm.). A solution of this compound in chloroform with a trace of toluene-p-sulphonic acid gave immediately the same mixture of 1,2- and 1,3-O-propylidene glycerols (as observed by T.L.C.) as could be obtained by the action of propionaldehyde on glycerol in the presence of toluene-p-sulphonic acid (compare the ease of acetal formation with hydroxyethyl vinyl ether (13)). This conversion of prop-1-enyl ethers into propylidene acetals is also of potential use in the preparation of derivatives of carbohydrates from the allyl ethers. The 1-O-prop-1'-enyl ether of glycerol is being used as a readily available model compound for synthetic work on the plasmalogens.

A mixture of α- and β-allyl glucosides was prepared by the action of allyl alcohol containing HCl on 1, 2:5, 6-di-O-isopropylidene-D-glucofuranose at 70° during one hour. The mixed glucosides were benzylated and the fully benzylated product purified by chromatography on alumina to give a syrup, Rf 0.5 - 0.6 (T.L.C. on silica gel using petrol (40°-60°)/ether 3/1 as solvent). After isomerisation the prop-1-enyl glucosides were hydrolysed with 0.1 N HCl in 90% aq. acetone at reflux during 15 minutes. On dilution with water the beautifully crystalline 2, 3, 4, 6-tetra-O-benzyl-α-D-glucose (m.p. 153-155°, $[\alpha]_D^{22}$ + 20.9° (C, 3.5 in $CHCl_3$)) (6, 14) was obtained in high yield.

Similarly 2, 3, 4-tri-O-benzyl-D-galactose has been obtained from allyl 2, 3, 4-tri-O-benzyl-6-O-trityl-β-D-galactopyranoside in excellent yield and identical to the material obtained in low yield by the acid hydrolysis of methyl 2, 3, 4-tri-O-benzyl-6-O-trityl-α-D-galactopyranoside. The 2, 3, 4-tri-O-benzyl-D-galactose is being used for the preparation of benzyl derivatives of L-lyxose.

To test the acid stability of the allyl ether, a solution of one gram of 1-O-allyl glycerol in 25 ml. of 1 N HCl was refluxed for 10 hours. After this time 80% of the 1-O-allyl glycerol was recovered. Under similar conditions only 20% of 1-O-benzyl glycerol could be recovered.

The application of the allyl ethers in the preparation of derivatives of amino sugars is under investigation.

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