GLYCOSYL THIO-, SELENO- AND TELLUROPHOSPHATES*

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Abstract - A review of the chemistry of glycosyl thio-, seleno- and tellurophosphates is given with emphasis on their glycosyl-donor properties.

INTRODUCTION

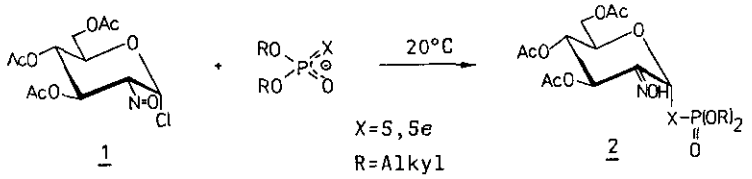
Sugar phosphates are of fundamental importance in phosphorus biochemistry. Relatively little attention was paid to sugar thio- and selenophosphates other than those derived from nucleosides.[1] Sulphur and selenium analogues of sugar phosphates represent a class of compounds of potential biological interest and synthetic application in carbohydrate chemistry.[2] This review covers the chemistry of glycosyl thio-, seleno- and tellurophosphates. Recently glycosyl thio- and selenophosphates were found to be efficient and highly stereoselective glycosylating reagents.[3] Glycosylation reaction is one of the most important but unresolved problem in carbohydrate chemistry. Continuously new glycosylating reagents are being proposed in order to fulfill requirements necessary for efficient and stereoselective synthesis of glycosides.

METHODS OF SYNTHESIS

From glycosyl halides

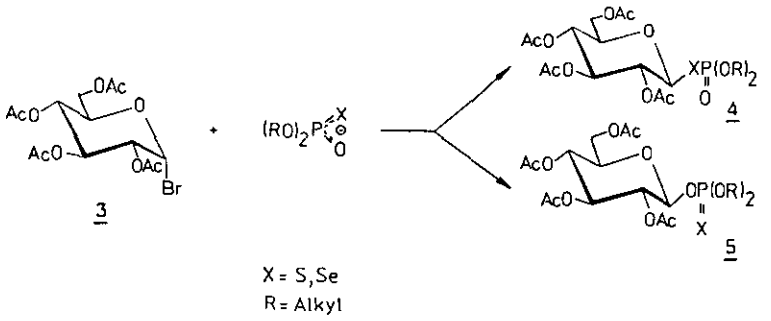
Glycosyl halides react with thio-, seleno- and telluroacids of phosphorus to give the corresponding S, Se and Te-glycosyl phosphates.[4] This reaction can be illustrated by glycosylation of O,O-dialkylphosphorothioic or selenoic acids alkylammonium salts with the so-called Lemieux's adduct 1 obtained by addition of nitrosyl chloride to 1,2-unsaturated sugars yielding the corresponding S- or Se-glycosyl-phosphorothioates or selenoates 2. This condensation is fully stereoselective yielding products of configuration α for the glycosidic linkage and Z for the oximino group.[5]

*Dedicated to Sir Derek Barton on the occasion of his 70th birthday.



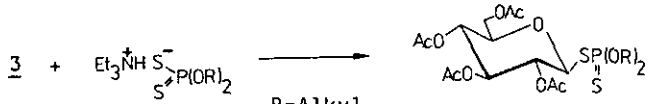
1 2

In the case of fully acetylated glycosyl halides 3 analogous reaction proceeds with inversion of configuration at the anomeric centre. S-Glycosyl phosphorothioates or Se-glycosyl phosphoroselenoates 4 are major products. O-Glycosyl phosphorothioates and selenoates 5 are usually minor products unless special reaction conditions or silver salts are employed.[4a,4c] This is illustrated by the reaction of glycosyl bromide 3 with O,O-dialkyl phosphorothio- or selenoate.



3 4 5

S-Glycosyl phosphorodithioates 6 can be obtained by similar condensation of O,O-dialkyl phosphorodithioates with glycosyl halides.



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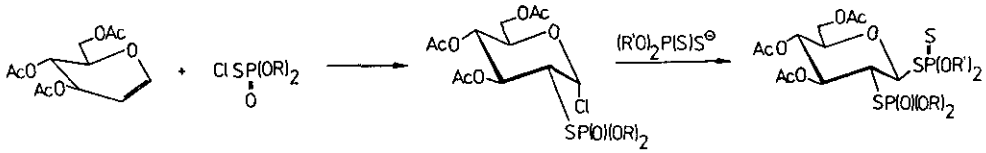
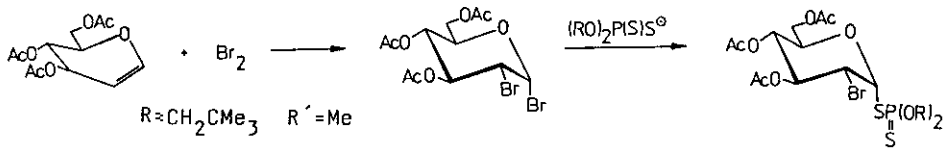
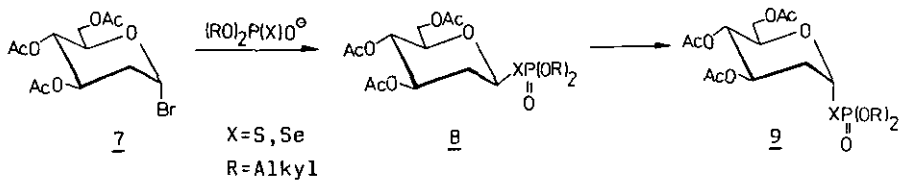
This method can be extended to a variety of 1-halogenosugar derivatives, e.g.:





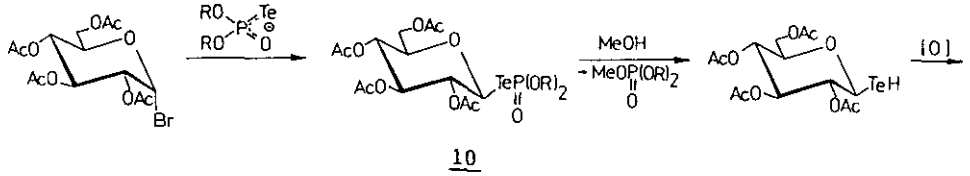
Glycosylation of thio- and selenoacids of phosphorus by 2-deoxyglycosyl bromide 7 proceeds in a similar manner.



7 8 9

The 2-deoxyglycosyl thiolo- and selenolophosphates 8 isomerize readily into the thermodynamically more stable α- anomers 9. Introduction of ^{t}butoxy groups at phosphorus centre prevents anomerization $\beta \longrightarrow \alpha$. All glycosylation reactions described above proceed usually with almost quantitative yield.

Glycosylation of O,O-dialkyl phosphorotelluroates leads to the rather unstable glycosyl phosphorotelluroates 10 which are intermediates in the synthesis of alkyl telluroglucosides 11.[4e]



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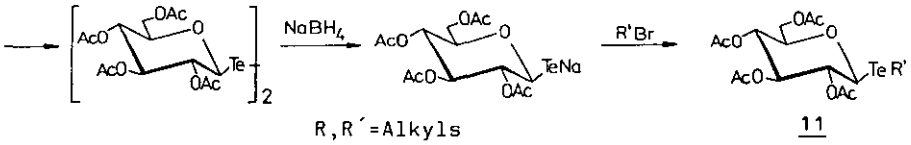


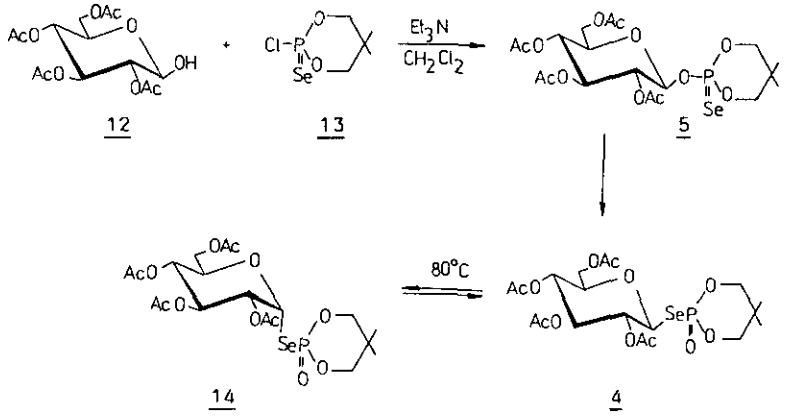
R,R´=Alkyls

11

From 1-OH sugars

O-Glycosyl phosphorothio- or selenoates 5, which are formed as minor products under kinetically controlled glycosylation reaction, are accessible in good yield from protected 1-OH monosaccharides by condensation with thio- or seleno-phosphorochloridates in the presence of a tertiary amine.

This reaction is illustrated by condensation of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose 12 with the selenophosphorochloridate 13.

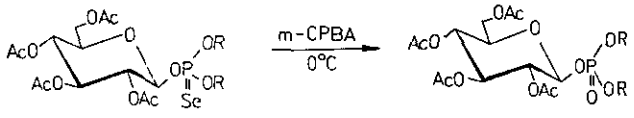


12 13 5 14 4

The selenoate 5 undergoes selenono-selenolo rearrangement >P(Se)OR ⟶ >P(O)SeR in boiling dichloromethane. The β-selenolophosphate 4 thus formed can further be isomerized in boiling benzene into its thermodynamically more stable α-anomer 14. The equilibrium is established in which the α-isomer 14 predominates. The same proportions of anomers were obtained when the pure 14 underwent equilibration.[4c]

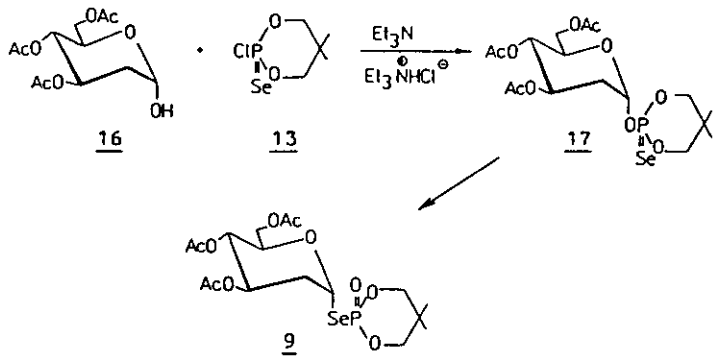
The analogous thiono-thiolo rearrangement requires more drastic conditions and anomerisation is not observed.

An interesting feature of glycosyl selenophosphates 5 is their easy quantitative oxidation into the corresponding phosphates 15 under very mild conditions.[4c]

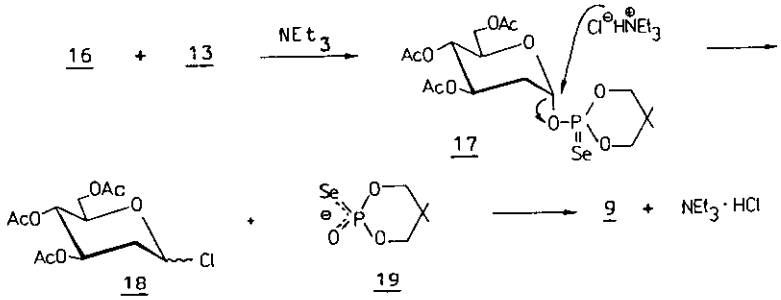


5 R=Alkyl 15

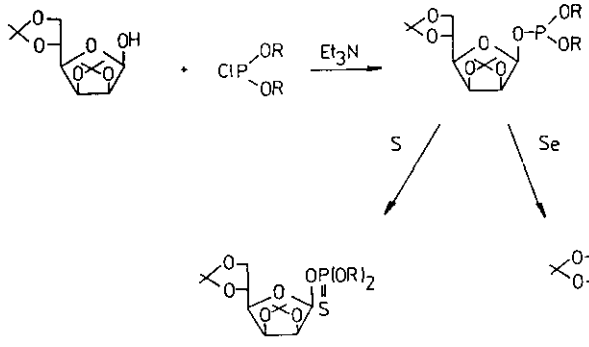
In the 2-deoxy series the selenono-selenolo isomerization proceeds so easily that the presence of the intermediate O-glycosyl phosphoroselenoate 17 can only be detected by spectroscopic methods (^{31}P nmr). The final reaction product of the reaction between the 3,4,6-tri-O-acetyl-2-deoxy-D-arabinohexopyranose 16 and selenophosphorochloridate 13 is the Se-(2-deoxyglycosyl) phosphoroselenoate 9 of α-configuration.



It has been demonstrated that the selenono-selenolo isomerization is catalyzed by the triethylammonium chloride formed during the condensation of 16 with 13. High concentration of 1-chloro-2-deoxyglucose 18 was found by ^{13}C nmr in the early stage of the reaction. The formation of the glycosyl chloride 18 is parallel with that of the selenoacid anion 19. These two intermediates react to give the selenophosphate 9. The formation of the glycosyl chloride 18 corroborates with the ability of sugar 1-thiophosphates to act as glycosyl donors.



Thiono- and selenophosphates can also be obtained, under very mild conditions, from 1-OH sugars by phosphitylation with O,O-dialkyl chlorophosphites and subsequent addition of elemental sulphur or selenium. This method, exemplified in Scheme 1 , is applicable to all sugars with a free 1-OH group.



Scheme 1

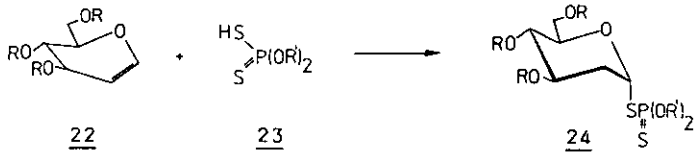
R=Alkyl

Free S(glycosyl) phosphorothioic acid and analogous Se(glycosyl)phosphoroselenoic acid 21 were obtained from the appropriate O,O-di-tert-butylphosphorothioate and selenoate 20.[4d,6] Removal of ^{t}butyl groups is best effected with boiling toluene for 5 min. or with catalytic amounts of trifluoroacetic acid in benzene, at ambient temperature.[6]

20 X=S,Se 21

From addition of phosphorodithioic and selenoic acids to 1,2-unsaturated sugars

Addition reactions to 1,2-unsaturated sugars are of interest as a way to a variety of 2-deoxysugar derivatives and in particular to glycosylating reagents. Addition of O,O-dialkylphosphorodithioic acids 23 to 3,4,6-tri-O-substituted D-glucal 22 proceeds smoothly in benzene at 20°C yielding the corresponding phosphorodithioates of α-configuration 24, in quantitative yield. The 1,2-unsaturated sugars derived from other D-hexoses and D-pentoses react in similar manner to give the α-adducts as predominant products readily separable from the β-isomers.

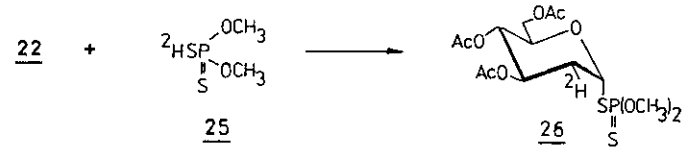


22 23 24

R = $COCH_3$; $CH_2C_6H_5$

R' = Alkyl

The stereochemical course of the addition is cis. This was demonstrated with the aid of S-deuteriophosphorodithioic acid which on addition to the unsaturated sugar 22 gave 26 with full stereoselectivity at both reactive centres (C-1 and C-2). The deuterium atom occupies the equatorial position and the dithiophosphate ligand the axial α-position.[7]



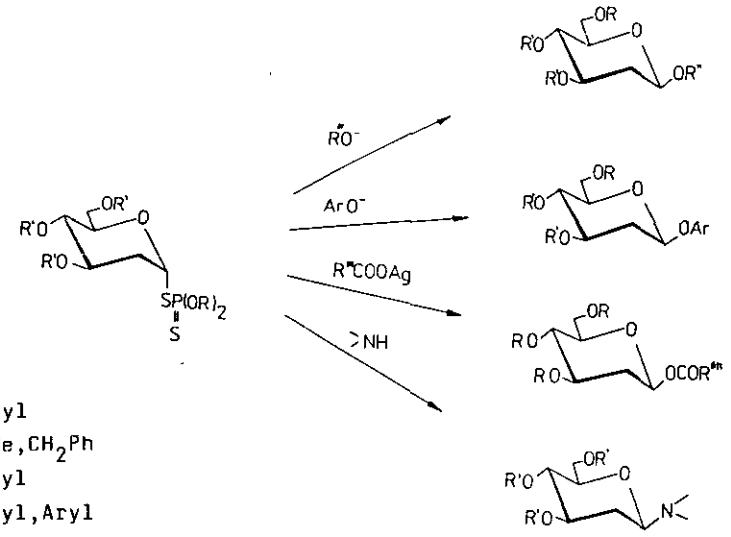
22 25 26

The procedure employed for the introduction of deuterium can easily be extended to the synthesis of tritium-labeled 2-deoxysugars.

2-Deoxyglycosyl dithiophosphates as glycosyl donors

The dithiophosphates 24 are stable, crystalline compounds which can be stored without decomposition. They represent a novel type of glycosylating reagents. It has been found that the dithiophosphoryl group at the anomeric centre of a 2-deoxysugar is a good leaving group in nucleophilic displacement. The substitution leading to 2-deoxyglycosides is a highly stereoselective process which most likely is a consequence of an S_N2 mechanism involved. Both β- and α-2-deoxyglycosides can be obtained by this procedure depending on the configuration of the dithiophosphate ligand at the anomeric centre of the glycosyl donor. This glycosylation method is particularly important as a route to difficultly accessible β-2-deoxyglycosides. High stereoselectivity with respect to β-glycosides is a consequence of mild reaction conditions and configurational stability of the glycosyl donor. Glycosylation of alcohols,[3a] phenols,[3c] carboxylic acids and amines proceeds at ambient temperature.

One of the most important applications of the dithiophosphates of 2-deoxysugars as glycosyl donors is the synthesis of disaccharide units containing the 2-deoxysugar residue. In a condensation reaction of the 2-deoxyglycosyl 1-dithiophosphate 24 with the appropriately protected monosaccharide in the presence of silver salts disaccharides are formed in good overall yield.



R=Alkyl
R'=COMe, CH_2Ph
R''=Alkyl
R'''=Alkyl, Aryl

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