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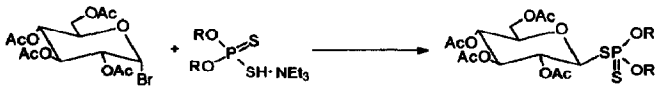
A Novel Synthesis of S-Glycosylphosphorodithioates

Wiesława Kudelska and Maria Michalska*

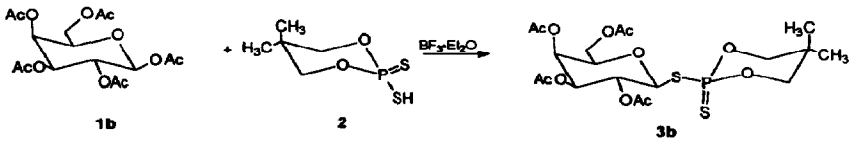
Laboratory of Organic Chemistry, Institute of Chemistry,
Medical University, Muszyńskiego 1, 90-151 Łódź, Poland

Abstract: Reaction of fully acetylated mono- and disaccharides with 0,0-dialkylphosphorodithioic acids in the presence of boron trifluoride etherate leads to the corresponding S-glycosylphosphorodithioates in high yield.

2-Deoxyglycosyl phosphorodithioates are excellent stereoselective glycosylating reagents in the 2-deoxy-sugar series.[1-8] They are readily available by the addition of O,O-dialkylphosphorodithioic acids to glycals.[4,9,10] We recently observed that O,O-dialkyl-S(peracetylglycosyl) phosphorodithioates of other sugars are also able to undergo nucleophilic substitution at anomeric centre.[11] This encouraged us to search for more convenient, general synthesis of these glycosyl donors. The only synthesis of these compounds used hitherto consisted of the reaction of glycosyl halides with O,O-dialkylphosphorodithioates.[12]This method is, however, limited by the availability of glycosyl halides and by their instability.

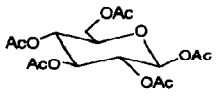
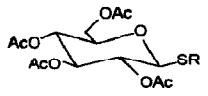
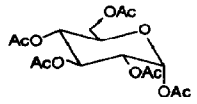
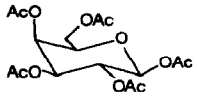
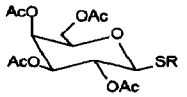
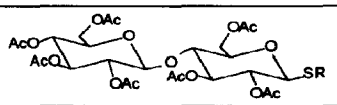
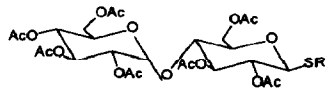
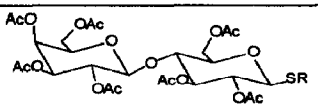
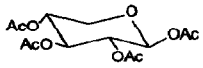
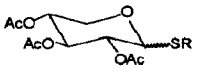
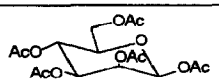
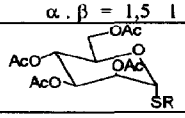
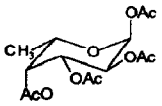
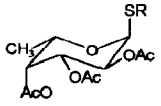
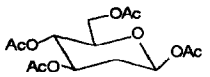
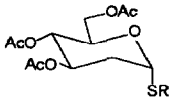
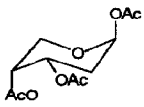
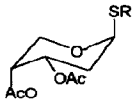


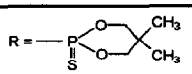
We discovered that fully acetylated sugars can be converted efficiently into S-glycosylphosphorodithioates by reaction with free O,O-dialkylphosphorodithioic acids in the presence of boron trifluoride etherate.[13] In this way the S-glycosylphosphorodithioates became available from easily accessible and stable acetylated mono and disaccharides.



1b 2 3b

Table. S-Glycosyl O,O-Dialkylphosphorodithioates Isolated (**3a - 3j**)

Entry	Substrates	**1a-1j**	Time	Products	**3a-3j**	δ ^{31}P NMR (ppm) ($CDCl_3$)
1		**1a** (β)	0,5h		**3a** (β)	83.98
2		**1a** (α)	48h	- | | -	**3a** (β)	83.98
3		**1b**	10min		**3b**	84 18
4	β - D - Cellobiose octaacetate	**1c**	24h		**3c**	83.69
5	β - D - Maltose octaacetate	**1d**	1h		**3d**	83 46
6	β - D - Lactose octaacetate	**1e**	24h		**3e**	83 69
7		**1f**	5h	 α . β = 1,5 1	**3f**	85.08 (α) 84 95 (β)
8		**1g**	24h		**3h**	84 92
9		**1h**	24h[18]		**3h**	84.92
10		**1i**	1 5h[19]		**3i**	83 70
11		**1j**	5min[20]		**3j**	87 64



All products showed spectroscopic and analytical data consistent with the assigned structure

The experimental procedure leading to S-(peracetylglycosyl) phosphorodithioates from peracetylated sugars is remarkably simple: Equimolar amounts of peracetylated mono or disaccharides and O,O-dialkyl-phosphorodithioic acid were dissolved in 1,2-dichloroethane. Reaction was carried out at ambient temperature in the presence of 1 - 5 equivalents of boron trifluoride etherate.[14] Monitoring by ^{31}P NMR enabled evaluation of the time necessary to accomplish the formation of glycosyl phosphorodithioates (see Table). After work-up [15] the crude material obtained in quantitative yield (according to ^{31}P NMR), was subjected to immediate ^{31}P, ^{13}C and ^{1}H NMR analysis. This revealed the stereochemical course of thiophosphorylation.

The general character of our new strategy is demonstrated by the variety of sugar components which were used in the synthesis of glycosyl phophorodithioates (see Table). This included the monosaccharides of the 2-deoxy series and disaccharides.

In the case of 1,2-trans acetates of fully acetylated hexo-pyranoses **1a - 1e** the reaction was stereospecific and afforded β-phosphorodithioates **3a - 3e** with retention of configuration at the anomeric centre This fact is atrributed to anchimeric assistance of the C-2 acetoxy group and formation of the intermediate acyloxonium cation However, the 1,2-trans arrangement did not secure stereospecificity in the case of xylopyranose tetracetate **1f**. In this case the reaction with the acid **2** led to a 1 5 : 1 mixture of anomers **3f**(α) and **3f**(β) due to facile anomerization of xylopyranose derivatives in the presence of boron trifluoride.[16]

The reactions of 1,2-cis-related peracetates of hexopyranoses **1a**(α) and **1g** proceeded stereospecifically, with inversion of configuration at the anomeric centre. This reaction is much slower than those of 1,2- trans-related isomers (e.g.: Entry 1 and 2). Also in this case vicinal participation of intermediate acyloxonium ion is postulated.

The reaction of deoxysugars (Entry 9, 10 and 11) with phosphorodithioic acid **2** was less stereoselective and led to a mixture of anomers. The α : β ratio observed under kinetic control is different from that observed on prolonged reaction time. The thermodynamically more stable axial isomer prevailed in this case and was easily isolated (Products **3h - 3j**).

Acknowledgements

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13. This reaction can be compared to that described by Ferrier and Furneaux for the synthesis of 1,2-trans- related-1-thioglycoside esters[17].
14. One equivalent of BF_3. Et_2O was employed in the case of substrates **1i** and **1j**, whereas in all other cases 5 equivalents were used.
15. The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution, water, dried ($MgSO_4$) and condensed *in vacuo*.
16. Erbing, B.; Lindberg, B. *Acta Chem. Scand. B*, **1976**, 30, 611-612
17. Ferrier, R.J.; Furneaux, R.H. *Carbohydr. Res.* **1976**, 52, 63-68.
18. In the case of α-L-fucose tetraacetate **1h** the reaction was completed within 10 min to yield the dithiophosphates as (α · β) mixture in 4 · 15 ratio. After 24 h the α : β ratio has changed to 12 · 3, respectively.
19. In the case of 2-deoxy-β-D-*arabino*hexopyranose tetraacetate, **1i**, the reaction with the acid **2** was accomplished within 10 min to yield **3i** as a (α : β) mixture in 4 :1 ratio which after 1.5 h showed only traces of the β anomer.
20. The 2-deoxy-β-D-ribose-triacetate **1j** gave after 5 min quantitative yield of **3j** as (α . β) mixture in 7 . 2 ratio , from which the axial anomer was easily isolated. In the latter case prolonging of the reaction time caused decomposition of the products

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