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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 2473–2476

A novel and practical synthesis of *S*-(1- and 2-halogenoalkyl)sugars by reaction of carbohydrate *S*-(*O*,*O*-dialkyl)phosphorodithioates and monothioates with fluoride anion

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Received 27 November 2003; revised 16 December 2003; accepted 23 December 2003

Abstract—A useful synthesis has been developed of *S*-(1- and 2-halogenoalkyl)sugars in high yield and purity. Readily available sugar *S*-(*O*,*O*-dialkyl)phosphorodithioates undergo S–P bond rupture on reaction with fluoride ions to yield the corresponding sugar thiolates, which further react in situ with dichloromethane or 1,2-dihalogenoalkanes in the reaction medium. In this reaction, the halogenoalkanes play the role of both reactants and solvents.

Intense investigation in the field of glycoproteins[1a–g] has demonstrated the involvement of sugar moieties in many crucial biological processes occurring on the surface of cell membranes. This is connected, in the broadest sense, with cell adhesion phenomena. Although ubiquitous in living organisms, native glycoproteins are not easily available as individual species for biological and structural investigations due to low bioavailability and instability towards chemical and enzymatic hydrolysis. To understand better the contribution of carbohydrates to biological function it is necessary to use synthetic glycoproteins of well-defined structure, isosteric with native ones in their stereochemistry and comparable in biological activity. The obvious approach to achieve this goal was the replacement of the innate C–O and C–N glycosidic linkages by their *S*-analogues. Such structurally modified neoglycoproteins are expected to show enhanced stability of the glycosidic linkage and resistance to enzymatic hydrolysis.[2] Thioglycosides containing a functionalized 'spacer arm' are best suited for condensation with peptide OH, NH_2 or SH groups. The length of the 'spacer arm' is very important. If it is too short, the arm is ineffective and the ligand fails to bind substances in the sample. If it is too long, nonspecific effects become pronounced and reduce the selectivity of separation. Very long 'spacer arms' can bind substances in the sample by hydrophobic interactions.[3] Thioglycosides with a short 'spacer arm' of the general formula: GlSR, where $R = CH_2CN$,[4] CH_2R,[5] CH_2CH_2X[6a] have proved to be suitable as carbohydrate ligands for the preparation of different types of glycoconjugates, in particular neoglycoproteins and affinity adsorbents. Thioglycosides of type $GlSCH_2CH_2X$ ($X = Cl$, Br) derived from glucose and galactose have been obtained by Cerny et al.[6a] and employed in the synthesis of neoglycoproteins.[6b] The intermediate thiols used in this procedure were obtained by a multistep synthesis from the corresponding glycosyl bromides by condensation with thiourea and subsequent hydrolysis of the isothiouronium salt thus formed. We reckoned that it would be of some interest to create the link between the protein and the sugar other than at the glycosidic position.

In this paper we describe a novel, general synthesis of *S*-(2-halogenoalkyl)sugars including some at the anomeric centre. The synthesis consists of reactions of sugar *S*-(*O*,*O*-dialkyl)phosphorodithioates at various positions in the carbohydrate ring, with fluoride anions, employing halogenoalkanes as solvents.

Our previous studies demonstrated the versatile character of readily available *S*-(*O*,*O*-dialkyl)phosphorodithioates as functionalizing reagents for carbohydrates. Their manifold applicability in synthetic carbohydrate chemistry depends on two alternative modes of bond breaking under the influence of nucleophilic reagents. Either the C–S bond between the sugar moiety and the

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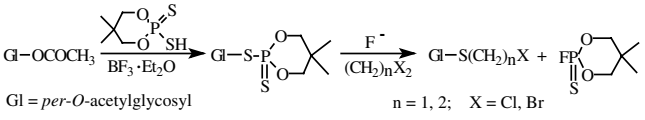
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.12.155

dithiophosphate group or the S–P bond undergo splitting depending on the type of sugar, the kind of nucleophile and/or ligands at phosphorus.[7] C–S Bond fission is responsible for the glycosylating properties of glycosyl *S*-phosphorodithioates. The latter proved to be highly stereoselective glycosyl donors, in particular in the 2-deoxysugar series, for alcohols,[8] including sugar alcohols,[9a–c] aliphatic[10] and heterocyclic amines,[11] carboxylic[12] and phosphorus acids.[13] 1-*O*-Acyl esters,[14] *O*-glycosides[15] and *C*-glycosides[16a,b] in the fully hydroxylated sugar series were also synthesized by this methodology. Base-catalyzed S–P bond breaking, which occurs in β-hydroxyphosphorodithioate systems and involves S → O transphosphorylation followed by elimination of phosphoromonothioate leads (depending on the reaction conditions) to sulfur-containing sugar derivatives such as episulfides,[17a,b] disulfides,[18] thiols[19] and oxathiaphospholanes.[20] S–P Bond breaking may also occur by the attack of fluoride anion due to the high affinity of fluorine towards phosphorus.[22] We decided to explore this fact by using sugar *S*-phosphorodithioates as easily accessible starting materials for sugar thiols. This idea was first evaluated on glycosyl *S*-phosphorodithioates using methylene chloride or ethylene chloride as solvents of choice. To our satisfaction the in situ generated glycosyl thiolate underwent condensation with the respective chloroalkane to give the *S*-(halogenoalkyl)thioglycoside[23] in quantitative yield (according to ^{31}P NMR). Thioglycosides of the type: Gl–SCH_2CH_2X, where Gl = glucose or galactose residues and X = Cl, Br, have been previously obtained in a different way.[6a] Our approach is simple and preparatively convenient. The methodology consists of two steps starting from duly protected sugars. The reaction course is shown in Scheme 1.



Scheme 1.

The fluoridothionate is easily removed by extraction with *n*-hexane. Both glycosyl *S*-phosphorodithioates and monothioates can be used as substrates for glycosyl thiolates. Monothioates react more quickly due to higher electrophilicity of the phosphoryl group in comparison with the thiophosphoryl group. We examined various sources of fluoride ions such as the macroreticular Amberlyst A-26 (F^-) resin, tetrabutylammonium fluoride (TBAF) and caesium fluoride. We found the best reaction when using Amberlyst A-26 (F^-) resin. Interestingly, the synthesis in chlorinated solvents ($ClCH_2Cl$, $ClCH_2CH_2Cl$) proceeded faster than in 1,2-dibromoethane. The yields were almost quantitative in the case of glycosidic derivatives. The reaction is highly stereoselective, the thioglycosides obtained having the same configuration at the anomeric centre as the starting phosphorodithioates (with the exception of lactose derivatives which were obtained as α,β mixtures). The general character of our synthetic procedure was demonstrated on models containing the dithiophosphate grouping in positions other than the glycosidic position (see Fig. 1).

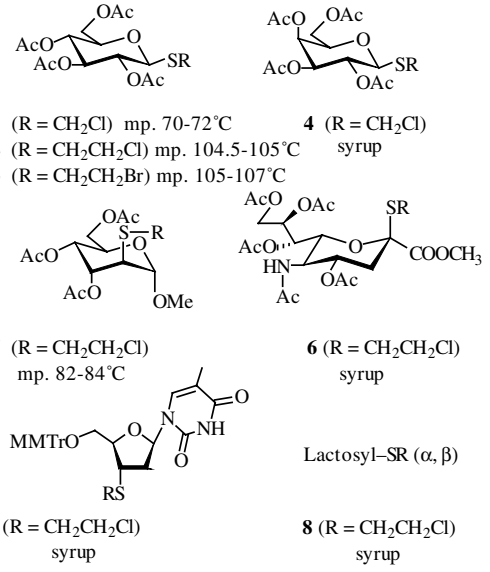
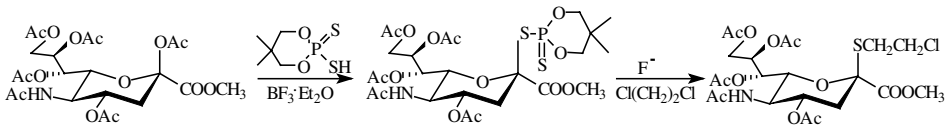


Figure 1. Structures of *S*-(1- and 2-halogenoalkyl) derivatives of sugar thiols.

Derivatives of sialic acid and thymidine are of special interest because of their pronounced biological properties. Naturally occurring sialic acid derivatives are most commonly found as terminal sugar constituents on cell surface glycoconjugates involved in many physiological phenomena. Thioglycosides of sialic acids are valuable not only as glycosyl donors, but also as biological probes and potential inhibitors of sialic acid recognizing proteins due to resistance to enzymatic degradation.[24] The synthesis of the anomerically pure *S*-glycoside of sialic acid ran into problems at the *S*-dithiophosphate stage. Four different routes for the introduction of the *S*-dithiophosphate group into the anomeric centre were examined. These routes consisted of: (a) addition of free phosphorodithioic acid to 2,3-eno sialic acid methyl ester, (b) reaction of peracetylated sialyl chloride with ammonium phosphorodithioic acid, (c) reaction of peracetylated sialyl chloride with trimethylsilyl phosphorodithioic acid and (d) reaction of penta-*O*-acetyl sialic acid methyl ester with free phosphorodithioic acid catalyzed by boron trifluoride etherate. The most successful, in terms of yield and stereoselectivity, proved to be route (d).[21] In this case only one anomer of the 2-*S*-phosphorodithioate of tetra-*O*-acetyl sialic acid methyl ester was produced, which was subsequently transformed into the desired *S*-(2-chloroethyl)glycoside **6** (Scheme 2).

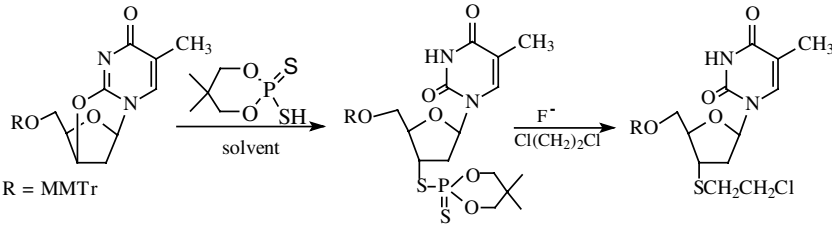
The therapeutic properties of some 3′-modified nucleosides turned our attention towards thymidine. Thus, compound **7** was synthesized via the respective 3′-*S*-phosphorodithioate obtained by our recently published procedure.[25,26] (Scheme 3).

All the reactions discussed above were performed at room temperature and were complete in ca. 3 h. How-



6

Scheme 2.



7

Scheme 3.

ever the reaction leading to compound **5**, required a considerably longer time for completion, presumably due to steric factors.

In a typical procedure, to a mixture of 1 equiv (1 mmol) of sugar *S*-(*O*,*O*-dialkyl)phosphorodithioate and 1.5 equiv of Amberlyst A-26 F^- resin (dried in vacuo at 80 °C for 48 h) freshly distilled dihalogenoalkane was added (ca. 10 mL) and the mixture stirred at ambient temperature. The reaction was monitored by ^{31}P NMR and TLC [plates were eluted using benzene/acetone/chloroform (3:1:1)]; detection of spots was effected with iodine vapour]. The resin was filtered off, the solvent evaporated in vacuo and the phosphorus-containing product removed by extraction with *n*-hexane (3×25 mL) from the semi-crystalline residue. The crude product was purified by crystallization or by silica gel chromatography (Table 1).

In conclusion, this synthesis of *S*-glycosides and *S*-substituted sugar thiols is simple, efficient and based on easily accessible starting materials. Our approach provides new opportunities to construct thioglycosides with an appropriately modified 'spacer arm', which could be exploited in affinity chromatography, the synthesis of carbohydrate-containing dendrimers,[27a–c] and solid-state oligosaccharide synthesis.[28] It also offers potential for structural modification of antibiotics containing sulfhydryl groups in the sugar ring. Unlike other methods of S–P bond breaking by nucleophiles,[18] the reaction of sugar *S*-phosphorothio- and dithioates with fluoride anions proceeds without deprotection of the sugar *O*-acetyl groups and without the need to isolate intermediate thiosugars. Extension of this strategy to derivatives of 2-deoxysugars is under investigation.

Table 1. Selected ^{13}C NMR ($CDCl_3$) data for compounds **1**–**8** (ppm)

Entry	$-CH_2X$	$-SCH_2-$	C-1	$-CH_2-$
1	45.22	—	82.95	61.64
2	43.28	32.55	83.80	62.00
3	32.55	30.62	83.84	62.00
4	45.42	—	81.67	61.36
5	42.52	34.44	101.22	62.39
6	42.56	30.82	C-2 84.79	C-3′ 37.06 C-9 62.63
7	43.07	33.84	80.73	C-2′ 40.83
8	43.71	32.72 32.62 (α,β)	Gal 101.02 Gl 84.83	C-6 61.77 61.13

Acknowledgements

We are indebted to Professor Andrzej Wróblewski for his kind interest and support. Thanks are also due to Mr. January Pluskowski for skilful technical assistance.

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