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THE EFFECT OF SUBSTITUENTS AT THE SULFUR ATOM ON THE GLYCOSYLATING ACTIVITY OF D-GLUCOSE THIOORTHOESTERS

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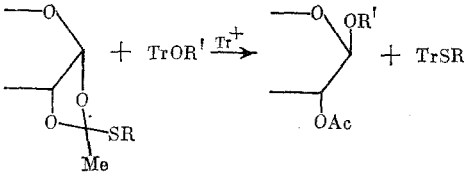
In our previous work [1-3], we showed that the 1,2-thioorthoesters of sugars are efficient and stereospecific glycoslyating agents in the synthesis of 1,2-trans-glycosides



The glycosylation by 1,2-thioorthoesters is accompanied by a side reaction involving the isomerization of the starting thioorthoesters to thioglycosides. This side reaction hinders the glycosylation of trityl ethers which have low activity [2] and the preparation of high-molecular-mass polysaccharides from sugar 1,2-thioorthoester monomers [4].

In our earlier work [2], we proposed a mechanism for glycosylation by thioorthoesters an and showed that the major contribution to the formation of thioglycosides is made by reaction (3), i.e., the reaction of sulfonium and/or acyloxonium ions with the starting thioorthoester.

This mechanism implies that the ratio of O- and S-glycosides formed in the reaction depends on the relative rates of reactions (2) and (3) [or of reactions (2) and (4)] (see top of next page). In addition to our previous procedure [2] which permits us to reduce the relative rate of reaction (3) and thereby increase the yield of the desired O-glycoside, the effect of the nature of the substituent at the sulfur atom should affect the ratio of the rates of reactions (2) and (3). A decrease in the nucleophilicity of the sulfur atom is required to reduce the rate of reaction (3). This may be achieved by the introduction of an electron-withdrawing substituent. The rate of reaction (3) may also be reduced by increasing the steric hindrance by the introduction of bulky substituents. The reaction of a series of D-glucose thioorthoesters (I)-(IX) with trityl ether (X) was studied in order to follow the effect of both factors on the glycosylating activity of thioorthoesters. Ether

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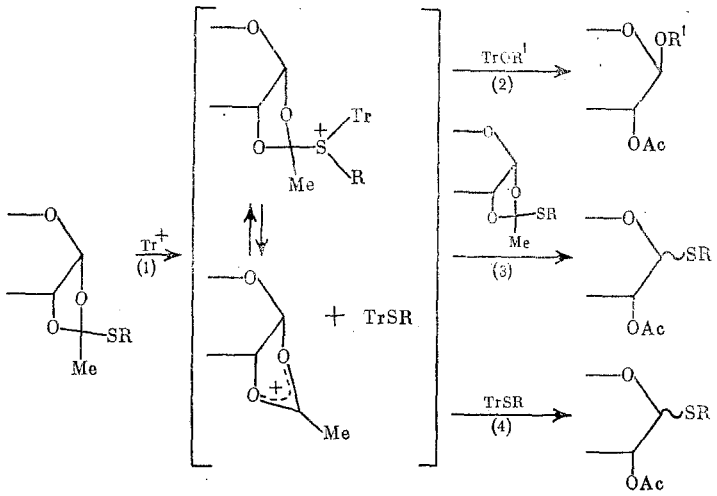
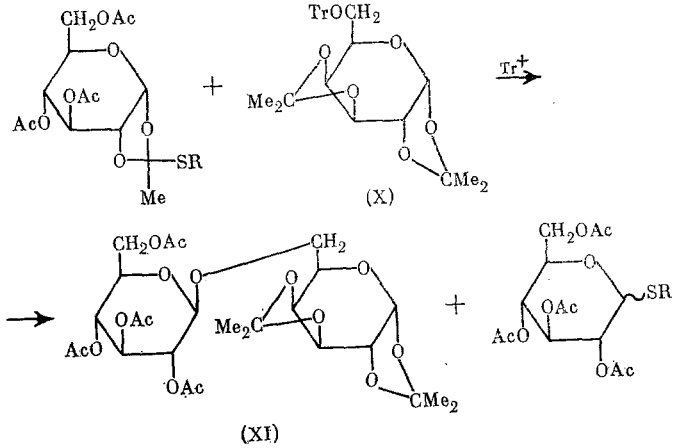


(X) was selected as the aglycone component for convenience in analyzing the reaction mixtures by gas-liquid chromatography.



(XI)

R = *m*-ClC_6H_4(I); *p*-ClC_6H_4(II); Ph(III); *p*-$MeOC_6H_4$(IV); *p*-MeC_6H_4(V); Bn(VI); Et(VII); cyclohexyl (VIII); *t*-Bu(IX).

The nucleophilicity of the sulfur atom in thioorthoresters which may be correlated with the acidity of the corresponding thiols should increase consecutively in the series (I)-(IX) in accord with the decrease in the acidity of the precursor thiols (the acidity of m-ClC_6H_4SH, for example, is more than five orders of magnitude greater than that of t-BuSH). Thus, for thioorthoesters beginning with (VII) (R = Et) and proceeding to (I) (R = m-ClC_6H_4), a decrease in the rate of reaction (3) may be expected, i.e., a decrease in the yield of the thioglycosides and increase in the yield of disaccharide (XI). On the other hand, despite the increasing nucleophilicity of the sulfur atom in the series (VII), (VIII), and (IX), we should also expect a decrease in the rate of reaction (3) due to an increase in the steric hindrance in going from a primary group to secondary and tertiary substituents.

The synthesis of thioorthoesters (I)-(IV), (VI), (VIII), and (IX) was carried out using the standard method of the reaction of the acetobromoglucose with thiols in the presence of 2,6-lutidine [1-4]. The PMR spectra in the case of aromatic thiols indicate that the thioorthoesters formed are mixtures of endo and exo C—Me isomers with the predominance of the endo forms. The isomer ratios found by integration of the C—Me group signals are given in Table 1. The pure endo isomers were isolated by column chromatography. In the case of aliphatic thiols, virtually pure endo C—Me isomers are formed. The PMR spectral data for the endo isomers of the thioorthoesters synthesized are given in Table 1.

The glycosylation reaction was carried out with a 1:1.1:0.1 ratio of the thioorthoester, trityl ether, and triphenylmethylium perchlorate by the addition of a solution of $TrClO_4$ to a mixture of the thioorthoester and trityl ether (X), i.e., under conditions giving competition of reactions (2) and (3).

The glycosylation was carried out using vacuum technique to achieve greatest standardization of the conditions. To check reproducibility, the glycosylation by each thioorthoester

TABLE 1. PMR Spectral Data for endo-C—Me Isomers of D-Glucose Thioorthoesters

Thiorthoester	CCH_3 endo	CCH_3 exo	endo:exo	CH_3CO	H^1 (J, Hz)	Other signals
(I)	1,80	1,65	13 : 1	2,07×2 2,13	5,77(5)	7,23–7,56 m (4H, Ar)
(II)	1,75	1,59	6,4 : 1	2,03×2, 2,09	5,72(5)	7,17 d, 7,41 d (J=8Hz), 4H, Ar)
(III)	1,74	1,56	3,6 : 1	1,98, 2,00 2,07	5,64(5)	7,05–7,35 m (5H, Ph)
(IV)	1,73	1,54	2,1 : 1	1,98×2, 2,07	5,58(5)	3,73 s (3H, OCH_3), 6,74 d, 7,33 d (J=8,5 Hz, 4H, Ar)
(VI)	1,81	–	–	2,01, 2,05×2	5,51(5)	3,74 s (2H, SCH_2Ph), 7,21 s (5H, Ph)
(VIII)	1,96	–	–	2,07×2 2,10	5,66(5)	1,27–1,57 m (10H, cyclohexyl)
(IX)	1,99	–	–	2,03, 2,06 2,08	5,56(5)	1,38 s (9H, t-Bu)

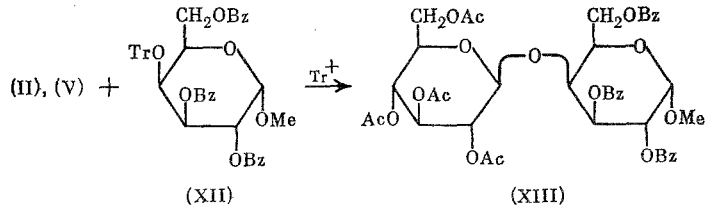
was carried out in three parallel runs. The glycosylation products were studied by gas-liquid chromatography using authentic samples of disaccharide (XI) and the corresponding thioglycosides. The quantitative analysis was carried out using sucrose octaacetate as the internal standard. The scatter in the yields of glycoside (XI) and of the thioglucosides found in each of the three parallel runs did not exceed 3-4%. The mean yields of the glycosylation products and the pK_a values for the corresponding thiols are given in Table 2.

These data support our hypothesis that the fraction of thioglycosides in the reaction products decreases while the fraction of the desired disaccharide (XI) increases with decreasing nucleophilicity of the sulfur atom in the starting thioorthoester (i.e., for a decrease in the pK_a value of the precursor thiol).

On the other hand, an increase in steric hindrance at the sulfur atom leads to virtually no increase in the yield of disaccharide (XI) [see the results for the glycosylation of thioorthoesters (VII)-(IX)], i.e., has no effect on the ratio of the rates of reactions (2) and (3), apparently since the steric hindrance produced by the substituents studied is not significant for the sulfur atom which has a large covalent radius.

As shown previously [2], the glycosylation of trityl ether (XII) by thioorthoester (VII) even under conditions excluding reaction (3) gives disaccharide (XIII) only in trace amounts This was explained by the predominance of reaction (4).

The relative rate of both reaction (4) and reaction (3) should decrease with increasing acidity of the precursor thiols since this should decrease the nucleophilicity of the sulfur atom in TrSR. Indeed, the glycosylation of (XII) by thioorthoesters (V) and (II) under conditions giving competition of reactions (2) and (4) [the addition of a solution of the thioorthoester to a mixture of (XII) and $TrClO_4$] [2] gives disaccharide (XIII) in 26 and 36% yields, respectively.



(XII) (XIII)

These results indicate aromatic thioorthoesters (I) and (II) with electron-withdrawing substituents in the phenyl ring as the most efficient glycosylating agents. The use of these agents permits the glycosylation of relatively inactive trityl ethers.

TABLE 2. Effect of the Sulfur Atom Substituent on the Glycosylating Activity of Thioorthoesters and pK_a Values of the Corresponding Thiols

R	Yield, %		pK_aRSH
	(XI)	thioglucoside	
m-ClC_6H_4	71	2,5	5,78 [5]
p-ClC_6H_4	69	4	6,14 [5]
Ph	64	17	6,62 [5]
p-$MeOC_6H_4$	56	19	6,78 [5]
p-MeC_6H_4	56	24	6,82 [5]
Bn	46	42	9,49 [6]
Et	27	72	10,61 [7]
Cyclohexyl	30	60	10,86 [7]*
t-Bu	22	75	11,12 [7]

*The literature lacks data on the acidity of cyclohexanethiol and the pK_a value for i-PrSH, which is a secondary thiol with similar structure, is given

EXPERIMENTAL

The melting points were taken on a Köfler block. The optical rotation was found using a Perkin-Elmer 141 polarimeter at 20 ± 2°C in $CHCl_3$. The PMR spectra were taken on Tesla BS-497 spectrometer at 100 MHz and on a Varian DA-60-IL spectrometer at 60 MHz with HMDS as the internal standard. The gas-liquid chromatography was taken on a Pye-Unicam 105 spectrometer using a 1-m-long glass column packed with 5% SE-30 on Chromaton N-AW-DMCS and nitrogen carrier gas. The column chromatography was carried out on Silica Gel L 100/250 μm (produced in Czechoslovakia) in a gradient of ether or ethyl acetate (EA) in benzene. Acetonitrile was distilled over P_2O_5 and then over CaH_2. Methylene chloride was washed with conc. H_2SO_4, water, and sat. aq. $NaHCO_3$, dried over $CaCl_2$, and distilled over CaH_2. The solutions were evaporated in vacuum at 40°C.

General Method for the Synthesis of Thioorthoesters. A sample of 1.36 ml (12 mmoles) 2,6-lutidine and 11 mmoles thiol were added to a solution of 4.11 g (10 mmoles) acetobromoglucose in 10 ml acetonitrile. The mixture was maintained for 48 h at 20°C, diluted with 200 ml chloroform, and then washed with three 100-ml portions of water. The solvent was evaporated. Chromatography of the residue gave the endo C–Me isomers of the thiorthoesters.

1,2-O-(1-p-Chlorophenylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glycopyranose (II). This was obtained in 49% yield with mp 102-104° (from ether–pentane), $[\alpha]_D$+89° (0.9). Found: C, 50.61; H, 4.82; Cl, 7.46; S, 6.74%. Calculated for $C_{20}H_{23}ClO_9S$: C, 50.58; H, 4.88; Cl, 7.46; S, 6.75%.

1,2-O-(1-p-Phenylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glucopyranose (III). This was obtained in 42% yield with mp 98-99°C (from ether–hexane), $[\alpha]_D$+80.3° (C 1.4). Found: C, 54.17; H, 5.43; S, 6.90%. Calculated for $C_{20}H_{24}O_9S$: C, 54.54; H, 5.49; S, 7.28%.

1,2-O-(1-p-Methoxyphenylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glucopyranose (IV). This was obtained in 40% yield as a syrup which partially crystallizes, $[\alpha]_D$ +81.8° (C 1.8).

1,2-O-(1-Benzylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glucopyranose (VI). The reaction was carried out for 120 h to give the product in 54% yield, mp 84-85°C (from ether–hexane) $[\alpha]_D$ +17.5° (C 0.8). Found: C, 55.60; H, 5.77; S, 6.80%. Calculated for $C_{21}H_{26}O_9S$: C, 55.51; H, 5.77; S, 7.05%

1,2-O-(1-Cyclohexylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glucopyranose (VIII). The reaction was carried out for 72 h to give a 42% yield of the product, mp 121-123°C (from ether–hexane), $[\alpha]_D$ +25.2° (C 2,9). Found: C, 53.78; H, 7.09; S, 7.23%. Calculated for $C_{20}H_{30}O_9S$: C, 53.75; H, 6.77; S, 7.18%.

1,2-O-(1-tert-Butylthioethylidene)-3,4,6-tri-O-acetyl-α-D-glucopyranose (IX). The reaction was carried out for 14 days with a threefold excess of 2-methylpropane-2-thiol to give a

50% yield of the product with mp 91-92°C (from ether–hexane), $[\alpha]_D$ +17.1° (C 1). Found: C, 51.46; H, 6.89; S, 7.32%. Calculated for $C_{18}H_{28}O_9S$: C, 51.41; H, 6.71; S, 7.63%.

Reaction of Thioorthoesters (I)-(IX) with Trityl Ether (X). A solution of 0.25 mmole D-glucose thioorthoester and 138 mg (0.275 mmole) trityl ether (X) in 2 ml benzene was placed in one arm of a Y-shaped ampul and a solution of 8.6 mg (0.025 mmole) triphenylmethylium perchlorate in 0.25 ml $MeNO_2$ was placed in the other arm. The ampul was attached to a vacuum system at $\sim 10^{-3}$ mm and the contents were lyophilized. A sample of 2 ml benzene which had been twice redistilled in vacuum over CaH_2 was distilled into the arm with the thioorthoester and trityl ether and the contents were again lyophilized and dried for 2-3 h. A sample of 2 ml CH_2Cl which had been twice redistilled in vacuum over CaH_2 was then distilled into the ampul and the $TrClO_4$ solution was added in one batch to the mixture of thioorthoester and (X). The mixture was maintained for 30 min at 20°C, opened to the atmosphere, one drop of pyridine and 85 mg (0.125 mmole) sucrose octaacetate were added, and the mixture was diluted with 50 ml chloroform. The mixture was washed with two 50-ml portions of water and evaporated. The residue was subjected to gas-liquid chromatography. The yields of disaccharide (XI) and thioglucosides (see Table 2) for each of the thioorthoesters were determined as the mean of three parallel runs.

2,3,6-Tri-O-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-methyl-D-galactopyranoside (XIII). a) A solution of 230 mg (0.505 mmole) thioorthoester (V) in 6 ml CH_2Cl_2 was added dropwise over 30 min to a solution of 380 mg (0.51 mmole) trityl ether (XII) [2] and 70 mg (0.2 mmole) triphenylmethylium perchlorate in 4 ml chloromethane. Then 0.5 ml 3:1 pyridine–methanol was added and diluted with 50 ml chloroform. The mixture was washed with two 50-ml portions of water. The organic layer was evaporated and the residue subjected to chromatography to yield 110 mg (26%) (XIII) as a syrup with $[\alpha]_D$ +64.2° (C 1) ($[\alpha]_D$ +56.6° ($CHCl_3$) [8]).

b) By analogy, 380 mg (0.51 mmole) (XII) and 240 mg (0.505 mmole) thioorthoester (II) in the presence of 70 mg (0.2 mmole) triphenylmethylium perchlorate yielded 150 mg (36%) (XIII) as a syrup with $[\alpha]_D$ +62.5° (C 1.05).

CONCLUSIONS

1. Syntheses are reported for D-glucose 1,2-thioorthoesters with aromatic and aliphatic substituents at the sulfur atom.

2. The activity of the thioorthoesters in the glycosylation of the trityl ethers of sugars increases with increasing acidity of the precursor thiols.

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