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Preliminary communication

A new approach to 1-thioglycosides by lowering the nucleophilicity of sulfur through trialkylstannylation

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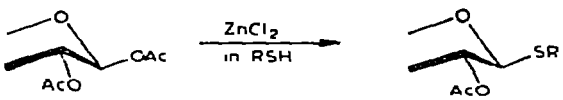
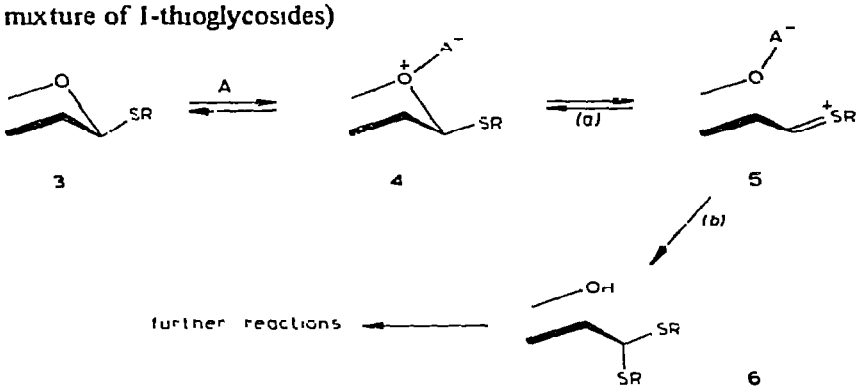
Among the established methods for the synthesis of 1-thioglycosides[1], transformation, catalyzed by zinc chloride, of 1,2-*trans*-glycosyl acetates (**1**) into 1,2-*trans*-1-thioglycosides (**2**) has been employed as an efficient procedure[2]. Several experiments[3] on this



1 **2**

type of transformation have, however, revealed that, in some cases, further introduction of sulfur into the molecule occurs, due to the high nucleophilicity of alkanethiols, hence restricting the versatility of this approach. Formation of the undesired dithioacetals (**6**) and their further transformation-products may result from the intermolecular reaction (*b*) of the carbosulfonium ion intermediate **5** with alkanethiol, instead of the intramolecular reaction (*a*) with the less nucleophilic oxygen function (which would lead back to the anomeric mixture of 1-thioglycosides).



3 **4** **5** **6**

(A = Lewis acid)

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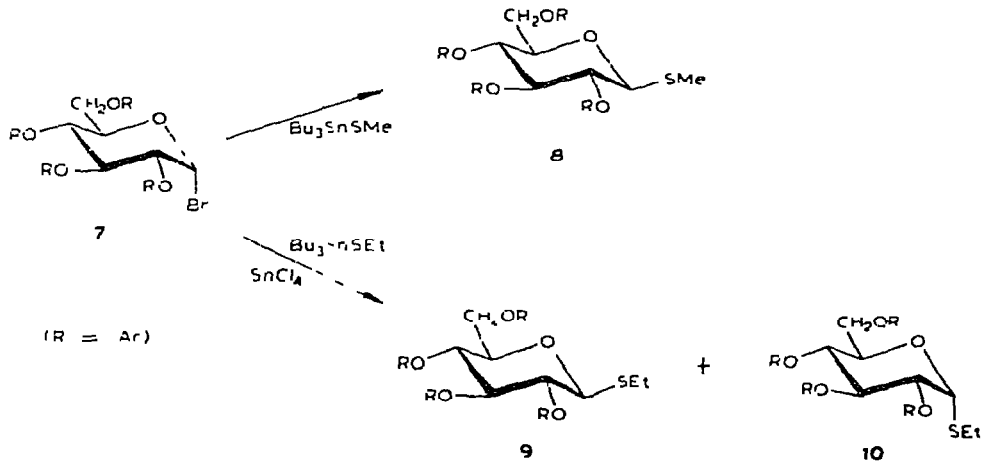
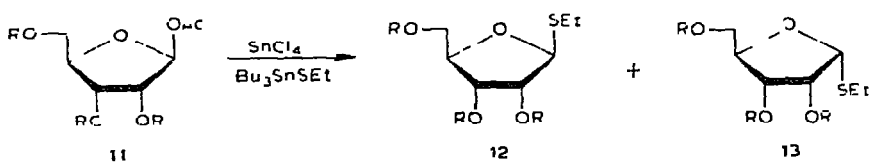
We report here a new approach to the synthesis of 1-thioglycosides, with modification of the nucleophilicity of the thiol group through its transformation into a tributylstannyl sulfide[4]. An equimolar mixture of tetra-*O*-acetyl-α-D-glucosyl bromide[5] (**7**) and methyl tributylstannyl sulfide[6] in 1,1,2,2-tetrachloroethane was heated at 100° to start the reaction, which, after 48 h, stereospecifically converted **7** into methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[7] (**8**) in 95% yield (45% conversion). It is to be noted that the transformation is also chemospecific (compared to the known reaction[8] of **7** with potassium thioxide, which attacks both the carbon atom bearing bromine and the carbon atom of the carbonyl group). Furthermore, the nucleophilicity of methyl tributylstannyl sulfide is shown to be lower than that of tributylstannyl methoxide, which requires a lower temperature[9] (60°) for reaction with **7**.



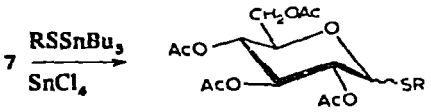
In an attempt to make this reaction proceed more satisfactorily, the reaction catalyzed by a Lewis acid was studied. Thus the reaction of **7** with ethyl tributylstannyl sulfide in the presence of an equimolar amount of stannic chloride at 15° gave ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[10] (**9**) and its α anomer[11] (**10**), in the ratio of 1 : 1, in 95% yield. Under essentially the same reaction-conditions, various 1-thioglucosides were prepared in high yields as shown in Table I.



The anomeric stereochemistry was assigned from the $[\alpha]_D$ value[12], and confirmed

TABLE I

REACTION[a] OF 7 WITH VARIOUS ALKYL TRIBUTYLSTANNYL SULFIDES



R	Anomer formed	Yield (%)	m.p (degrees)	$[\alpha]_D$ (degrees)[b]	Reaction time (hours)	Reaction temp (degrees)	References
Ph	β	90 (50)	116–118	-14.9	5	20	8a, 16
$PhCH_2$	β	68	88–90	-88.2	30	20	8b, 15
	α	17	syrup	+190.1			
Et	β	47	78–81	-22.1	23	15	10
	α	47	92–94	+190.3			11
Cyclohexyl	β	38	120–122	-20.1	24	15	15
	α	36	73–75	+186.9			
Me_3C	β	22	144–146	-8.6	24	25	18
	α	41	53–55	+165.9			

[a] All of the reactions were performed in dry 1,2-dichloroethane. The yield in parentheses is the percent of conversion. [b] In chloroform. All compounds for which $[\alpha]_D$ is recorded gave both an acceptable elemental analysis and reasonable p.m.r. data.

by p.m.r. data*, the β anomer shows signals at δ 4.29–4.81 (J 9–10 Hz) for H-1 and at δ 3.6–3.8 for H-5, and the α anomer shows signals at δ 5.53–5.93 (J 6 Hz) for H-1 and at δ 4.4–4.6 for H-5.

The formation of an anomeric mixture may be rationalized in terms of the anomerization of the initially formed β anomer into the α anomer under the reaction conditions. As, to the best of the authors' knowledge, there seems to be no precedent for the experimental demonstration of the anomerization of 1-thioglycosides, the following experiment was undertaken in order to evaluate the possibility of anomerization under the aforementioned conditions. Both the methyl 1-thio-β-D-glucoside 8 and its anomer, m.p.[8b] 104–106°, $[\alpha]_D$ +183.7° ($CHCl_3$), were treated with an equivalent amount of stannic chloride in 1,2-dichloroethane during 5 to 48 h at room temperature, to give the same ratio of anomers in the mixture, α:β = 2.5:1, thus demonstrating that the equilibrium between the anomers is in favor of the α anomer, in accordance with the anomeric effect[13].

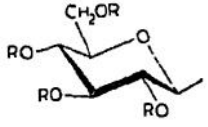
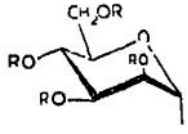
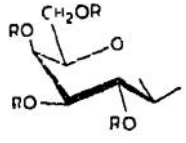
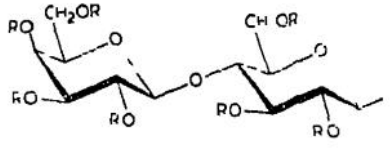
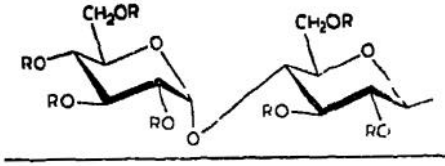
In contrast to the behavior of 7, the reaction of 1,2,3,4,6-penta-*O*-acetyl β-D-glucopyranose with methyl tributylstannyl sulfide in the presence of the stoichiometric amount of stannic chloride stereospecifically afforded methyl 1-thio-β-D-glucopyranoside (8). Other hexopyranosyl acetates examined also gave 1,2 *trans*-1-thioglycopyranosides in high yields, without recourse to chromatographic separation (see Table II).

*All p.m.r. data given in this paper were obtained for solutions in $CDCl_3$, with Me_4Si as the internal standard.

TABLE II

REACTION OF METHYL TRIBUTYLSTANNYL SULFIDE WITH VARIOUS PERACETYLATED MONO- AND DI SACCHARIDE

$$R'OAc + Bu_3SnSMe \xrightarrow[\text{in } ClCH_2CH_2Cl]{SnCl_4} R'SMe + Bu_3SnCl + SnCl_3OAc$$

R' (R = Ac)	*Yield (%)*	*m p (degrees)*	*$[\alpha]_D$ (degrees)*[a]	*Reaction time (hours)*	*Reaction temp (degrees)*	*Reference*
	85	83–85	−9 8	2 5	15	
	72	123–125	+93 1	30	20	
	91	109–111	+3 7	3 0	20	18
	60	124–125	−9 0	3 5	20	
	81	133–135	+56 0	3 5	20	

[a] In chloroform

This approach to 1-thioglycosides was also shown to be applicable to the (more-reactive) furanose derivatives[14] Thus, the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl acetate (**11**) with an equivalent amount of stannic chloride for 2 h at room temperature, followed by the addition of an equivalent amount of ethyl tributylstannyl sulfide for 2 h at −5° gave an 81% yield of a mixture of ethyl 2,3,5-tri-*O*-benzoyl-1-thio-β-D-ribofuranoside (**12**), $[\alpha]_D$ −14 3° ($CHCl_3$)[14] and its α anomer (**13**), $[\alpha]_D$ +84 3° ($CHCl_3$), in the ratio of 3 2

In conclusion, by employing alkyl tributylstannyl sulfides, we have developed a mild and efficient approach to 1-thioglycosides, which is further recommended both by its versatility and by the almost complete disappearance of the odor of the thiol during the operation

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