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NOVEL HIGHLY STEREOSPECIFIC METHOD OF 1,2-CIS-GLYCOSYLATION. SYNTHESIS OF α-D-GLUCOSYL-D-GLUCOSES

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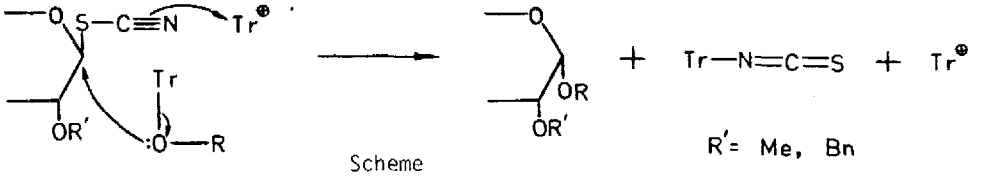
Abastract. Triphenylmethylium perchlorate-catalysed glycosylation of 2-, 3-, 4-, and 6-O-trityl-D-glucose derivatives with β-D-glucopyranosyl thiocyanates bearing a non-participating substituent at O-2 affords stereospecific derivatives of α-D-glucosyl-D-glucose

Creation of 1,2-cis-glycosidic linkages with a high degree of stereospecificity is one of central problems of synthetic carbohydrate chemistry and its solution, despite considerable progress[1], is far from being satisfactory and general. This produces well-known difficulties in the synthesis of oligosaccharides and makes impossible synthesis of regular polysaccharides with 1,2-cis-linkage between units by way of polycondensation.

The obvious prerequisites for 1,2-cis-stereospecific introduction of a nucleophile to C-1 of a pyranose ring are i) the absence of an anchimeric assistance by an acyl group so that a non-participating O-2-substituent must be employed and ii) realisation of an S_N2 mechanism of substitution or the S_N2-like one which can best be achieved in a concerted push-pull process. An appropriate leaving group should be employed which should be transformed in the course of the reaction so as to prevent competition with the original nucleophile.

Here we describe a novel glycosylation reaction which meets these demands, viz., glycosylation of trityl ethers as glycosyl-acceptors with 1-thiocyano sugars as glycosyl-donors in the presence of triphenylmethylium perchlorate. (Scheme)

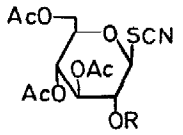


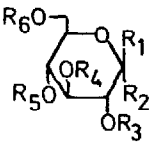
Scheme

Applicability of this novel glycosylation method is exemplified by the synthesis of α-D-glucosyl-D-glucoses with different linkage positions.

The glucosyl thiocyanate 1 and its 6-bromo-6-deoxy derivative have been described[2,3] but they have not found any synthetic application. Glucosyl thiocyanates 1-3 were prepared as follows: A solution of a protected glucosyl bromide (2 mmol), KSCN (6 mmol, dried at 110° for 2 h at 5 Torr), and 18-crown-6 (0.2 mmol) in dry acetone (8 mL) was stirred at room temperature for several hr (TLC control). Acetone was distilled off in vacuo at 30°, benzene was added to and distilled from the residue several times, and a solution of the residue in benzene was filtered through silica gel. The thiocyanates 1-3 were isolated by column chromatography on silica gel (benzene-ether) in 65-70% yields. Compounds 2, 3, and 1 (synthesised for pur-

poses of comparison) are relatively stable crystalline compounds[4] exhibiting in their IR-spectra ν_{SCN} 2160 cm^{-1} (cf. ν_{NCS} 2050-2080 cm^{-1} for isothiocyanates[2]). That they were β-anomers is indicated by $J_{1,2}$ values (9.5 Hz) in their ^{1}H-n.m.r. spectra, δ_{H-1} for 1, 2, and 3 being 4.90, 4.59, and 4.66.





1. R = Ac
2. R = Me
3. R = Bn

4. R^1 = H, R^2 = OMe, R^4=R^5=R^6= Ac, R^3 = Tr
5. R^1 = OMe, R^2 = H, R^3=R^5=R^6= Ac, R^4 = Tr
6. R^1 = OAc, R^2 = H, R^3=R^4=R^6= Ac, R^5 = Tr
7. R^1 = H, R^2 = OMe, R^3=R^4=R^5= Ac, R^6 = Tr

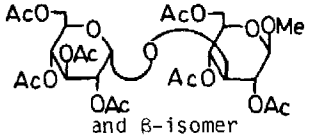
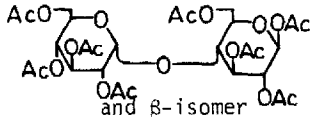
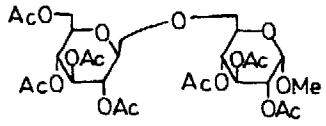
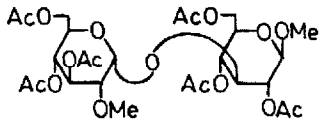
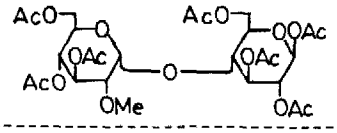
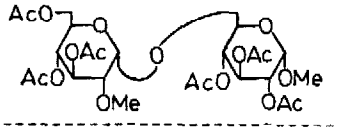
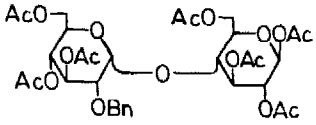
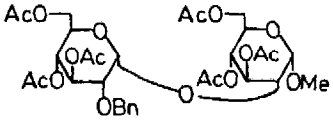
Glycosylations of the known trityl ethers 4 (ref. 5), 5 (ref. 6), 6 (ref. 7), and 7 (ref. 8) with glycosyl thiocyanates were run under standars conditions: a solution of a thiocyanate (0.2-0.3 mmol). trityl ether (0.2 mmol), and triphenylmethylium perchlorate (0.016-0.02 mmol) in dry dichloromethane (2-2.5 mL) was kept at room temperature for 1-2 hr, the course of the reaction being monitored by TLC. The reaction mixture was then treated with pyridine (1 drop), diluted with chloroform (30 mL), and washed with water (5 x 20 mL). The organic layer was concentrated to dryness and the residue was treated with acetic anhydride in pyridine (15 hr, 20°). Following conventional work-up the disaccharide derivatives obtained were isolated by column chromatography on silica gel (see Table 1).

As can be seen, thiocyanate 1 bearing a participating group at O-2 afforded a mixture of α- and β-linked disaccharides (entries 1,2) or only the β-isomer (entry 3). In contrast, with glycosyl thiocyanates 2 (entries 4-6) and 3 (entries 7,8) possessing non-participating substituent at O-2 the reactions were completely stereospecific and only 1,2-cis-linked disaccharides were obtained in moderate to good yields (not optimised). Even admixture of β-isomer could not be detected by n.m.r. of the disaccharide fraction and TLC. The structure of all disaccharides was proved by n.m.r. data (Bruker WM-250, $CDCl_3$) and correct elemental analyses.

The mechanism of the reaction can be represented as follows (Scheme). The concerted push-pull process is initiated when the triphenylmethylium ion attacks the nitrogen atom of a thiocyanate group. Simultaneous attack by the nucleophilic oxygen of the O-trityl group results in formation of a glycosidic bond (only rear-side approach is possible) to produce 1,2-cis-glycosidic bond from 1,2-trans-thiocyanate, regeneration of the triphenylmethylium ion, which continues the process, and liberation of trityl isothiocyanate which is not prone to act as a nucleophile. The yield of isothiocyanate was equivalent to that of disaccharide(s) formed, m.p. 138-139° (ether-hexane), ν2056, 2088 cm^{-1} (KBr pellet); ref.9, m.p. 138-138.5°, ν 2046 (chloroform).

Although sulfur-containing leaving groups were recently employed in glycosylation reactions[10,11], complete stereospecificity was not achieved when applied to 1,2-cis-glycosidic synthesis[11,12]. That the reaction is stereospecific in the present case seems to be due to realisation of a concerted, triphenylmethylium-catalysed process as is believed to take

Table I Properties of disaccharide derivatives

Entry	Reagents (molar ratio)		Yield %	^{13}C-n.m.r.(δ) C-1/C-1'	M.p. °C (solvent)	$[\alpha]_D$ ($CDCl_3$)
1	1 + 5 (1.3:1)	 and β-isomer	43.5	101.74 96.15	146-147 (ether)	+50.2° (c 1.18)
			36	101.83 101.06	178 (ether)	-41.8° (c 2.75)
2	1 + 6 (1.1:1)	 and β-isomer	28	91.38 95.84	159-160 (ethanol)	+64.0° (c 1)
			43	91.89 100.69	198-200 (ethanol)	-12.2° (c 2.6)
3	1 + 7 (1 : 1)		65	96.53 100.99	94-96 (ethanol)	+62.4° (c 2)
4	2 + 5 (1.5 : 1)		77[a]	101.73 98.74	147 (ethanol)	+49.5° (c 1.14)
5	2 + 6 (1.5 : 1)		82.5[b]	91.57 98.54	179-180 (ethanol)	+54.8° (c 1.6)
6	2 + 7 (1.3 : 1)		77.5	96.41 96.03	138-139 (ether-hexane)	+146.6° (c 2)
7	3 + 6 (1.5 : 1)		77[c]	91.86 98.46	syrup	+33.3° (c 3.75)
8	3 + 4 (1.5 : 1)		55[d]	97.76 97.76	syrup	+127.0° (c 4.5)

[a] δ_{H-1} 4.29, $J_{1,2}$ 8 Hz; $\delta_{H-1'}$ 5.02, $J_{1',2'}$ 3.5 Hz. [b] δ_{H-1} 5.72, $J_{1,2}$ 8 Hz; $\delta_{H-1'}$ 5.15, $J_{1',2'}$ 3.5 Hz. [c] δ_{H-1} 5.71, $J_{1,2}$ 8 Hz; [d] $\delta_{H-1'}$ 4.88, $J_{1',2'}$ 3.5 Hz.

[d] δ_{H-1} 4.90, $J_{1,2}$ 3.5 Hz; $\delta_{H-1'}$ 4.85, $J_{1',2'}$ 3.5 Hz.

place with trityl-cyanoethylidene condensation which affords 1,2-trans-glycosides[13].

The data obtained demonstrate that the use of glycosyl thiocyanates as new glycosylating agents opens good perspectives for stereospecific 1,2-cis-glycosylation. According to preliminary results, the method is applicable to other monosaccharides and seems to be of general character.

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4. 1, m.p. 132.5-133.5° (ether), $|\alpha|_D^{26}$ -22° (c 2, chloroform); ref.3, m.p. 132-133°, $|\alpha|_D$ -20.9° (chloroform); 2, m.p. 127° (ether-light petroleum), $|\alpha|_D^{26}$ -4.8° (c 1, chloroform); 3, m.p. 110-111° (ether), $|\alpha|_D^{28}$ +16.25° (c 1.6, chloroform).
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