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STEREOSELECTIVE SYNTHESES OF 1,2-**TRANS**-1-THIOGLYCOSES USING ALUMINIUM CHLORIDE: EVIDENCE FOR 1,2-**CIS**-1-CHLOROGLYCOPYRANOSYLPERACETATES AS THE ACTUAL REACTION INTERMEDIATES

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Abstract: Synthesis of 1,2-**trans**-1-thioglycosylacetates has been achieved in excellent yields from corresponding 1,2-**trans**-glycosylacetates using aluminium chloride **via** 1,2-**cis**-1-chloroglycopyranosylacetates with retention of configuration.

The synthesis[1] and biological activity,[2-5] of thioglycosides and thioglycosyl oligosaccharides have attracted attention in recent years. So far, nucleophilic substitution of glycosylhalides,[6-8] zinc chloride catalysed reaction of peracetylated sugar acetates with alkanethiols[9] or arylthiols[10] are the main synthetic strategies usually adopted for the synthesis of thioglycosides and thioglycoses. Recently introduced zirconium chloride method,[11] seems very attractive for the synthesis of 1-thioglycoses, but for longer reaction periods and excess amounts of catalyst required. We have tried to overcome these deficiencies in the existing methodology and report here an efficient method for the synthesis of 1,2-**trans**-1-thioglycoses using anhydrous aluminium chloride, an inexpensive Lewis acid, by reaction of thiolacetic acid with 1,2-**trans**-glycopyranosyl acetates in refluxing dichloromethane.

Typically, to anhydrous aluminium chloride (10 mmol) suspended in dry dichloromethane, thiolacetic acid (10 mmol) and 1,2-**trans**-glycopyranosylacetate (5 mmol) were added at room temperature. The reaction mixture was stirred at 50°C for 1-2 h with a provision to remove liberated hydrochloric acid. The mixture was poured onto ice-cold dilute hydrochloric acid solution and extracted with dichloromethane. The organic phase was successively washed with sodium bicarbonate solution and water. After drying and evaporation of solvent, the crude product was recrystallised from absolute alcohol (Table). The reaction takes 3-4 h at ambient temperature for completion.

Anhydrous aluminium chloride has been used by earlier workers,[12] for the synthesis of 1,2-**cis**-1-chloroglycopyranosyl tetraacetate as well as for its further alkylation[13]. The aluminium chloride catalysed thiolysis of glycopyranosylacetates appear to proceed faster with 1,2-**trans**, diequatorially related configurational isomers when compared with their 1,2-**cis**, axial-equatorial counterparts. When α-D-glucopyranose pentaacetate was refluxed for 20 h with thiolacetic acid and aluminium chloride, corresponding 1-S-acetyl-1-thio-β-D-glucopyranose tetraacetate in 40% yield was obtained. Reaction of α-D-mannose pentaacetate gave α:β anomeric mixture (6:4 by ^{1}H-NMR) of tetra-O-acetyl-1-S-acetyl-1-thiomannopyranoses in 82% yield after refluxing for 1 h together with a 10% yield of peracetyl α-D-mannopyranosyl chloride (mp 75°C, $[\alpha]_D^{25}$ + 92).

When β-D-glucopyranosyl pentaacetate was refluxed with aluminium chloride (1:1 moles) for 2 h, it yielded **cis**-1-chloroglucopyranosyl tetraacetate (90%, mp 75°C, $[\alpha]_D^{25}$ +166 When the same reaction was repeated at ambient temperature for 3 h, a mixture of α:β (6:4, 85% yield) 1-chloroglycopyranosyl tetraacetates were obtained. α-D-Glucopyranosyl pentaacetate yielded 1,2-**cis**-glucopyranosyl chloride (60%, 20 h). Since β-D-glucopyranosylpentaacetate had been shown to produce 1,2-**cis**-1-chloroglucopyranose tetraacetate on reaction with aluminium chloride, we envisage 1-chloroglycosylacetates formed **in situ** are the actual reaction intermediates in the reaction of β-D-glucopyranosyl pentaacetate and thiolacetic acid. Further, **cis**-1-chloro-glucopyranosyl tetraacetate has been isolated and characterised by ^{1}H-NMR when the reaction of β-D-glucopyranose pentaacetate with thiolacetic acid in presence of aluminium chloride stirred at room temperature for 30 min and worked up before completion of the reaction. That 1-chloroglycopyranosyl acetates are the actual reaction intermediates has been confirmed when 1,2-**cis**-1-chloroglucopyranose tetraacetate[14] (10 mmol) was refluxed with thiolacetic acid (20 mmol), aluminium chloride (10 mmol) and dichloroaluminium acetate[15] (10 mmol) for 2 h, yielded β-D-1-thioglycosylpentaacetate (80%).

Lemieux and Brice[16] have proposed a displacement mechanism for the mercaptolysis of 1,2-**trans**-glycopyranosyl acetates involving 1,2-cyclic acyloxonium ion by an anchimeric assistance of C_2 acetate. The formation of **cis**-1-chloroglycopyranosyl acetates as described (scheme), assumes that the acetylated aldose would undergo initial chlorination to yield 1,2-**trans**-halide which, in presence of dichloroaluminium acetate anomerises to more stable 1,2-**cis**-halide. By analogy of reaction between titanium tetrachloride and 1,2-**trans**-glycosylperacetates,[17] we assume a similar 1:1 complex formation between 1,2-**trans**-glycosyl acetate and aluminium chloride, which decomposes when ice-cold water is added but anomerises rapidly at refluxing temperature. 1,2-**cis**-halide thus formed would then react with aluminium salt of thiolacetic acid **via** acyloxonium ion (scheme) to yield 1,2-**trans**-1-thioglycosylacetate. Since the overall reaction of 1,2-**trans**-glycosylperacetates require 2 moles of aluminium chloride and actual identification of glycopyranosyl chlorides has been demonstrated, it is apparent that the above reaction proceeds as envisaged with the double inversion and hence retention of the configuration.

Table: Yields and physical constants of per-O-acetylated 1-S-acetyl-1-thioglycopyranoses.

Entry	Per-O-acetyl 1-S-acetyl-1-thioglycopyranoses	% yield[a,b]	m.p.,°C		$[\alpha]_D^{25}$ (C 1, chloroform)	
			Found	Reported	Found	Reported
1.	β-D-glucopyranose	88	114-115	115-116	+11.0	+10.5
2.	α-D-glucopyranose	40	114-115	115-116	+10.0	+10.5
3.	β-D-xylopyranose	89	95-97	99-103	-7.0	-7.7
4.	α-D-mannopyranose[c]	82	syrup	-	-	-
5.	β-D-galactopyranose	84	112-113	115-116	+32	+31.3

a) Yields are based on recovery after first recrystallisation.
b) All the products were characterised by I.R., H-NMR and GC-MS.
c) Product obtained as determined ^{1}H-NMR is a 6:4 mixture of α:β anomers.

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