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A FACILE, ONE-STEP PROCEDURE FOR THE CONVERSION OF 2-(TRIMETHYLSILYL)ETHYL GLYCOSIDES TO THEIR GLYCOSYL CHLORIDES*

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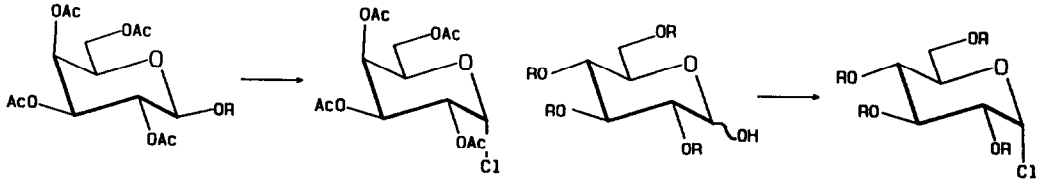
SUMMARY: Treatment of a variety of protected 2-(trimethylsilyl)ethyl (SE) mono, di and trisaccharide glycosides and hemiacetal sugars with α,α-dichloromethyl methyl ether (DCMME) in the presence of $ZnCl_2$, $SnCl_4$ or $FeCl_3$ in dichloromethane gave their corresponding 1,2-cis glycosyl chlorides in excellent yields.

Successful application of a protective group for temporarily masking the anomeric centre in a carbohydrate during oligosaccharide synthesis depends upon its stability to various reaction conditions as well as its amenability to easy and selective transformations when necessary. The SE group is very stable to a variety of experimental manipulations[1], even some in which the thioglycosides proved to be unstable[2], and therefore holds potential for wide application in oligosaccharide synthesis. It can be easily converted to 1-O-acyl glycosides which serve as glycosyl donors in Lewis acid mediated glycosidation reactions as well as precursors for glycosyl chlorides[3]. We now report a convenient method for the direct conversion of the SE group to the chloride.

We observed that when DCMME was added to a stirred mixture of 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (1) in



1 R = $CH_2CH_2SiMe_3$
2 R = CH(Cl)OMe

3

4 R = Ac
5 R = $CH_2C_6H_5$

6 R = Ac
7 R = $CH_2C_6H_5$

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dichloromethane with $ZnCl_2$ (Entries 1-5, Table 1) a vigorous reaction took place, with evolution of gaseous reaction products in which 1 was transformed to acetochloro-α-D-galactopyranose (3).

TABLE 1. Treatment of 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (1) or hemiacetal sugars 4 and 5 with DCMME in presence of a Friedel Craft's catalyst.[a]

No.	Starting Material (1 mmol)	Catalyst[b] (mmol)	DCMME (mmol)	Reaction Time	Product[c]
1	1	A (0.1)	1.1	16 h	3
2	1	A (0.1)	2.2	90 min	3
3	1	A (0.1)	4.0	90 min	3
4	1	A (0.5)	2.2	20 min	3
5	1	A (1.0)	2.2	<10 min	3
6	1	B (0.1)[d]	2.2	50 min	3
7	1	C (0.1)	2.2	40 min	3
8	4	A (0.1)	2.2	3 h	6
9	4	A (0.1)	8.0	3 h	6
10	4	A (1.0)	8.0	2 h	6
11	5	A (0.1)	2.2	5 min	7

[a]All reactions were carried out in anhydrous dichloromethane at 20°C. [b]A = $ZnCl_2$, B = $FeCl_3$, C = $SnCl_4$. [c]92-95% isolated yield, except for Entry 1 where the yield was 70%. All products were characterized by NMR and gave satisfactory elemental analysis. Products were crystalline except for Entry 11. [d]$FeCl_3$ went into solution on addition of DCMME.

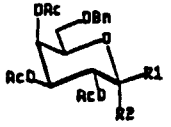
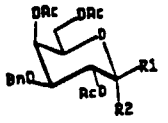
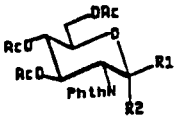
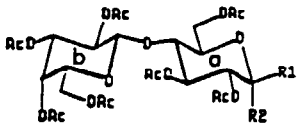
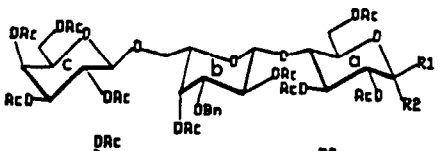
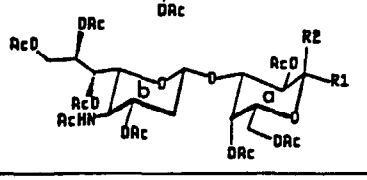
The reaction probably proceeds by the direct chloride displacement of the 1-chloro-1-methoxy-methyl glycoside (2) as proposed for the reaction of DCMME with alkyl glycosides[4], and the rate is dependent on both the amount of DCMME and $ZnCl_2$ (Table 1). $FeCl_3$ (Entry 6, Table 1) and $SnCl_4$ (Entry 7, Table 1) were also good catalysts for the reaction.

The $ZnCl_2$ reaction was then used[5] in the successful synthesis of the α-D-chlorides of a number of other substituted monosaccharide (Entries 1-3, Table 2) and oligosaccharide (Entries 4-6, Table 2) derivatives including those having acid labile sialic acid (Table 2), and isopropylidene groups[6].

The $ZnCl_2$ reaction was also found to be adaptable to the one-step synthesis of the α-D-chlorides from glycose hemiacetal derivatives (Entries 8-11, Table 1). Compounds 4 and 5 were converted to their α-D-chlorides (6 and 7) respectively), 7 being a valuable glycosyl donor which is often difficult to obtain pure by synthesis[7]. The above reactions probably also

Table 2. Conversion of 2-(trimethylsilyl)ethyl glycosides to their glycosyl chlorides.

Sugar-OSE $\xrightarrow[\text{Dichloromethane, } 20^{\circ}C]{\text{DCMME, } ZnCl_2}$ Sugar-Cl*

No	Compound	Selected NMR Data (anomeric H/C only, $CDCl_3$, δ, ppm) ^{1}H-NMR($J_{1,2}$Hz) R_1=OSE, R_2=H	^{13}C-NMR	^{1}H-NMR($J_{1,2}$Hz) R_1=H, R_2=Cl	^{13}C-NMR
1		4.47 (7.5)	100.7	6.37 (3.7)	91.4
2		4.38 (7.8)	100.6	6.37 (3.7)	91.7
3**		5.52 (8.2)	97.6	6.22 (9.5)	85.4
4**		a 4.48 (8.0) b 4.49 (7.7)	100.9 99.6	6.22 (4.1) 4.52 (7.9)	90.7 100.7
5		a 4.46 (8.0) b 4.43 (8.0) c 4.35 (7.9)	100.9 101.4 100.0	6.21 (4.0) 4.52 (8.0) 4.44 (8.0)	90.2 101.6 100.2
6		a 4.59 (7.7) b	100.4 96.7	6.26 (4.2)	91.7 96.8

* 92-95 % isolated yield. All products gave satisfactory elemental analysis.
** Prouducts were crystalline.

occur via the 1-chloro-1-methoxy-methyl glycosides of 4 and 5; the exclusive formation of 1,2-cis chlorides in these cases being due to the rapid isomerization of any initially formed 1,2-trans chlorides.

The results of the foregoing experiments indicate that these methods should prove to be valuable in the synthesis of complex oligosaccharides.

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5. Experimental procedure: DCMME (2.2 mmol) was introduced into a stirred mixture of the SE glycoside (1 mmol) and the catalyst (0.1 mmol) in anhydrous dichloromethane (1 ml/100 mg sugar derivative) at 20°C and stirring was continued until TLC showed complete conversion to the chloride. The reaction mixture was then diluted with dichloromethane and washed successively with cold dilute aqueous sodium carbonate solution and water. It was then dried over anhydrous Na_2SO_4 and filtered through a celite-bed. Evaporation of the solvent under vacuum afforded the desired product in nearly quantitative yield and was pure enough for direct use in the next step. Yields reported in the Tables are those obtained after filtration through a silica gel column.

6. 2-(Trimethylsilyl)ethyl-2,6-di-O-acetyl-3,4-O-isopropylidene-β-D-galactopyranoside, and 2-(trimethylsilyl)ethyl-2,3-di-O-acetyl-4,6-O-isopropylidene-β-D-glucopyranoside were also converted to their respective α-chlorides without degradation.

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