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Note

A facile preparation of peracylated α-aldopyranosyl chlorides with thionyl chloride and tin tetrachloride

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Dedicated to Professor Yongzheng Hui on the occasion of his 70th birthday

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ABSTRACT

Aldopyranose peracetates react with thionyl chloride and tin tetrachloride, producing the corresponding peracylated aldopyranosyl chlorides in very good to excellent yields (88–100%) with exclusive α-anomeric selectivity and short reaction times. The use of peracylated sugars as the substrate in large scale reactions also proceeds in high yield.

Glycosyl halides are a very valuable and versatile group of synthetic intermediates widely used in the field of carbohydrate chemistry.[1,2] Although their reactivity is lower as synthetic donors, glycosyl chlorides are superior to the bromides as their thermal and chemical stabilities are higher. In addition, they can be easily converted into O-glycosides,[3] *C*-glycosylic compounds (C-glycosides)[4,5] or glycals[6] via the generation of intermediate anomeric carbocations,[7] radicals, or cabanions.[6] Methods for the synthesis of these important compounds include treatment of sugar peracetates with PCl_5[8] or with $SOCl_2$–AcOH.[9] The reaction of 1,2-*trans*-peracetates with anhydrous titanium tetrachloride is also used frequently,[10] though the efficiency is very low. Thionyl chloride–zinc chloride had earlier been suggested as a useful reagent combination for the formation of 1,2-*cis*-glycopyranosyl chlorides from either of the corresponding anomeric peracetates.[11] However, the use heavy metal salts in these conversions is not environmentally friendly. Peromo and Krepinsky used BCl_3[12] as chlorine source and several groups utilized dichloromethyl methyl ether in the synthesis of glycosyl chlorides.[13] However, these reagents are powerful lachrymators and are highly toxic. Thus, the reported methods have limitations in terms of yield and selectivity of the products or in respect of the stability, toxicity and cost of the promoter or reaction time. The development of new methodologies for their preparation has been a challenging task.

We first tried the conversion of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**1**, Scheme 1) using tin tetrachloride alone as the chlorination reagent, as the glycosyl chloride has been postulated as the intermediate in the tin tetrachloride-catalyzed glycosylation with glycosyl acetate donors. When a solution of **1** in dichloromethane was treated with tin tetrachloride, and allowed to attain ambient temperature over a period of 4 h, TLC revealed only the presence of one component. If the reaction time is prolonged, the starting material is not fully consumed and the yield of product decreases gradually. Under these conditions, a 76% yield of the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride could be isolated and identified.

Treatment of D-galactopyranose peracetates, as was described for **1**, furnished the corresponding α-D-chloride also in very good yield. However, peracetates of D-mannopyranose, L-rhamnopyranose, and D-arabinopyranose hardly reacted and gave many by-products when treated in the same manner as for **1**. Ghosh et al. synthesized a variety of α-chlorides from the corresponding monosaccharide peracetates, employing a mixture of thionyl chloride and BiOCl as a procatalyst.[14] The method compares favorably with all of those described hitherto, especially with respect to the ease of availability of the reagents and simplicity of the reaction conditions. However, the literature method uses BiOCl as the promoter, which is not common in carbohydrate chemistry and

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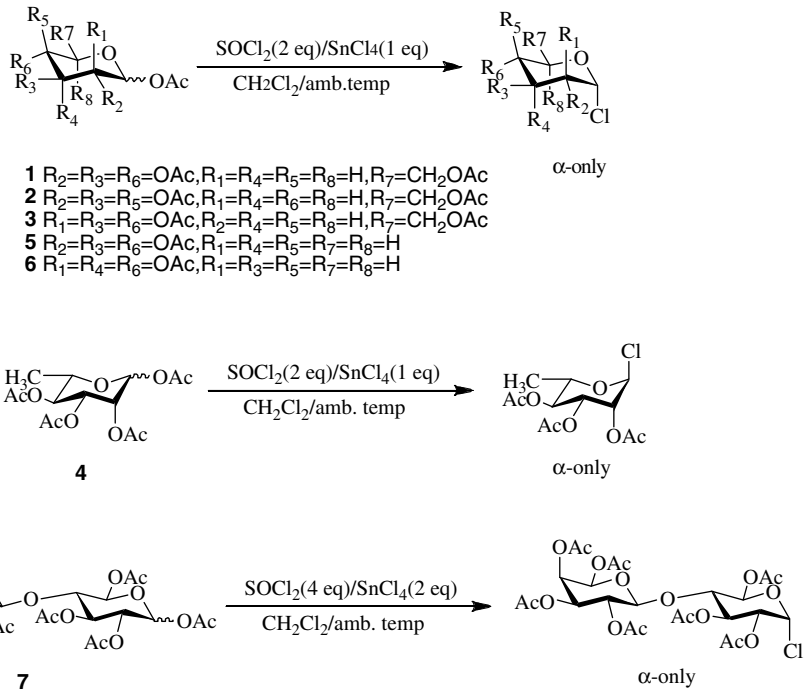

Scheme 1.

reaction time is very long. We, therefore, studied the use of thionyl chloride as a procatalyst for the tin-mediated chlorination of sugar peracetates. Fortunately, the conversion went well, and in good yield and stereoselectivity, and the reaction proved to be very reliable.

To establish optimal conditions, a number of experiments were performed. These experiments identified that reaction of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose **1** (1 equiv) with thionyl chloride (2 equiv) in the presence of tin tetrachloride (1 equiv) in dry dichloromethane at ambient temperature furnishes exclusively the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride in 98% yield (Table 1, entry l). Similarly, 1,2,3,4,6-penta-*O*-acetyl-D-galactopyranose (entry 6), 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose pentaacetate (entry 8) and 1,2,3,4-tetra-*O*-acetyl-D-L-rhamnopyranose (entry 10) were converted into the corresponding α-glycosyl chloride derivatives quickly, and in very good to excellent yields. Pentose sugars such as 1,2,3,4-tetra-*O*-acetyl-D-xylopyranose (entry 12) and 1,2,3,4-tetra-*O*-acetyl-D-arabinopyranose (entry 14) also reacted efficiently with thionyl chloride in the presence of tin tetrachloride resulted in the formation of the corresponding α-chlorides in almost quantitative yield. Similarly, reaction of 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (lactose octaacetate, entry 16) proceeded smoothly in the presence of thionyl chloride and tin tetrachloride. Due to the larger size of the lactose octaacetate, we doubled the amount of a thionyl chloride–tin tetrachloride complex. Using this improved method, the yield of the desired product is much more than the existing methods. Furthermore, there is no cleavage of the glycosidic bond compared to the reported methods.[15,16] It was found that a thionyl chloride–tin tetrachloride complex is a mild chlorinating reagent and it can speed up the chlorination reaction.

In the reactions described above, thionyl chloride and $SnCl_4$ were added to the appropriate sugar (50 mg, 1 equiv) in CH_2Cl_2 giving excellent yields of the product. To examine further the efficacy of the present procedure, the scale of the reaction was increased for 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose **1** and 1,2,3,4,6-penta-*O*-acetyl-D-galactopyranose **2** from 50 mg to 2 g (5.1 mmol). At this scale, the reactions proceeded efficiently fur-

Table 1
Synthesis of peracylated α-aldopyranosylchlorides

Entry	Products	$SnCl_4$ (equiv)	$SOCl_2$ (equiv)	Time (h)	Yield (%)
1	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	1	—	4.0	76
2	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	1	2	1.3	98
3	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	1	2	1.5	98[a]
4	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	1	2	2.0	98[b]
5	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	1	—	4.5	82
6	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	1	2	1.2	98
7	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	1	2	1.2	98[a]
8	2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl chloride	1	2	3.0	88
9	2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl chloride	1	2	3.0	88[a]
10	2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl chloride	1	2	4.0	88
11	2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl chloride	1	2	4.0	86[a]
12	2,3,4-Tri-*O*-acetyl-α-D-xylopyanosyl chloride	1	2	1.0	100
13	2,3,4-Tri-*O*-acetyl-α-D-xylopyanosyl chloride	1	2	2.0	95[a]
14	2,3,4-Tri-*O*-acetyl-α-D-arabinopyanosyl chloride	1	2	1.5	99
15	2,3,4-Tri-*O*-acetyl-α-D-arabinopyanosyl chloride	1	2	2.5	90[a]
16	2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-α-lactosyl chloride	2	4	8.0	90
17	2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-α-lactosyl chloride	2	4	8.0	88[a]

[a] 40-fold increase in scale of starting carbohydrate substrate (from 50 mg to 2 g).
[b] 200-fold increase in scale of starting carbohydrate substrate (from 50 mg to 10 g).

nishing the desired product in excellent yield and with α-selectivity as in the case of **1** (Table 1, entries 3 and 7). Subsequently, compounds **3**, **4**, **5**, **6** and **7** were also further evaluated at larger scale and in all cases the reactions furnished the desired products in excellent yield, 88%, 86%, 95%, 90% and 88%, respectively. However, as the reaction times were prolonged, a few by-products appeared from TLC. The same methodology was also shown to be reliable on scales as large as 10 g (26 mmol) of **1** (Table 1, entry 4).

The conversion of monosaccharides and disaccharides to the corresponding α-chlorides proceeds irrespective of the stereochemistry of the anomeric and C-2 of the starting materials. The results indicate that participation of the C-2 acetoxy group is not involved in the exclusive formation of the α-products. One of the by-products in this process, acetyl chloride, was also trapped successfully with *p*-nitrophenol as *p*-nitrophenyl acetate (data not shown). Therefore, we proposed the mechanism is similar to that proposed by Ghosh.[14] In this mechanistic scheme, the C-l acetoxy group is removed by thionyl chloride and $SnCl_4$ via anomeric participation, and then attacked by the chloride ion at C-l with concomitant regeneration of $SnCl_4$. Thus, we chose to add thionyl chloride to the reaction system first.

In summary, we have demonstrated a new, highly efficient stereoselective synthesis of peracylated-α-aldopyranosyl chlorides from aldopyranose peracetates using a mixture of thionyl chloride and $SnCl_4$ in anhydrous CH_2Cl_2. The advantages of the present procedure are that the method is simple and high yielding, and the reactions proceed with exclusive α-selectivity. The applied reagents, $SnCl_4$ and thionyl chloride are easily available. Moreover, the efficient applicability of this methodology to gram scale amounts of the starting carbohydrate substrates make thus this approach worthy for further research.

1. Experimental

1.1. General experimental methods

^{1}H NMR spectra were recorded on a Bruker DRX-500 MHz spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent. All reagents were purchased with purity of AR, and used as such. Silica gel (10–40 μm, Yantai, China) was used for column chromatography. All the solvents for chromatography were distilled before use. TLC plates (10–40 μm, Yantai, China) were applied to monitor reactions.

2.2. General procedure for chlorination of aldopyranose peracetates a small scale

To a solution of aldopyranose peracetate (50 mg, 1 equiv) in dichloromethane (2 mL), was added first thionyl chloride (2 equiv) and then $SnCl_4$ (1 equiv). The mixture was stirred at ambient temperature until completion (monitored by TLC, EtOAc–petroleum ether as eluant). The reaction mixture was then poured onto cold saturated $NaHCO_3$ solution and the product was extracted with dichloromethane (3×10 mL). The combined organic layer was washed with cold saturated salt water (1×15 mL) and then dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the crude residue was purified by column filtration, where necessary. All products were characterized by NMR by comparing the physical data with those in the literature.[11,17–20]

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