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Reaction of 1,2-*trans*-glycosyl acetates with phosphorus pentachloride: new efficient approach to 1,2-*trans*-glycosyl chlorides

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Abstract—Reaction of phosphorus pentachloride with 1,2-*trans*-glycosyl esters is described. The reaction mechanism presumably involves formation of a tetrachlorophosphonium ion as one of the key reactive intermediates, which can be induced either by Lewis acids or by using acetonitrile as the reaction solvent. Two novel, efficient methods for the synthesis of the thermodynamically unstable glycosyl chlorides were developed based on this reaction.

Acylated 1,2-*trans*-glycosyl halides are important synthetic intermediates for stereoselective 1,2-*cis* glycosylation. They have been widely employed for synthesis of various 1,2-*cis* linked sugar derivatives including nitrophenyl glycosides,[1] glycosyl azides,[2] thioglycosides,[1,3] glycosyl thioesters,[4] and, consequently, thiooligosaccharides.[4a,b,5]

Several methodologies have been developed to synthesize thermodynamically unstable glycosyl chlorides.[6] Generally, they involve the reaction of 1,2-*trans*-glycosyl acetates with various chlorinating reagents in an appropriate solvent. According to this approach β-glycosyl chlorides were prepared using anhydrous tin tetrachloride,[7] titanium tetrachloride[8] or aluminum chloride[9] in non-polar solvents or with hydrogen chloride in dry ether.[10] A combination of dichloromethyl methyl ether–boron trifluoride etherate has been suggested as a more convenient chlorinating reagent,[11] but the high toxicity of dichloromethyl methyl ether and its relatively high price are obvious drawbacks of the approach. Recently, a mixture of thionyl chloride and acetic acid has been utilized for conversion of sugar peracetates into the title compounds,[12] though the conversion requires considerable time (18 h) for completion.

Although 1,2-*trans*-glycosyl chlorides can also be prepared by chlorination of alkyl or aryl thioglycosides under milder conditions, allowing the use of acid sensitive protecting groups,[13–15] sugar peracetates are still more attractive precursors of acetylated glycosyl chlorides due to their availability at a lower price.

In the course of our investigation of Lewis acid catalyzed reactions of 1,2-*trans*-glycosyl esters with various nucleophiles,[16] it has been established that phosphorus pentachloride is a convenient reagent for synthesis of 1,2-*trans*-glycosyl chlorides. Previously, phosphorus pentachloride was used for β-glycosyl chloride synthesis under quite strong reaction conditions.[17] According to the report, β-glucosyl and β-galactosyl chlorides were prepared by passing a stream of hydrogen chloride over 5 h through the heated (90–100°C) mixture of corresponding β-D-peracetates with a 19 fold excess of freshly distilled PCl_5. The real role of the phosphorus pentachloride in the process is not clear; however, it certainly slows the reaction, because in the absence of PCl_5 the conversion proceeds faster and under much milder conditions.[10,18]

Phosphorus pentachloride has also been applied for the conversion of 1,2-*trans*-glycosyl acetates into 2-*O*-trichloroacetyl-β-D-glycosyl chlorides by a 2.5–5 h reflux of the reactants in carbon tetrachloride.[19] Formation of 1,2-*trans*-glycosyl chlorides was not observed in that case. Moreover, the proposed reaction mechanism did not consider 1,2-*trans*-glycosyl chlorides, even as possible intermediates. We, however, believe that per-

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acetylated 1,2-*cis*-glycosyl chlorides, isolated as minor products of the reaction,[19e] are the result of anomerization of initially formed 1,2-*trans*-glycosyl chlorides.

We have found that in the presence of Lewis acids, phosphorus pentachloride readily reacts with sugar β-D-peracetates under very mild reaction conditions leading to β-glycosyl chlorides. So, treatment of a stirred solution of 1,2-*trans*-glycosyl acetate in methylene chloride with a slight excess of PCl_5 and a catalytic amount of boron trifluoride etherate causes a weak exothermic reaction, which is usually complete in a few minutes producing the target compounds in high yields.

Boron trifluoride etherate and anhydrous aluminum chloride were the best catalysts for the reaction, although in case of $AlCl_3$ the reaction has an induction period, probably due to its slower solubility in the reaction mixture.

The reaction mechanism presumably involves initial formation of a tetrachlorophosphonium ion, PCl_4^+, induced by the Lewis acid. The phosphonium ion attacks the carbonyl oxygen of the acetoxy group at the anomeric position, producing phosphorus oxychloride, acetyl chloride and a 1,2-acyloxonium ion (Scheme 1). The acyloxonium ion, in turn, reacts with PCl_5 and produces glycosyl chloride and a PCl_4^+ ion which initiates a new cycle of the transformation.

The formation of the tetrachlorophosphonium ion as an initial intermediate may occur due to the ease of ionization of phosphorus pentachloride in the presence of Lewis acids.[20] It is also known that in polar solvents, for example, in acetonitrile, PCl_5 is almost completely dissociated into PCl_4^+ and PCl_6^- ions.[20] Therefore, to prove the proposed mechanism, the reaction was performed in acetonitrile without any catalyst. Like the Lewis-catalyzed reaction, fast disappearance of starting peracetates and simultaneous formation of β-glycosyl chlorides was observed by TLC analysis. The conversion required less than 15 min for its full completion. Thus, it can be concluded that the reaction of phosphorus pentachloride with 1,2-*trans*-glycosyl acetates proceeds via primary formation of tetrachlorophosphonium ion, induced either by Lewis acid or by the ionizing power of the solvent.[21]

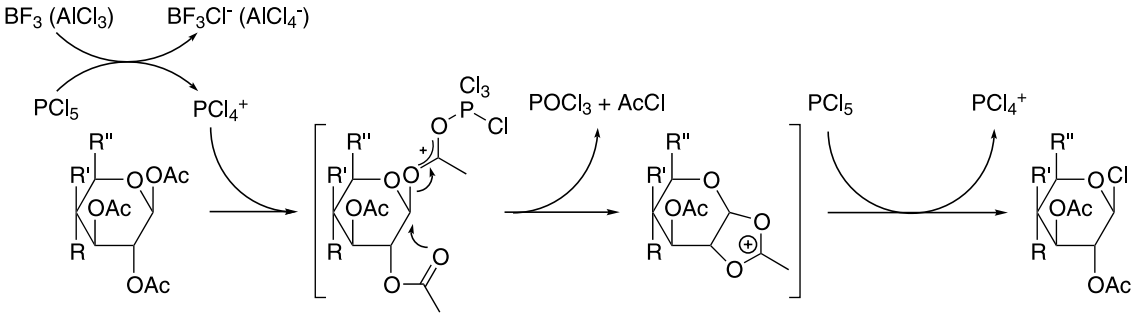
Based upon these observations, we have developed a novel approach for the conversion of sugar peracetates into 1,2-*trans*-glycosyl chlorides.

Typical procedures are as follows. Method A. To a stirred suspension of a peracetylated sugar (10 mmol) and phosphorus pentachloride (2.3 g, 11 mmol) in dry methylene chloride (20 mL), boron trifluoride etherate (10–20 μL) was added. After stirring for 5 min TLC analysis showed complete disappearance of the starting material. The reaction mixture was diluted with DCM (20 mL) and then washed with ice-cold water, saturated ice-cold $NaHCO_3$ solution (2×30 mL), and again ice-cold water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was co-evaporated with toluene, triturated under hexane and crystallized (if necessary) from an appropriate solvent to give the desired compound.

Method B. To a stirred solution of a peracetylated sugar (10 mmol) in anhydrous acetonitrile (20 mL) powdered phosphorus pentachloride (2.5 g, 12 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 5–15 min to completion, then diluted with DCM (40 mL) and toluene (20 mL), and worked up as described above to give the desired product.

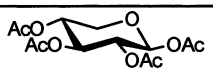
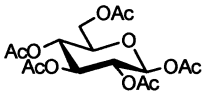
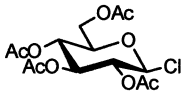
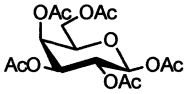
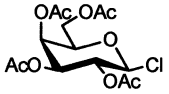
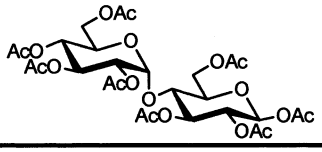
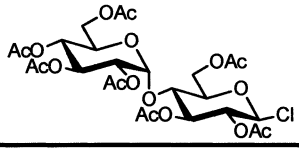
Contrary to the high reactivity of 1,2-*trans*-glycosyl acetates, 1,2-*cis*-isomers do not react with phosphorus pentachloride under the described conditions for steric reasons. In this case, the possible elimination of the acetoxy group from the anomeric position of the sugar can not be accompanied by 1,2-acyloxonium ion formation. Moreover, phosphorus pentachloride generally does not react with the carbonyl group of esters.[22] The only known exception is the reaction of PCl_5 with alkyl formates, leading to dichloromethyl methyl ether,[23] which is often utilized for the conversion of sugar acetates into the title compounds by treatment with a large (up to 13 molar) excess of the reagent.[11]

It has been reported that synthesis of glycosyl halides of oligosaccharides is often accompanied by interglycosidic bond cleavage, decreasing the yield of target products.[11d,12] To evaluate the stability of interglycosidic bonds under the described conditions, we synthesized β-maltosyl chloride using our methods. In both cases



Scheme 1. Proposed mechanism for halogenation of sugar acetates with phosphorus pentachloride.

Table 1. Synthesis of 1,2-*trans*-glycosyl chlorides

Entry	Sugar	Starting sugar peracetate	Product	Method	Yield (%)
1	D-Xylose			A	88
2				B	77
3	D-Glucose			A	90
4				B	87
5	D-Galactose			A	94
6	Maltose			A	92
7				B	83

the compound was isolated in 92% yield. NMR spectra and optical rotation values of the obtained samples were essentially the same, leading to the conclusion that cleavage of interglycosidic bonds under the described conditions does not occur.

The proposed methods have been applied for the synthesis of β-chlorides of D-glucopyranose, D-galactopyranose, D-xylopyranose and maltose (Table 1).[24] Some of the syntheses were scaled up to 100 mmol amounts.

The crude products obtained by method A are sufficiently pure and do not require additional purification. This is an essential advantage, because of the low stability of these compounds. Method B also affords pure enough crude products, although some were recrystallized to give satisfactory elemental analyses. In each case, only the β-anomer of glycosyl chlorides was formed during halogenation, according to chemical-shift data. The glycosyl chlorides obtained have been successfully utilized in the synthesis of various 1,2-*cis*-glycosyl azides, 1,2-*cis*-thioglycosides and 1,2-*cis*-thiooligosaccharides.

Conclusion

The reactions described here of 1,2-*trans*-glycosyl acetates with phosphorus pentachloride provides two novel efficient methods for the synthesis of 1,2-*trans*-glycosyl chlorides with yields comparable to those from the best available methods, but superior in terms of simplicity, mild reaction conditions, rapidity, and availability of reagents.

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24. All synthesized compounds gave satisfactory elemental analyses and were identified by optical rotations, ^1H, ^{13}C NMR, EI–MS spectroscopy. Selected spectral data:[25] 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl chloride, ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (m, 1H, H–1), 5.05–4.97 (m, 2H, H–2, H–3), 4.86 (m, 1H, $J_{4,5a}=3.0$ Hz, $J_{4,5b}=3.7$ Hz, H–4), 4.36 (dd, 1H, $J_{5a,5b}=12.9$ Hz, H–5a), 3.76 (dd, 1H, H–5a), 2.10, 2.099, 2.096 (3 × s, 9H, 3 × Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.2, 169.0 (3 × CO-Ac), 88.5 (C-1), 70.1, 67.3, 66.8 (C-2, C-3, C-4), 61.5 (C-5), 20.75, 20.7, 20.6 (3 × CH_3-Ac).
2,3,4,6-tetra-*O*-Acetyl-β-D-glucopyranosyl chloride, ^1H NMR (500 MHz, $CDCl_3$): δ 5.28 (d, 1H, $J_{1,2}=8.2$ Hz, H–1), 5.20–5.12 (m, 3H, $J_{4,5}=9.7$ Hz, H–2, H–3, H–4), 4.24 (dd, 1H, $J_{6a,6b=}12.5$ Hz, H–6a), 4.15 (dd, 1H, H–6b), 3.80 (ddd, 1H, $J_{5,6a}=4.7$ Hz, $J_{5,6b}=2.3$ Hz, H–5), 2.08, 2.06, 2.01, 1.99 (4s, 4 × 3H, 4 × Ac); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.0, 169.2, 169.0 (4 × CO-Ac), 87.5 (C-1), 75.5 (C-5), 73.3 (C-3), 72.7 (C-2), 67.5 (C-4), 61.5 (C-6), 20.6, 20.5, 20.4 (4 × CH_3-Ac).
2,3,4,6-tetra-*O*-Acetyl-β-D-galactopyranosyl chloride, ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (dd, 1H, $J_{4,5=}1$ Hz, H–4), 5.36 (dd, 1H, $J_{2,3=}10.1$ Hz, H–2), 5.24 (d, 1H, $J_{1,2=}8.8$ Hz, H–1), 4.99 (dd, 1H, $J_{3,4}=3.4$ Hz, H–3), 4.14 (d, 2H, H–6a,b), 4.01 (td, 1H, $J_{5,6a=}J_{5,6b=}6.4$ Hz, H–5), 2.16, 2.07, 2.04, 1.97 (4s, 4 × 3H, 4 × Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 170.0, 169.8, 169.1 (4 × CO-Ac), 88.1 (C-1), 74.5, 70.8, 70.6, 66.7 (C-2, C-3, C-4, C-5), 61.2 (C-6), 20.6, 20.5, 20.4 (4 × CH_3-Ac).
2,3,6-tri-*O*-Acetyl-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl chloride (2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltosyl chloride), ^1H NMR (500 MHz, $CDCl_3$): δ 5.39 (d, 1H, $J_{1',2'}=4.0$ Hz, H–1′), 5.36 (d, 1H, $J_{1,2}=8.0$ Hz, H–1), 5.33 (dd, 1H, $J_{3',4'}=9.8$ Hz, H–3′), 5.19 (dd, 1H, $J_{3,4}=8.6$ Hz, H–3), 5.03 (dd, 1H, $J_{4',5'}=$ 10.0 Hz, H–4′), 4.98 (dd, 1H, $J_{2,3'}=8.3$ Hz, H–2), 4.83 (dd, 1H, $J_{2',3'}=10.5$ Hz, H–2′), 4.49 (dd, 1H, $J_{6a,6b}=12.4$ Hz, H–6a), 4.22 (dd, 1H, $J_{6'a,6'b}=12.4$ Hz, H–6′a), 4.21 (dd, 1H, H–6b), 4.12 (dd, 1H, $J_{4,5}=9.7$ Hz, H–4), 4.04 (dd, 1H, H–6′b), 3.94 (ddd, 1H, $J_{5',6'a}=3.9$ Hz, $J_{5',6'b}=2.3$ Hz, H–5′), 3.81 (ddd, 1H, $J_{5,6a}=2.7$ Hz, $J_{5,6b}=4.6$ Hz, H–5), 2.14, 2.08, 2.05, 2.02, 2.01, 2.00, 1.98 (7s, 7 × 3H, 7 × Ac); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.43, 170.4, 170.3, 170.0, 169.9, 169.3, 169.2 (7 × CO-Ac), 95.8 (C-1′), 87.2 (C-1), 75.5, 75.3, 74.2, 72.2, 70.0, 69.2, 68.6, 68.0 (C-2, C-2′, C-3, C-3′, C-4, C-4′, C-5, C-5′), 62.5, 61.5 (C-6, C-6′), 20.77, 20.71, 20.6, 20.5, 20.49, 20.48, 20.46 (7 × CH_3-Ac).
The same compound was prepared using method B. Although the crude product, isolated in 92% yield, was sufficiently pure, it was recrystallized from ether–hexane to give the sample with satisfactory elemental analysis (yield 83%).
25. The NMR data is presented using the convention followed in *Carbohydrate Research*, (see Instructions to Authors).