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Note

Reaction of some 1,2-*trans*-aldose peracetates with thionyl chloride–acetic acid — a convenient synthesis of some 1,2-*trans*-per-*O*-acetyl-D-glycosyl chlorides

Gordon J.F. Chittenden

Department of Organic Chemistry, NSR Centre for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen (Netherlands)

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Several procedures have been employed[1–8] for the preparation of the thermodynamically less stable 1,2-*trans*-*O*-acetylglycosyl chlorides. Treatment of 1,2-*trans*-glycosyl peracetates with saturated dry ethereal hydrogen chloride at 0°C constitutes[1] one of the mildest procedures. This method has the advantage that there need be no contact with water during the isolation of the product, and it can be used for the preparation of very reactive derivatives. The reactions of 1,2-*trans*-peracetates with anhydrous aluminium chloride[3] or titanium tetrachloride[4] are also used frequently. Even under mild reaction conditions, mixtures of the anomeric chlorides often result.

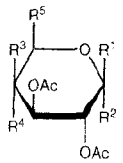
Dichloromethyl methyl ether–boron trifluoride etherate has been suggested[9] more recently as a superior alternative reagent combination.

A new simple procedure for the synthesis of a variety of 1,2-*trans*-per-*O*-acetyl-β-D-glycosyl chlorides from the corresponding β-D-peracetates, employing a mixture of thionyl chloride and glacial acetic acid, is now described. The method compares favourably with all of those described hitherto, especially with respect to the ease of availability of the reagents and the simplicity of the reaction conditions. It also permits the preparation of glycofuranosyl chlorides, which are unstable and less readily accessible.

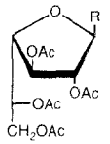
Thionyl chloride–zinc chloride had earlier been suggested[10] as a useful reagent combination for the formation of 1,2-*cis*-glycopyranosyl chlorides from either of the corresponding anomeric peracetates.

When a cooled (0°C) solution of β-D-glucopyranose pentaacetate (**1**) in dichloromethane was treated with a mixture of thionyl chloride and glacial acetic acid, and then allowed to attain ambient temperature over a period of 18 h, TLC revealed only one component, and 91% of the chloride **2** could be isolated and identified.

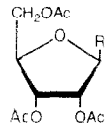
Treatment of peracetates **3–7**, as for **1**, furnished the corresponding β-D-chlorides **8–12**, also in good to excellent yields. Compound **11** could not be obtained



1 $R^1 = R^4 = OAc$, $R^2 = R^3 = H$, $R^5 = CH_2OAc$
2 $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OAc$, $R^5 = CH_2OAc$
3 $R^1 = R^3 = OAc$, $R^2 = R^4 = H$, $R^5 = CH_2OAc$
4 $R^1 = R^4 = OAc$, $R^2 = R^3 = R^5 = H$
8 $R^1 = Cl$, $R^2 = R^4 = H$, $R^3 = OAc$, $R^5 = CH_2OAc$
9 $R^1 = Cl$, $R^2 = R^3 = R^5 = H$, $R^4 = OAc$
13 $R^2 = R^4 = OAc$, $R^1 = R^3 = H$, $R^5 = CH_2OAc$
14 $R^2 = R^3 = OAc$, $R^1 = R^4 = H$, $R^5 = CH_2OAc$



5 R = OAc
10 R = Cl



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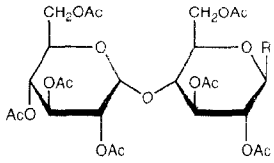

7 R = OAc
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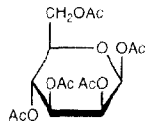

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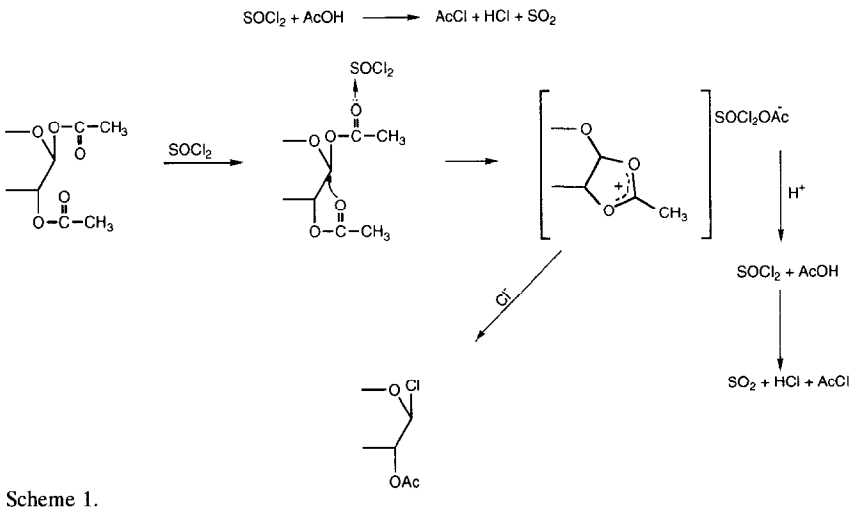
crystalline, despite a report[11] that treatment of the tetraacetate **6** with anhydrous hydrogen chloride in dichloromethane at −78°C yielded crystalline **11**. The specific rotation value and the ^1H NMR spectrum, in which the anomeric proton signal occurred as a sharp singlet at δ 6.05 (ref 11), confirmed the purity of the product obtained here.

The products from the various reactions usually crystallised spontaneously during concentration of the reaction mixtures, and were sufficiently pure for further use without recrystallisation. Compound **12** was more difficult to purify, possibly due to some interglycosidic bond cleavage.

The formation of the chlorides must occur via the corresponding 1,2-acetoxonium ions, since the peracetates of α-D-glucopyranose (**13**), α-D-galactopyranose (**14**), and β-D-mannopyranose (**15**), which are 1,2-*cis* compounds, were recovered unchanged when treated in the same manner as for **1**.

Treatment of **1** with thionyl chloride alone, or in an admixture with pure acetyl chloride, also failed to yield **2**; compound **1** was recovered unchanged.

The reactions were also shown to be solvent dependent. Treatment of solutions of compound **1** in oxolane or 1,2-dimethoxyethane under the same conditions failed to yield **2**, and only unreacted **1** was recovered. When the reactions were performed in toluene or carbon tetrachloride, compound **2** (81–88%) was isolated. These results show that, in ether-type solvents, preferential co-ordination of the



Scheme 1.

ethereal oxygen atoms with thionyl chloride, a Lewis acid, must occur and illustrate that thionyl chloride plays an essential role in the formation of **2** from **1**. When a solution of benzoic acid in 1,2-dimethoxyethane was treated with thionyl chloride, benzoyl chloride (78%) was isolated, demonstrating that the oxonium complexes are nevertheless capable of reacting with carboxylic acids, and that the formation of compound **2** does not occur by reaction of **1** with the limited amounts of hydrogen chloride that are produced. This was emphasised by the lack of reactivity[1] shown by compounds **13**, **14**, and **15** with the reagent mixture.

The sequences are probably initiated by the reaction of thionyl chloride with acetic acid, to produce a mixture of acetyl chloride and hydrogen chloride, which, in combination with the remaining excess of thionyl chloride, acts as the effective reagent as indicated (Scheme 1).

When thionyl chloride was added to a solution of **1** in ice-cold dichloromethane which had been treated briefly (30–60 s) with anhydrous hydrogen chloride, compound **2** was obtained in 89% yield. This observation was in accord with the above proposal and demonstrated that acetic acid functions merely to produce sufficient hydrogen chloride to promote the transformations.

Treatment of **1** with an ice-cold 10% solution of acetic acid in dichloromethane, pre-treated briefly (30–60 s) with a slow stream of anhydrous hydrogen chloride, yielded a syrupy mixture (TLC) of unchanged **1**, compound **2**, and the corresponding 1,2-*cis* isomer. Compound **1** (46%) was obtained from the material by fractional crystallisation (isopropyl ether).

Although it had been demonstrated earlier[3] that treatment of **1** or **13** with a mixture of acetyl chloride and hydrogen chloride yielded **2** (54–62%), analysis of the crude products suggested that ~ 30% of the 1,2-*cis* isomer was also present.

The reactions described here are essentially stereospecific, as demonstrated by the high yields of the pure material obtained.

EXPERIMENTAL

Optical rotations were determined on 1% solutions in $CHCl_3$ at 20°C with a Perkin–Elmer Model 241 polarimeter. TLC was performed on Kieselgel 60 (Merck) with 3:2 1,2-dimethoxyethane–cyclohexane and detection by charring with 5% H_2SO_4 in ethanol. ^1H NMR spectra were recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal Me_4Si) and were used routinely to identify products, and for the determination of anomeric purity.

Reaction of thionyl chloride–acetic acid. — (a) With β-D-glucopyranose pentaacetate (**1**). A stirred, ice-cold solution of **1**[12] (3.90 g, 0.01 mol) in CH_2Cl_2 (20 mL) containing thionyl chloride (5 mL) and acetic acid (2 mL) was allowed to attain ambient temperature over 18 h, then concentrated in vacuo at 30°C, and toluene (2 × 10 mL) was distilled in vacuo from the residue. The residue was recrystallised from isopropyl ether–hexane to give 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**2**; 3.33 g, 91%); mp 96–98°C; $[\alpha]_D$ −18°; lit.[6] mp 98–98.5°C; $[\alpha]_D$ −20°.

In another experiment, thionyl chloride (5 mL) was added to a stirred solution of **1** (3.9 g) in ice-cold CH_2Cl_2 (20 mL) that had been treated briefly (30–60 s) with anhyd HCl. The mixture was then treated as described above, to yield **2** (3.25 g, 89%); mp 95–97°C; $[\alpha]_D$ −17.4°.

(b) With β-D-galactopyranose pentaacetate (**3**). Treatment of **3**[12] (3.90 g, 0.01 mol) as described in (*a*) yielded 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl chloride (**8**; 3.22 g, 88%); mp 91–93°C; $[\alpha]_D$ +15.5°; lit.[3] mp 93°C; $[\alpha]_D$ +15°.

(c) With β-D-xylopyranose tetraacetate (**4**). Treatment of **4** (ref 13; 3.18 g, 0.01 mol) as described in (*a*) yielded 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl chloride (**9**; 2.42 g, 82%); mp 111–113°C; $[\alpha]_D$ −132°; lit.[3,14] mp 112–113°C; $[\alpha]_D$ −130°, −141°.

(d) With β-D-galactofuranose pentaacetate (**5**). When compound **5** (ref 15; 3.90 g, 0.01 mol) was treated as in (*a*), 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl chloride (**10**; 3.21 g, 87.5%) was obtained; mp 74–76°C; $[\alpha]_D$ −80°; lit.[3] mp 72–73°C; $[\alpha]_D$ −79°.

(e) With β-D-ribofuranose tetraacetate (**6**). Treatment of **6** (ref 16; 3.18 g, 0.01 mol) as described in (*a*) yielded as a syrup 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride (**11**; 3.67 g, 100%); $[\alpha]_D$ −24.5°; lit.[11] mp 50–51.5°C; $[\alpha]_D^{27}$ −26°.

(f) With β-maltose octaacetate (**7**). Compound **7** (ref 17; 3.393 g, 0.005 mol) was treated as in (*a*), the syrupy residue crystallised from ether–light petroleum, and the resulting material recrystallised (thrice) from isopropyl ether–pentane to give hepta-*O*-acetyl-β-maltosyl chloride (**12**; 1.90 g, 58%); mp 110–114°C; $[\alpha]_D$ +63°; lit.[3,6,9] mp 125°C, 110–113°C and 114–116°C; $[\alpha]_D$ +57.4°, +72°, and +60°.

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