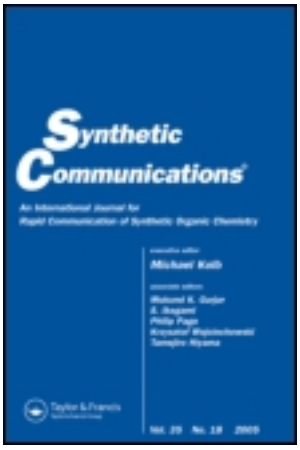

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 22 Aug 2006.

To cite this article: Valérie Rolland, Mitsuharu Kotera & Jean Lhomme (1997): Convenient Preparation of 2-Deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl Chloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:20, 3505-3511

To link to this article: http://dx.doi.org/10.1080/00397919708007071

SYNTHETIC COMMUNICATIONS, 27(20), 3505-3511 (1997)

CONVENIENT PREPARATION OF 2-DEOXY-3,5-di-O-*p*-TOLUOYL-α-D-*erythro*-PENTOFURANOSYL CHLORIDE

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Abstract: By using acetyl chloride as HCl generator, the procedure for the Hoffer preparation of the α-chloro sugar **4a** was significantly improved. The α-configuration of the chloro atom was confirmed by using NOE measurement. Sequential transformation of **4a** to the β-anomer and to the furfuryl derivative **6** was studied.

We recently required an efficient preparation of the title compound **4a** in large scale. This 2-deoxyribosyl chloride is one of the most widely used precursors for synthesis of a variety of deoxyribonucleosides[1-3]. The standard procedure[1] for preparing **4a** was described by Hoffer in 1960. The 2-deoxy-D-ribose **1** was first converted to the anomeric mixture of methyl pentofuranosides **2** which was directly acylated to the crude mixture of bis(4-methylbenzoates) **3**. The pure crystalline α-chloride **4a** was obtained by passing dry gaseous hydrogen chloride through the solution of **3** in acetic acid. The overall yield from 2-deoxy-D-ribose **1** was 70%.

This original procedure seems to present difficulties. Thus, in the course of the preparation of a 5-ethyluridine derivative Vorbrüggen et al.[4] reported that the

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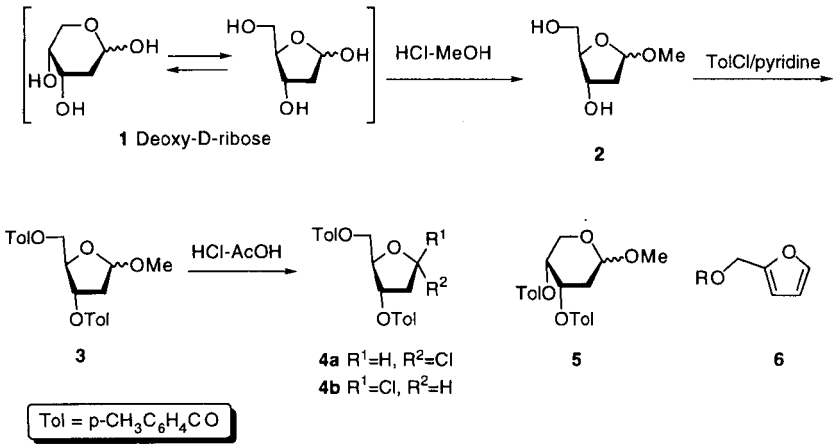
acidic treatment of 2-deoxy-D-ribose in methanol followed by acylation gave a mixture of variable composition of the furanoside and pyranoside 1-epimers (**2** and **5**) from which only 35% of the crystalline 1-α-chloro sugar **4a** was obtained.



We also experienced difficulties to reproduce the yields reported by Hoffer for this preparation, which probably requires delicate and tedious handling of gaseous dry hydrogen chloride. In the present paper we report a handy preparation method for this important deoxyribosyl chloride **4a** which makes use of acetyl chloride to generate HCl *in situ* to prepare an acetic acid solution saturated with HCl. We also describe NMR studies of the stability of this chloro sugar **4a**, the assignment of the α-configuration and the spontaneous transformation into the β-anomer and furfuryl derivative **6**.

In this preparation, we used essentially the same reactions as those reported by Hoffer, while the experimental protocol was simplified. In the first stage of the transformation (**1** to **2**), we used methanolic hydrogen chloride prepared by adding acetyl chloride to methanol according to *Fieser & Fieser* [5]. The resulting mixture of the methylfuranosides anomers **2** was acylated as reported by treatment with *p*-toluoyl chloride in pyridine to give **3**[6]. For converting this mixture of **3** into the

α-chloro sugar **4a** we found equally convenient to use an HCl solution in acetic acid prepared according to the same experimental protocol as used in the first step. The solubility of HCl gas in 100 grams of acetic acid is reported[7] to be 8.35 g. We thus prepared this solution simply by adding 16.3 g of acetyl chloride to a solution of acetic acid (81 mL) and water (4 mL). The crude mixture of the methyl furanosides **3** was treated with this HCl saturated solution. Precipitation of a crystalline product occurred readily to afford the pure α-chloro derivative after filtration and washings. The overall yield in pure compound **4a** is 58% calculated from 2-deoxy-D-ribose **1**.

While this chloro sugar **4a** is stable in the solid state, it decomposes in solution[8]. The decomposition of the analogous bis(*p*-chlorobenzoate) was described[9] to yield the furfuryl derivative **6** (R=*p*-chlorobenzoyl). We indeed observed similar decomposition of **4a** in $CDCl_3$. The NMR spectrum of **4a** was recorded at different time intervals after dissolution in $CDCl_3$. We first observed the caracteristic spectrum of the α–anomer and a set of small signals which were assigned to the β-chloro isomer **4b**. The ratio of this β–isomer was initially 5 % (15 min after preparation of the solution) and increased to 15 % within 1 h. While this ratio remained constant, another set of signals corresponding to the furfuryl derivative **6** (R=toluoyl) appeared after 4 h (about 10 %) and increased to become predominant after 48 h. This anomerisation-decomposition process is significantly slower in the presence of TMSCl. Thus in a solution of **4a** in $CDCl_3$containing one equivalent of TMSCl, the β–isomer **4b** is initially undetectable and accounted for 5 % only after 1 h. The chloride **4a** is still the major compound (>70 %) after 24 h. Similarly, in C_6D_6 solution in the presence of 1 equivalent of TMSCl, anomeric equilibration was attained only after 24 h (α/β=9/1) and the extent of decomposition to the furfuryl derivative **6** (R=toluoyl) was estimated to be about 5

% after 48 h. So using the C_6D_6-TMSCl solution of **4a**, we examined the configuration of the chloro atom.

The stereochemistry of the chloro atom in **4a** has been assigned earlier to be α based on optical rotatory data[8], by stereochemical outcome of the glycosilation reactions[3,8,9] and by comparison with the NMR spectra of the corresponding α- and β- derivatives of 6-chloropyridazinone[10].

Upon irradiation on H3 in the above solution, we observed NOE on the H1 signal. To our knowledge, this observation is the first direct structural evidence of the α–configuration in compound **4a**.

In summary, the use of acetyl chloride in the Hoffer preparation allowed ready preparation of the α-chloro sugar with hight reproducibility. Compared to the original Hoffer method, the present procedure is significantly safe, convenient, less laborious and inexpensive. This procedure is good candidate for practical preparation of this chloro sugar.

Experimental

All chemicals and solvants were used as purchased except for the "dry ether" obtained by simple drying over 4 Å molecular sieves. All preparations were carried out in a hood. Melting points were measured on a REICHERT THERMOVAR apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER WP200 and WP300 spectrometers.

2-Deoxy-α-D-*erythro*-pentofuranosyl chloride bis(4-methylbenzoate) 4a; To a solution of 10.0 g (74.5 mmol) of 2-deoxy-D-ribose **1** in MeOH (120 mL) was added 1% methanolic hydrogen chloride (20 mL ; prepared by adding 1.7 mL of acetyl chloride to 100 mL of MeOH)[3]. The reaction mixture was stirred at room temperature for 25 minutes and neutralized by adding solid sodium bicarbonate (4.0 g). After filtration, the methanol was removed by repeated

coevaporation with pyridine (1×50 mL and 2×25 mL) under water pressure. The residual sirup was dissolved in pyridine (60 mL), cooled to 0°C and p-toluoyl chloride (22 mL, 160 mmol) was added dropwise. The solution was stirred at room temperature overnight. The reaction mixture was diluted with cold water (150 mL) and extracted 3 times with CH_2Cl_2. The combined organic layers were washed twice with $NaHCO_3$ saturated aqueous solution, once with 2N HCl solution and once with water, dried on anhydrous $NaHCO_3$ and evaporated.

To the resulting colored sirup (25.5 g) dissolved in acetic acid (40 mL) was slowly added a saturated solution of HCl in acetic acid (63 mL; prepared by adding 16.3 mL of acetyl chloride to a mixture of 81 mL of acetic acid and 4 mL of water on cooling). An additionnal amount (about 5 mL) of acetyl chloride was added, whereupon the chloride precipitated forming a thick crystalline mass. The crystals were rapidly filtered off by suction, thoroughly washed with cold dry ether, dried in a vacuum dessicator; yield 16.8 g (58%). mp107-109°C (dec.) (litt. 109°C[1,11]; 108-111°C[12]); ^{1}H NMR ($CDCl_3$+ 1eqTMSCl) δ ppm 2.39 and 2.40 (two singlets, 6H), 2.7-3.0 (m, 2H), 4.5-4.7 (ABX, 2H), 4.8 (m, 1H), 5.5 (m, 1H), 6.46 (d, 1H, J=3 Hz), 7.2 (two doublets, 4H, J=9 Hz), 7.88 (d, 2H, J=9 Hz), 7.98 (d 2H, J=9 Hz). ^{13}C NMR ($CDCl_3$+ 1eqTMSCl) δ ppm 21.6, 44.5, 63.4, 73.5, 84.6, 95.2, 126.7, 126.8, 129.2, 129.6, 129.9, 144.0, 144.2, 166.0, 166.3.

This compound is stable in the solid state and may be stored without decomposition (NMR assay).in a closed bottle for months. When exposed to atmospheric humidity, it decomposed to a grey colored powder.

NMR study of 4a

The solutions of **4a** in $CDCl_3$ and in C_6D_6 were prepared by dissolving 25 mg (65 μmol) of **4a** in 0.7 mL of deuterated solvants. TMSCl (10 μL, 80μmol) was immediately added to prepare stabilized solutions. The following signals appeared in $CDCl_3$ solution were assigned:

β-Anomer 4b; δ ppm 3.08 (ddd, J=14, 7 and 2 Hz, H2'); 5.77 (m, H3'); 6.38 (dd, J=7 and 2 Hz).

Furfuryl 4-methylbenzoate 6; 5.27 (s, CH_2); 7.41 (d, J=2 Hz)

NOE experiment was carried out with the C_6D_6-TMSCl solution prepared as described above.

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(Received in the UK 21st March 1997)