



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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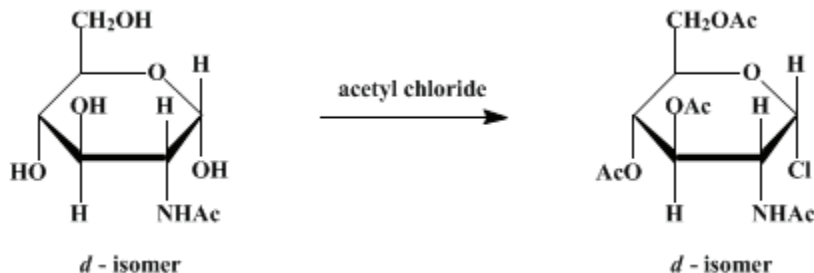
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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2-ACETAMIDO-3,4,6-TRI-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSYL CHLORIDE

[Glucopyranosyl chloride, 2-acetamido-2-deoxy-,triacetate, α -D-]



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1. Procedure

In a 500-ml. round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser protected by a tube of calcium chloride is placed 100 ml. of **acetyl chloride**; this operation and the subsequent reaction are conducted in a hood. The condenser is temporarily removed, and 50 g. (0.226 mole) of dried **2-acetamido-2-deoxy-D-glucose** (*N*-acetylglucosamine) (**Note 1**) is added in the course of 2 or 3 minutes with good stirring. The mixture is stirred for 16 hours without external heating at a room temperature of approximately 25°. The mixture boils spontaneously during the first hour of reaction. It is a clear, viscous, amber liquid at the end of the reaction (**Note 2**).

Through the condenser there is added 400 ml. of **chloroform** (U. S. P. grade), and the solution is poured with vigorous stirring onto 400 g. of ice and 100 ml. of water in a 3-l. beaker. The mixture is transferred to a 1-l. separatory funnel and shaken. The organic solution is drawn off without delay into a 3-l. beaker containing ice and 400 ml. of saturated **sodium bicarbonate** solution. The mixture in the beaker is stirred, and the neutralization is completed by shaking the mixture in the separatory funnel. The organic layer is run directly into a flask containing about 25 g. of anhydrous **magnesium sulfate**. The entire washing procedure should be completed within 15 minutes (**Note 3**). The solution is shaken or stirred with the drying agent for 10 minutes (**Note 4**). The drying agent is separated on a 7.5-cm. Büchner funnel and is well washed with *dry, alcohol-free chloroform* or **methylene chloride** (**Note 5**). The filtrate passes through an adaptor directly into a 1-l. round-bottomed flask. The filtrate is concentrated to 75 ml. on a rotary evaporator at 50°, and dry **ether** (500 ml.) is rapidly added with swirling to the warm solution (**Note 6**). Crystallization usually begins after about 30 seconds. The flask is stoppered and set aside for 12 hours at room temperature.

The product is scraped from the walls of the flask and broken up by means of a curved spatula. The solid is collected on a 12.5-cm. Büchner funnel, washed with two 150-ml. portions of dry **ether**, dried by suction on the filter for 5 minutes, and stored in a desiccator over **sodium hydroxide** and **phosphorus pentoxide**. Analytically pure **2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl chloride** is obtained; weight 55–65 g. (67–79%); m.p. 127–128° (Fisher-Johns apparatus) (**Note 7**); typical -NHCOCH₃ absorptions at 6.09 μ and 6.49 μ in the infrared; nmr (CDCl₃) δ 6.25 and J_{1,2} 3.5 Hz for the H-1 doublet. Evaporation of the mother liquors and addition of **ether** to the concentrated solution gives an additional 4–6 g. (5–7%) of crystalline product, m.p. 125–127°, that is sufficiently pure for most purposes. The pure product may be stored in an open dish in a desiccator at room temperature for at least 3 years without decomposition (**Note 8**).

2. Notes

1. Suitable material is available from Pfanstiehl Laboratories, Waukegan, Illinois. It may also be prepared from the hydrochloride of 2-amino-2-deoxy-D-glucose (**D-glucosamine**) in 95% yield by a facile procedure.² The **2-acetamido-2-deoxy-D-glucose** should be dried at 25° (1 mm.) for at least 12 hours before use. If this material is in the form of a powder rather than compact crystals, more **acetyl chloride** may have to be added in order to get a stirrable mixture; the checkers found that an extra 50 ml. of **acetyl chloride** did not lower the yield.
2. The reaction mixture may be left for longer periods, as over a weekend, without adverse effect. If the ambient temperature is too low, undissolved material may be present after 16 hours, in which case a longer period of stirring is indicated, or the reaction mixture may be gently heated (not above 30°).
3. It is essential that isolation of the product be conducted rapidly and at 0° throughout, especially while the solution is acidic. All apparatus and solutions should be at hand before the reaction mixture is poured on ice. The product reacts fairly rapidly with water in the presence of an acid catalyst, undergoing acetyl migration to give the water-soluble **1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride**.
4. An extended period of drying is unnecessary and should be avoided.
5. Commercial **methylene chloride** is usually sufficiently dry to use without pretreatment in place of dry, alcohol-free **chloroform**. The checkers used a pressure funnel under dry **nitrogen** for the filtration; filtration was rapid and exposure to atmospheric moisture was slight.
6. The solution must not be evaporated to a volume that permits crystallization to begin before the **ether** is added. The addition of **ether** should be sufficiently rapid that the heavy syrup is diluted to a clear, homogeneous solution before crystallization begins.
7. The checkers observed m.p. 118–119° when an open capillary tube containing a sample of analytical purity was placed in a stirred oil bath at 100° with the temperature rising several degrees a minute. The melting point of **benzoic acid**, determined simultaneously, was 122–123°. The checkers found $[\alpha]^{24D} + 110^\circ$ (c. 1, CHCl₃); literature values range from +109.7° to 118°.
8. Material of lesser purity may decompose within a much shorter time. If the product is exposed to moist air, it is converted into **1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride**, which is insoluble in **chloroform**.

3. Discussion

The direct one-step preparation of **2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl chloride** was reported by Micheel and co-workers,³ and the described procedure is essentially the method of Horton and Wolfrom.⁴ The product was first prepared through a two-step route from **2-amino-2-deoxy-D-glucose hydrochloride** by Baker and co-workers,⁵ and a number of adaptations of this method have been described.^{6,7,8}

4. Merits of Preparation

The procedure permits acetylation of the **sugar** and replacement of the 1-acetoxy group by **chlorine** in one operation in only 2–3 hours of working time, gives good yields of pure product, and does not require gaseous **hydrogen chloride**. The two-step procedure from **2-amino-2-deoxy-D-glucose hydrochloride**^{5,6,7} is time-consuming, and yields are very low if the acetylated intermediate is isolated.⁸ The yield is better when the second stage is performed without isolation, of the intermediate,⁹ but gaseous **hydrogen chloride** is required, and the preparation takes considerably more working time than the method described.

The product is used in the preparation of glycoside, thioglycoside, oligosaccharide, and glycosylamine derivatives of **2-acetamido-2-deoxy-D-glucose**.¹⁰ A number of these compounds are current interest; several seem to be involved in viral penetration of cells, and others are of interest in the synthesis of model substrates for enzymes. The product has the α -D configuration, and normally reacts to give glycosides with the β -D configuration, presumably through participation of the acetamido group in a bicyclic, closed-ion intermediate. Under controlled conditions it reacts with water to give **1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride**.¹¹

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Glucopyranosyl chloride, 2-acetamido-2-deoxy-, triacetate, α -D-

hydrochloride of 2-amino-2-deoxy-D-glucose

glycoside

thioglycoside

oligosaccharide

glycosylamine

hydrogen chloride (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

sugar

chlorine (7782-50-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

2-amino-2-deoxy-D-glucose hydrochloride (66-84-2)

D-glucosamine

phosphorus pentoxide (1314-56-3)

N-acetylglucosamine,
2-acetamido-2-deoxy-D-glucose

2-ACETAMIDO-3,4,6-TRI-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSYL CHLORIDE (3068-34-6)

1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride

1,3,4,6-tetra-O-acetyl-2-amino-deoxy- α -D-glucopyranose hydrochloride