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Working with Hazardous Chemicals

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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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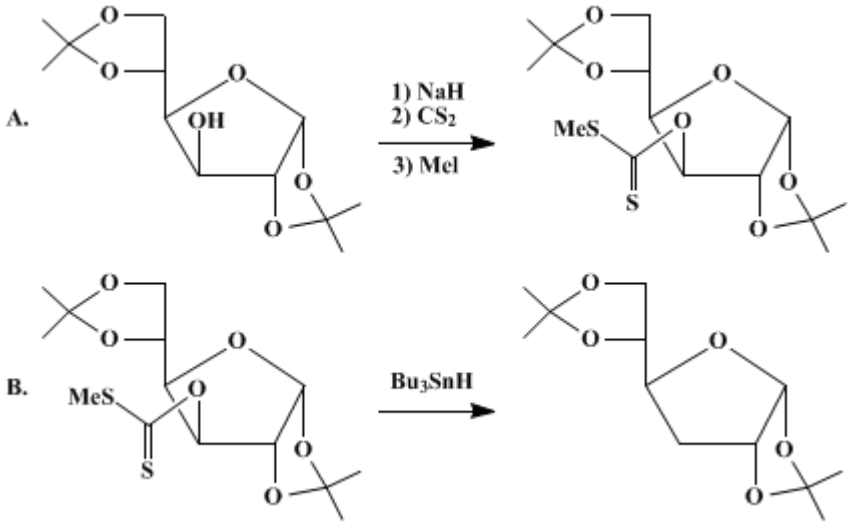
DEOXYGENATION OF SECONDARY ALCOHOLS: 3-DEOXY-1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-d-*ribo*-HEXOFURANOSE

[α-d-*ribo*-Hexofuranose, 3-deoxy-1,2:5,6-bis-*O*-(1-methylethylidene)-]



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Checked by Peter J. Card and Bruce E. Smart.

1. Procedure

Caution! Carbon disulfide, iodomethane, and tributyltin hydride are poisonous and should be handled in a well-ventilated hood.

A. *1,2:5,6-Di-O-isopropylidene-3-O-(S-methyldithiocarbonate)-α-D-glucofuranose*. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-inlet adapter, pressure-equalizing addition funnel, and stopper is charged with 26.0 g (0.10 mol) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 25 mg of imidazole (Note 1), and 400 mL of anhydrous tetrahydrofuran (Note 2). The reaction vessel is flushed with nitrogen and a nitrogen atmosphere is maintained during the ensuing steps. Over a 5-min period, 7.2 g (0.150 mol) of a 50% sodium hydride dispersion (Note 3) is added. Vigorous gas evolution is observed. After the reaction mixture is stirred for 20 min, 22.8 g (0.30 mol) of carbon disulfide is added all at once. Stirring is continued for 30 min, after which time 25.3 g (0.177 mol) of iodomethane is added in a single portion. The reaction mixture is stirred for another 15 min, and 5.0 mL of glacial acetic acid is added dropwise to destroy excess sodium hydride. The solution is filtered (Note 4) and the filtrate is concentrated on a rotary evaporator. The semisolid residue is extracted with three 100-mL portions of ether, and the combined ether extracts are washed with two 100-mL portions of saturated sodium bicarbonate solution and two 100-mL portions of water. The ethereal solution is dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed by rotary evaporation. The product is dried further at 0.05 mm overnight. The resulting orange syrup is distilled (Kugelrohr) to give 32.2–33.0 g (92–94%) of product, bp 153–160°C (0.5–1.0 mm) (Note 5).

B. *3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose*. A dry, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a reflux condenser to which a nitrogen inlet is attached. The apparatus is charged with 500 mL of anhydrous toluene (Note 6), 24.7 g (0.085 mol) of tributyltin hydride (Note 7) and 19.25 g (0.055 mol) of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*S*-methyldithiocarbonate)-α-D-glucofuranose. The reaction mixture is heated at reflux under a nitrogen atmosphere until TLC analysis indicates the disappearance of starting materials (4–7 hr) (Note 8). During this time the reaction solution changes from deep yellow to nearly colorless. The toluene is

removed on a rotary evaporator to yield a thick, oily residue that is partitioned between 250-mL portions of petroleum ether and acetonitrile. The acetonitrile layer is separated and washed with three 100-mL portions of petroleum ether and is then concentrated on a rotary evaporator. The residual yellow oil is taken up in hexane-ethyl acetate (10 : 1) and filtered through a pad of silica gel (Note 9). The filtrate is concentrated and the residual oil is distilled to give 10.0 g (75%) of product as a colorless syrup, bp 72–73°C (0.2 mm); n_D^{25} 1.4474 (Note 10).

2. Notes

1. 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose and imidazole were purchased from Aldrich Chemical Company, Inc. and used without further purification. Alternatively, the glucofuranose starting material can be prepared by standard methods from D-glucose.[2]
2. Reagent-grade tetrahydrofuran was freshly distilled from a purple solution of sodium and benzophenone.
3. Sodium hydride, a 50% dispersion in mineral oil, was purchased from Alfa Products, Morton Thiokol, Inc. It is not necessary to remove the mineral oil before conducting the reaction.
4. The collected salts should be disposed of carefully by first rinsing with isopropyl alcohol to ensure that no sodium hydride remains.
5. The submitters report pure product with bp 135–136°C (0.07 mm). The material obtained by the checkers is pure by NMR analysis. It shows ^{1}H NMR ($CDCl_3$) δ: 1.35 (s, 6 H), 1.42 (s, 3 H), 1.55 (s, 3 H), 2.60 (s, 3 H), 3.90–4.40 (m, 4 H), 4.68 (d, 1 H), 5.85–6.0 (m, 2 H).
6. Reagent-grade toluene was dried by distilling the toluene–water azeotrope and then cooling the remaining liquid under an atmosphere of nitrogen.
7. Tributyltin hydride was purchased from Aldrich Chemical Company, Inc. and stored under nitrogen at 4°C.
8. An E. Merck Silica Gel 60 F-254 0.25-mm plate was used for the TLC analysis.
9. Silica Woelm TSC, obtained from Woelm Pharma, was used.
10. The product is pure by NMR and TLC analyses and shows ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.60–1.90 (m, 1 H), 2.05–2.30 (dd, 1 H), 3.65–4.25 (m, 4 H), 4.71 (t, 1 H), 5.77 (d, 1 H).

3. Discussion

This procedure illustrates a simple, general method for the deoxygenation of secondary hydroxyl groups. It is particularly useful for reducing hindered alcohols. The method was first described by Barton and McCombie,[3] who have reviewed a number of other examples.[4]

A variety of thiocarbonyl derivatives, in addition to xanthate esters, undergo reductive homolytic cleavage when treated with tributyltin hydride. These include thiobenzoates,[3] thiocarbonylimidazolides,[3,5] and phenyl thionocarbonate esters.[6] The *S*-methyl xanthate ester is a particularly convenient intermediate to prepare because of its ease of formation and the low cost of the reagents. Its use is precluded, however, by the presence of base-labile protecting groups and, in such cases, the thiocarbonylimidazolide or phenyl thionocarbonate ester will generally prove satisfactory. Additional methods for the radical deoxygenation of alcohols are described in a review by Hartwig.[7]

The tributyltin hydride reduction usually proceeds without complications. The most common byproduct is starting alcohol, which is postulated to be derived from a mixed thioacetal.[3] Use of the phenyl thionocarbonate ester has been reported to minimize this side reaction in cases where it is a problem.[6]

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose has been prepared by a variety of other methods, the most widely used of which is the Raney nickel reduction of the 3-*S*-[(methylthio) carbonyl]-3-thioglucofuranose derivative.[8]

References and Notes

1. Department of Chemistry, Cornell University, Ithaca, NY 14853. Present address: Genzyme Corporation, 75 Kneeland Street, Boston, MA 02111.
2. Schmidt, O. T. "Methods in Carbohydrate Chemistry," Whistler, R. L.; Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol. 2, pp. 318–325.
3. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.
4. Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem*. **1981**, *53*, 15–31.
5. Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem*. **1981**, *46*, 4843–4846.
6. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc*. **1983**, *105*, 4059–4065.
7. Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
8. Hedgley, E. J.; Overend, W. G.; Rennie, R. A. C. *J. Chem. Soc*. **1963**, 4701–4711.

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

petroleum ether

3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose

thioacetal

1,2:5,6-Di-O-isopropylidene-3-O-(S-methyldithiocarbonate)-α-D-glucofuranose

3-S-[(methylthio)carbonyl]-3-thioglucofuranose

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

carbon disulfide (75-15-0)

iodomethane (74-88-4)

d-Glucose (492-62-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

Imidazole (288-32-4)

tributyltin hydride (688-73-3)

phenyl thionocarbonate

thiocarbonylimidazolide

S-methyl xanthate

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (582-52-5)

thiobenzoate

α-d-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)- (4613-62-1)