Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section “Handling and Disposal of Hazardous Chemicals” in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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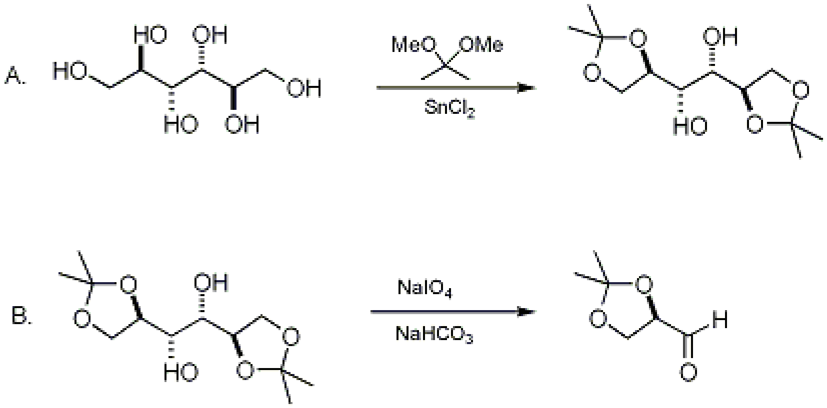
Organic Syntheses, Coll. Vol. 9, p.450 (1998); Vol. 72, p.6 (1995).

D-(R)-GLYCERALDEHYDE ACETONIDE

[1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)-]



Submitted by Christopher R. Schmid and Jerry D. Bryant[1].
Checked by Marc J. McKennon and Albert I. Meyers.

1. Procedure

A. *1,2:5,6-Diisopropylidene-D-mannitol*. A 1-L, three-necked flask equipped with overhead stirrer, heating mantle, and condenser with drying tube is charged with 100 g of D-mannitol (0.549 mol), 240 mL of freshly-distilled 1,2-dimethoxyethane (Note 1), and 160 mL of 2,2-dimethoxypropane (1.3 mol). Stirring is begun and 0.1 g of stannous chloride is added. The remaining neck is capped with a septum and the stirred slurry is heated to reflux. Reflux is maintained until the mixture becomes clear (30–50 min) and is continued for 30 min after clarity is attained. The heating mantle is removed and the solution is cooled below reflux. Pyridine (200 µL) is added through the septum via syringe. After the solution is cooled to room temperature, it is transferred to a tared, 1-L, one-necked flask, and the contents are concentrated on a rotary evaporator, beginning at room temperature and increasing the temperature to 95–100°C. The flask contents are held at that temperature until no more evaporate is collected (15–30 min). The semi-solid is then cooled to room temperature, to yield 130–160 g of crude solid product of 50–55% purity (72–80 g, 50–56% yield) as assayed by ^{1}H NMR against dichloromethane (Note 2).

B. *2,3-O-Isopropylidene-D-glyceraldehyde*. A large, magnetic stir bar is added to the flask that contains the crude solid diacetonide from procedure A above and 700–800 mL of dichloromethane (10 mL/g of diacetonide) is added. The flask is equipped with a condenser and heating mantle, and the slurry is stirred vigorously and heated to reflux until the solids are digested to an even consistency. The mantle is removed, the slurry is allowed to cool below reflux, and Celite (10 g) is added with stirring. The contents are further cooled to room temperature and vacuum-filtered through a pad of Celite on a glass frit filter into a three-necked, 2-L vessel. The flask is rinsed with 50 mL of dichloromethane and the rinse is filtered through the funnel. The 2-L vessel is then equipped with an overhead stirrer, thermometer, and water bath, and stirring is begun at 300–350 rpm. A solution of 30–40 mL of saturated aqueous sodium bicarbonate (0.4 mL/g of diacetonide) is added with stirring, followed by 130–140 g of sodium metaperiodate (2.0 mol equiv), added portionwise over 2–3 min. The resulting mixture is stirred while the internal temperature is maintained below 35°C with water bath cooling. After the solution is stirred for 2 hr, 35–50 g of magnesium sulfate (0.5 g/g of diacetonide) is added and stirring is continued for 20 min. The slurry is vacuum-filtered through a glass frit filter into a 2-L, one-necked, round-bottomed flask. The filter cake is removed, transferred back into the three-necked vessel, 200 mL of dichloromethane is added, and the resulting slurry is stirred for 10 min. The slurry is vacuum-filtered (Note 3) and the filtrate is added to the one-necked flask (Note 4).

The filtrate-containing flask is equipped with a 12"-Vigreux column, distillation head, receiver, and heating mantle, and dichloromethane is removed by distillation (head temperature to 40°C) (Note 5). The residual oil is cooled and transferred to a 250-mL, round-bottomed flask and the flask is equipped with a simple distillation head, cow receiver, and heating mantle. After a brief forerun (2–3 g), product is collected by distillation at 30 mm (65–120°C) into a chilled receiver (5°C) to afford 54–68 g (75–85%) of crude 2,3-O-isopropylidene-D-glyceraldehyde (Note 6). The crude product is transferred to a 100-mL, round-bottomed flask equipped with a 6"-Vigreux column, cow receiver, and heating mantle, and redistilled (Note 7) at 30 mm, collecting the fraction distilling at 67–73°C into a chilled receiver to afford 50–64 g of product (70–80%, 34–45% overall, (Note 8)).

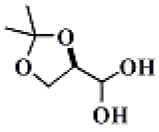
2. Notes

1. Commercial samples of 1,2-dimethoxyethane were found to contain trace impurities that inactivate the stannous chloride catalyst. Simple distillation affords purified solvent.[2]

2. Samples of about 50 mg are weighed and dissolved in 0.5 mL of (methyl sulfoxide)-d_6(DMSO-d_6) and 10 µL of dichloromethane is added. A small portion of this solution is then withdrawn and diluted in an NMR tube with DMSO-d_6. ^1H NMR integration parameters are as follows: 32K data points, recycle delay of 5 s, 30° pulse angle. Measurement is against the hydroxyl proton doublet (2 H) at δ 4.63. If the hydroxyl doublet is not satisfactorily resolved, additional dilution is performed.

Physical data for material purified by slurry in dichloromethane followed by recrystallization from butyl ether is as follows: mp 121.8–123.4°C (lit.[3] mp 118–120°C); $[\alpha]_D^{23}$ +1.9° (CH_3OH, *c* 1.74), lit.[4] $[\alpha]_D^{20}$ +1.9° (CH_3OH, *c* 2); ^1H NMR ($CDCl_3$) δ: 1.36 (s, 6 H), 1.42 (s, 6 H), 2.70 (d, 2 H, J = 6.7), 3.75 (approx. t, 2 H, J = 6.2), 3.98 (dd, 2 H, J = 8.4, 5.4), 4.10–4.22 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ: 25.19, 26.72, 66.74, 71.16, 76.22, 109.39; IR (KBr) cm^{-1}: 3400, 3292, 2980, 2933, 2895, 1386, 1372, 1265, 1212, 1070, 859. Anal. Calcd. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.80; H, 8.50.

3. In the presence of water, 2,3-O-isopropylidene-D-glyceraldehyde forms the highly water soluble hydrate **1**. Failure to dry the reaction and reslurry the filter cake results in loss of about 10% yield.



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4. On standing, the filtered solids take on a color characteristic of iodine; the solids can be decomposed by treatment in water with sodium thiosulfate or bisulfite to a negative starch-iodide endpoint.

5. Removal of dichloromethane (CH_2Cl_2) in the final step was performed by the checkers using a rotary evaporator. The pressure was monitored during evaporation and was not allowed to drop below 100 mm. In this fashion the same yield of material was obtained as reported.

6. On standing, both the initially distilled and redistilled material may deposit a small amount of flocculent solid or gel characteristic of polymerized material, which results in some thickening of the product oil.

7. The checkers found that a single distillation of the final product was sufficient to obtain pure material.

8. The physical characteristics are as follows: $[\alpha]_D^{23}$ +70–80° (*c* 1.0–1.5, benzene, taken immediately upon completion of distillation); ^1H NMR ($CDCl_3$) δ: 1.40 (s, 3 H), 1.47 (s, 3 H), 4.12 (m, 2 H), 4.36 (m, 1 H), 9.70 (d, 1 H, J = 1.9); ^{13}C NMR ($CDCl_3$) δ: 24.73, 25.84, 65.11, 79.49, 110.79, 201.38; IR (neat) cm^{-1}: 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840. Material obtained from this scale procedure is approximately 90% monomeric; the presence of polymeric material is shown in the ^1H NMR by broad signals at δ 4.7, 3.9 and 1.23.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

2,3-O-Isopropylidene-D-glyceraldehyde has been obtained from D-mannitol by a bis-ketalization/glycol cleavage sequence using a number of ketalizing reagents,[3] [5] [6] [7] [8] [9] [10] [11] and either lead tetraacetate[11,12] or lead periodate[13] [14] [15] [16] [17] [18] [19] [20] to effect glycol cleavage. The compound has also been prepared using alternative methodology,[21] and from other chiral pool sources.[22] This procedure represents recently disclosed[2] optimization efforts on previously reported syntheses of 1,2:5,6-diisopropylidene-D-mannitol[3] and 2,3-O-isopropylidene-D-glyceraldehyde.[20]

A review article reports information regarding the preparation, handling, and storage of this important 3-carbon chiral source.[23] Our experience with the compound demonstrates that it tends to polymerize and readily adds water to form hydrate **1** in aqueous solution, from which it is extracted only with difficultly. Both hydrated and polymerized aldehyde can contaminate samples and result in lowered optical rotation values, even though no racemization has occurred. The present procedure provides anhydrous aldehyde, that polymerizes on standing. Polymerized material can be cracked by redistillation (threshold temperature ca. 90°C) at reduced pressure to provide monomer without compromise of enantiomeric integrity; monomeric aldehyde has been obtained routinely in our labs by distillation from still pots that contain substantially polymerized material. Although polymeric material can be stored for months at room temperature in sealed containers and recracked to provide monomer with good recovery, refrigerated storage retards polymerization rates and probably extends the useful lifetime of the compound, as polymerized material failed in some instances to recrack to monomer. Other workers have recommended storage in a frozen benzene matrix,[24] and a report on successful recracking of refrigerated polymerized material has appeared.[25] We recommend the use of freshly-distilled material in synthetic applications.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 52
- Org. Syn. Coll. Vol. 9, 454
- Org. Syn. Coll. Vol. 10, 152

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

1,2:5,6-Diisopropylidene-D-mannitol

D-(R)-GLYCERALDEHYDE ACETONIDE

DMSO-d_6

sodium thiosulfate or bisulfite

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

stannous chloride

iodine (7553-56-2)

pyridine (110-86-1)

butyl ether (142-96-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

1,2-dimethoxyethane (110-71-4)

2,2-dimethoxypropane (77-76-9)

sodium metaperiodate (7790-28-5)

D-mannitol (69-65-8)

2,3-O-Isopropylidene-D-glyceraldehyde (22323-80-4)

1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)- (15186-48-8)

lead tetraacetate (546-67-8)

lead periodate