A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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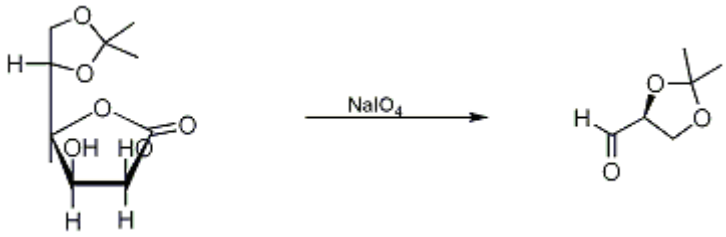
L-(S)-GLYCERALDEHYDE ACETONIDE

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



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Checked by Todd M. Heidelbaugh and Leo A. Paquette.

1. Procedure

A 500-mL, four-necked, reaction flask, equipped with a mechanical stirrer, thermometer, and glass pH electrode combined with an automatic titrator (Note 1), is charged with sodium (meta)periodate (85.5 g, 0.4 mol) (Note 2) and water (200 mL). The suspension is cooled to 0°C in an ice bath and 3 N sodium hydroxide (about 133 mL, 0.4 mol) is added dropwise at a rate such that the temperature does not exceed 7°C. The final pH of the suspension is 5.5. The cooling bath is removed and finely powdered 5,6-O-isopropylidene-L-gulono-1,4-lactone (Note 3) (43.6 g, 0.2 mol) is added in one portion. The temperature of the mixture is kept below 30°C (Note 4). The pH of the suspension is maintained at 5.5 during the course of the reaction by addition of aqueous 15% sodium carbonate (about 15 mL). The suspension is further stirred at room temperature for 30 min, saturated with sodium chloride (105 g), and filtered by suction using a Büchner funnel. The white solid (Note 5) is washed thoroughly with two 50-mL portions of brine and the pH of the combined aqueous layers is adjusted to 6.7 with aqueous 15% sodium carbonate before extraction with dichloromethane (6 × 100 mL) (Note 6). The combined organic extracts are dried over magnesium sulfate (25 g). The magnesium sulfate is removed by filtration and washed with two 50-mL portions of dichloromethane. The organic solutions are combined and slowly concentrated to about 50 mL under reduced pressure (Note 7). The remaining solution is placed in a 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 10-cm, vacuum-jacketed, Claisen-Vigreux column (10-mm diameter). With constant stirring by a magnetic stirrer, the solution is further concentrated by distillation under reduced pressure (400 mbar) at 35°C (bath temperature) (Note 8). The temperature of the oil bath is then gradually increased to 80°C and the glyceraldehyde acetonide is distilled between 51°C and 52°C. The distillate is collected in a receiver cooled with an ice-methanol bath (Note 9). Approximately 14.5 g of L-(S)-glyceraldehyde acetonide (56% based on 5,6-O-isopropylidene-L-gulono-1,4-lactone) is obtained.

2. Notes

1. A 200-mm Radiometer combined glass/reference electrode (Ag/AgCl) was used. To control the pH the submitters used a Radiometer standard pH meter PHM82 coupled to a TTT80 titrator. The end point was set to pH 5.5. If an automatic delivery system is not used the pH range should be kept between 4 and 6 during the oxidation process. Low pH values favor hydrolysis of the acetonide protective group, high pH values lead to epimerization of the aldehyde. The checkers did not use an automatic titrator. The pH was adjusted manually; 1.25 hr was required to bring the solution to pH 5.5.
2. Sodium (meta)periodate (puriss. p.a.) was purchased from Fluka Chemical Corporation and used without any purification.
3. 5,6-O-Isopropylidene-L-gulono-1,4-lactone was purchased from Fluka Chemical Corporation and used without any purification. It can also be synthesized from ascorbic acid in a two-step procedure.[2]
4. The temperature of the solution was kept between 20°C and 30°C by occasional cooling with an ice-water bath.

5. The white solid is mainly sodium iodate and sodium chloride.
6. GLC analysis of a sample of the crude, aqueous solution indicates the presence of 95% of the theoretical amount of glyceraldehyde acetonide. This crude, aqueous solution can be used for further chemical transformations,[2] but was not stored for more than 6 hr at 0°C. GLC analysis of the aqueous layer after dichloromethane extraction still indicates the presence of about 30% of the total amount of glyceraldehyde acetonide in the aqueous solution.
7. The submitters used the following conditions: rotatory evaporator bath temperature: 35°C, cooling water temperature: −5°C; pressure: 500 mbar.
8. In the condenser, the cooling water was replaced by a methanol-ice mixture.
9. (S)-Glyceraldehyde acetonide is an unstable liquid that starts to polymerize on standing even at low temperature. It can be depolymerized by distillation before use. The ^{1}H NMR spectrum is as follows ($CDCl_3$) δ: 1.43 and 1.49 (2 s, 2 × 3 H), 4.08–4.21 (2 dd, 2 × 1 H, J = 4.4, 7.6), 4.38 (ddd, 1 H, J = 2, 4.4, 7.6), 9.72 (d, 1 H, J = 2), internal tetramethylsilane standard). The optical rotation is $[\alpha]_D^{20}$ −75.4° (benzene, *c* 8) [lit. $[\alpha]_D^{20}$ −67.9°/69.7° (benzene, *c* 8/2.2)[3,4]].

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

Optically pure glyceraldehyde acetonides are widely used in the synthesis of enantiomerically pure compounds (EPC synthesis).[5] Whereas D-(R)-glyceraldehyde acetonide is easily obtained from the inexpensive D-mannitol,[6,7] there are only a limited number of practical syntheses of the enantiomeric L-(S)-glyceraldehyde acetonide.[8,9] Difficulties arise from different sources: 1) availability of the starting material diisopropylidene-L-mannitol; 2) length of the synthesis;[10] 3) nature of the reactants used : mercury acetate, mercaptans, lead tetraacetate, ozone at −78°C, 4) moderate yields.[11,12,13,14]

The procedure reported here is practical, uses readily available, non-toxic starting materials, and can be easily scaled up. No harmful by-products are formed during the synthesis, and sodium iodate, generated during the periodate cleavage, can be recycled into sodium metaperiodate.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 13

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

brine

D-(R)-GLYCERALDEHYDE ACETONIDE

(S)-Glyceraldehyde acetonide

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

mercury acetate (1600-27-7)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

sodium metaperiodate,
sodium (meta)periodate (7790-28-5)

sodium iodate (7681-55-2)

ascorbic acid

D-mannitol (69-65-8)

5,6-O-isopropylidene-L-gulono-1,4-lactone

L-(S)-Glyceraldehyde acetonide (22323-80-4)

1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)- (22323-80-4)

diisopropylidene-L-mannitol

lead tetraacetate (546-67-8)