



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.

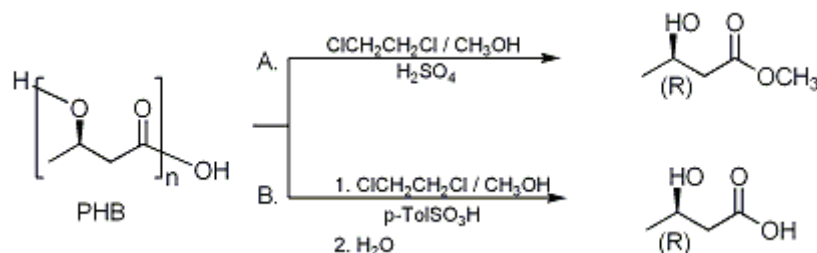
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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DIRECT DEGRADATION OF THE BIOPOLYMER POLY[(R)-3-HYDROXYBUTYRIC ACID] TO (R)-3-HYDROXYBUTANOIC ACID AND ITS METHYL ESTER

[Butanoic acid, 3-hydroxy-, (R)-, homopolymer to Butanoic acid, 3-hydroxy-, (R)- and Butanoic acid, 3-hydroxy-, methyl ester, (R)-]



Submitted by Dieter Seebach, Albert K. Beck, Richard Breitschuh, and Kurt Jobl.
 Checked by Eugene R. Hickey and Leo A. Paquette.

1. Procedure

A. *(R)-(-)-Methyl 3-hydroxybutanoate.* A 2-L, round-bottomed flask is charged with 50 g (0.58 mol) of poly-[(R)-3-hydroxybutyric acid] (PHB) (Note 1) and 500 mL of absolute 1,2-dichloroethane. The flask is equipped with a reflux condenser, and the mixture is heated at reflux for 1 hr. A solution of 10 mL of concd sulfuric acid in 200 mL of absolute methanol is added and the reaction mixture is heated at reflux for 3 days. During this time the mixture becomes homogeneous.

After the reaction mixture is cooled to room temperature, 100 mL of half-saturated brine is added to the reaction mixture, which is stirred for 10 min before the layers are separated. The aqueous layer is extracted three times with 200 mL each of chloroform. The combined organic layers are washed with 100 mL of brine, 100 mL of saturated sodium bicarbonate solution, and 100 mL of brine. After the solution is dried over magnesium sulfate and removed in a rotary evaporator, a residue of 59 g is isolated.

This crude product is distilled under reduced pressure to give 48 g (70%) of pure (R)-(-)-methyl 3-hydroxybutanoate (bp 61–62°/18 mm) with a specific rotation of $[\alpha]_D^{25} -47.6^\circ$ (CHCl_3 , c 1.0) (Note 2).

B. *(R)-(-)-3-Hydroxybutanoic acid.* In a 1-L, two-necked, round-bottomed flask, fitted with a precision-ground stirrer and a coil condenser bearing a distillation bridge, are placed 200 mL of 1,2-dichloroethane and 50 g (0.58 mol) of PHB (Note 1). The mixture is stirred and heated at 150°C until a milky solution is formed (Note 3). *p*-Toluenesulfonic acid monohydrate (2.5 g, 0.013 mol) is added and the solution heated an additional 30 min at 150°C. A total amount of 9.3 g (11.8 mL, 0.29 mol) of methanol is then added carefully through the condenser to the boiling solution in approx 1-mL portions (Note 4). The light brown, cloudy solution is heated at reflux (oil bath, 140°C) for another 48 hr (Note 5). The oil bath temperature is reduced to 130°C and 60 mL of water is carefully added. The resulting two-phase mixture is heated for another 4 hr (Note 6). Methanol, 1,2-dichloroethane, and approx 150 mL of water are removed by distillation through the condenser within 1–2 hr (Note 7). During the distillation nine 30-mL portions of water are added; the resulting homogeneous aqueous solution is heated at reflux for another 4 hr. During this period the temperature of the oil bath is increased to 180°C. Methanol/water (50 mL) is removed by distillation and, after the addition of 50 mL of water (Note 8), the solution is again heated at reflux for 15 hr. The reaction mixture is cooled to about 30°C, followed by the addition of 0.6 g (0.015 mol) of sodium hydroxide in 10 mL of water. Water is first removed in a rotary evaporator at a maximum temperature of 30°C, 15 mm, followed by drying at 0.1 mm (Note 9). The residue is dissolved in 250 mL of ether, the solution is dried over magnesium sulfate,

filtered, concentrated in a rotary evaporator and dried at 0.1 mm. The resulting light-brown clear oil (Note 10) is distilled at 80–100°C (air bath)/10⁻³mm by bulb to bulb distillation (Note 11). The crude product is either crystalline or a colorless oil that crystallizes upon standing at room temperature. After the crystals are crushed in a mortar, they are dried for 2 days in a desiccator over phosphorus pentoxide (P₂O₅) (Note 12), to yield 32 g (53%) of (R)-3-hydroxybutanoic acid, mp 44–46°C, $[\alpha]_D^{RT}$ -24.7° (H₂O), *c* 5.0 (Note 13), (Note 14), (Note 15).

2. Notes

1. The submitters used PHB=Poly-(R)-3-hydroxybutyric acid obtained from Marlborough Biopolymers Ltd., Rudby Hall, Hutton Rudby, Yarm, Cleveland, England, PHB homopolymer, BX GO4, technical grade powder, MBL 100/703. The checkers used PHB from Fluka Chemie AG, CH-8470 Buchs, Switzerland. The submitters report that the procedure works well on batch sizes of 200–250 g.
2. The spectroscopic properties are as follows: IR (neat) cm⁻¹: 1735 (C=O); ¹H NMR (90 MHz, CDCl₃) δ: 1.25 (d, 3 H, CH₃), 2.45 (d, 2 H, CH₂), 3.00 (br s, 1 H, OH), 3.75 (s, 3 H, OCH₃), 4.20 (m, 1 H, CH). For further data see ref. ².
3. The submitters used an oil bath to insure vigorous reflux. The time required to obtain the desired solution consistency depends on the PHB used (30 min to over 2 hr).
4. The reaction solution should be maintained at a vigorous reflux. Should the solution cool during the addition a white flaky precipitate may form that redissolves upon extended heating (up to 4 hr at 140° C).
5. This results in a mixture of oligomeric methyl esters with an average degree of polymerization of 2.1–2.3, according to ¹H NMR analysis (ratio of the CH₃C-signals vs. CH₃O-signals of the esters).
6. Most of the methyl ester groups are saponified with release of methanol.
7. It is crucial that all the methanol and 1,2-dichloroethane be removed from the reaction mixture to insure that all the oligomers are in the aqueous phase.
8. Newly formed methanol is removed at this stage. Only a small amount of methyl esters remains in the mixture at this point.
9. Low temperature during evaporation avoids condensation back to oligomers.
10. According to ¹H NMR analysis the crude product consists of more than 93% monomeric (R)-3-hydroxybutanoic acid, contaminated by 1–2% of methyl (R)-3-hydroxybutanoate and less than 0.2% of crotonic acid.
11. The crude product is placed in a 1-L, round-bottomed flask and distilled in an Aldrich Kugelrohr apparatus, heated with an air bath, the receiver bulb being cooled with ice water. Partial condensation of (R)-3-hydroxybutanoic acid to oligomers occurs if the temperature is too high during distillation (Note 12).
12. Drying in an evacuated desiccator over P₂O₅ removes water as well as methyl (R)-3-hydroxybutanoate and crotonic acid.
13. The spectra are as follows: IR (neat) cm⁻¹: 1710 (C=O); ¹H NMR (90 MHz, CDCl₃) δ: 1.25 (d, 3 H, CH₃), 2.50 (d, 2 H, CH₂), 4.20 (m, 1 H, CH), 7.70 (br s, 2 H, OH). For further data see ref. ².
14. The distillation residue (8–9 g) consists of water-soluble oligomers that can be saponified without loss of optical purity by heating at reflux with aqueous acid for 15 hr.
15. The submitters report a yield of 45–48 g (74.5–79%) using PHB obtained from Marlborough Biopolymers. The checkers verified this result using PHB obtained from the submitters. The yield reported here represents the checker's results with PHB obtained from Fluka Chemie.

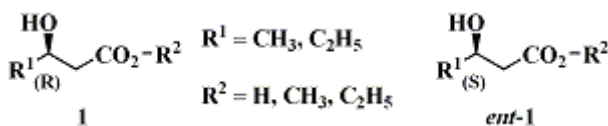
Waste Disposal Information

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

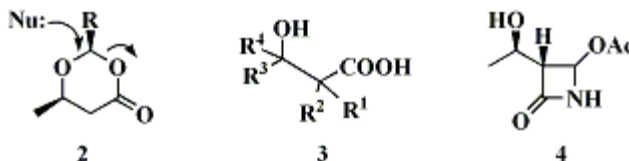
3. Discussion

Optically active 3-hydroxybutanoic acid and its methyl ester were first prepared by McKenzie, Magnus-Levy, and Emil Fischer.³ The biopolymer PHB and mixed polymers containing (R)-3-hydroxybutanoate and (R)-3-hydroxypentanoate were also discovered long ago,^{4,5} and are now produced on an industrial scale.^{6,7,8} As described here, depolymerization by transesterification [H⁺ or Ti(OR)₄

catalysis], or by hydrolysis, produces^{9,10 11 12} the corresponding monomeric (R)-esters and (R)-acids **1**. The 3-hydroxybutanoic acid can also be prepared by hydrolysis of the ester.^{2,13}



The enantiomeric compounds, ent-**1**, are available from **1** by inversion through sulfonates¹⁴ or through β -lactones.^{15 16} Ethyl (S)-3-hydroxybutanoate of 86–95 % ee has also been made by yeast reduction of acetoacetate.¹⁷ Either the ester **1** or ent-**1** can be prepared by enantioselective hydrogenation of the methyl acetoacetate with a Ru-BINAP catalyst.¹⁸



The hydroxy acid derivatives **1** are most versatile auxiliaries and building blocks for the synthesis of enantiomerically pure products.^{7,11,19} Thus, in an improvement of Johnson's method,²⁰ the dioxanones **2** can be used for overall enantioselective nucleophilic additions to aldehydes.²¹ Through open-chain²² or cyclic²³ lithium enolates derived from **1** and, through dioxinones,²⁴ new substituents can be introduced at carbons (2), (3) and (4) of hydroxybutanoic or hydroxypentanoic acid to give enantiomerically pure products^{25,26} of type **3**. Another application is the incorporation of (R)-3-hydroxybutanoic acid into the antibiotic thienamycin²⁷ through the β -lactam **4**.

References and Notes

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

H₂O

P₂O₅

brine

(R)-(-)-Methyl 3-hydroxybutanoate

(R)-(-)-3-Hydroxybutanoic acid

PHB

POLY[(R)-3-HYDROXYBUTYRIC ACID]

homopolymer to Butanoic acid, 3-hydroxy-, (R)-

poly-[(R)-3-hydroxybutyric acid]

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

1,2-dichloroethane (107-06-2)

magnesium sulfate (7487-88-9)

crotonic acid (3724-65-0)

Methyl acetoacetate (105-45-3)

3-Hydroxybutanoic acid (300-85-6)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

(R)-3-Hydroxybutanoic acid,
Butanoic acid, 3-hydroxy-, (R)- (625-72-9)

methyl (R)-3-hydroxybutanoate,
Butanoic acid, 3-hydroxy-, methyl ester, (R)-,
(R)-3-hydroxybutanoic acid, methyl ester (3976-69-0)

(R)-3-hydroxybutanoate

(R)-3-hydroxypentanoate

Ethyl (S)-3-hydroxybutanoate (56816-01-4)

hydroxypentanoic acid (13392-69-3)

(S)-3-hydroxybutanoic acid (6168-83-8)