



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

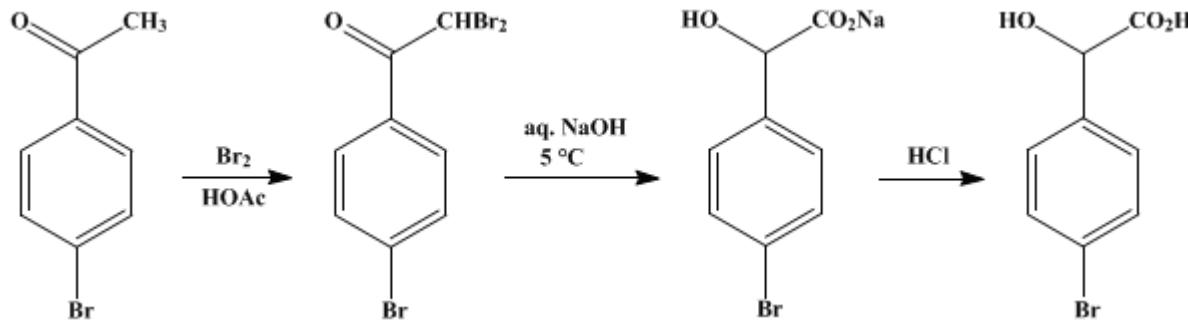
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The 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.

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.

Organic Syntheses, Coll. Vol. 4, p.110 (1963); Vol. 35, p.11 (1955).

p-BROMOMANDELIC ACID**[Mandelic acid, *p*-bromo]**Submitted by J. J. Klingenberg¹

Checked by R. T. Arnold and C. D. Wright.

1. Procedure

A. *p,a,a-Tribromoacetophenone*. In a 1-l. three-necked flask (Note 1) equipped with an efficient mechanical stirrer, a dropping funnel, and a gas outlet leading to a hood or trap are placed 100 g. (0.5 mole) of *p*-bromoacetophenone (Note 2) and 300 ml. of glacial acetic acid. The resulting solution is stirred and cooled to 20°, and a solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise (Note 3). Crystals of the mono- α -brominated derivative separate during the addition, which requires about 30 minutes. When the addition is completed, a second solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise. Slight heating may be necessary to keep the reaction proceeding, as indicated by decolorization of the bromine, but the temperature should be kept as near 20° as possible. During the addition, which requires about 30 minutes, the solid dissolves and crystals of the di- α , α -brominated derivative appear toward the end of the addition. The flask is heated to dissolve the contents, which are transferred, preferably in a hood, to a 1-l. beaker and cooled rapidly by means of an ice-water bath (Note 4). The mixture is filtered with suction (Note 5), and the solid is washed with 50% ethanol until colorless. The air-dried product has a slight pink cast and melts at 89–91°. The yield is 130–135 g. (73–75%) (Note 6). A pure, white solid melting at 92–94° is obtained by recrystallization from ethanol, but the initial product is sufficiently pure for the next step.

B. *p-Bromomandelic acid*. In a Waring-type blender are placed 89 g. (0.25 mole) of *p,a,a*-tribromoacetophenone and 100–150 ml. of cold water. The mixture is stirred for 10–15 minutes, and the contents are transferred to a 1-l. wide-mouthed bottle. The mixing vessel is rinsed with 150–200 ml. of ice-cold water. The material from the rinse is combined with the mixture in the bottle, and sufficient crushed ice is added to bring the temperature below 10°. One hundred milliliters of a chilled aqueous solution containing 50 g. of sodium hydroxide is added slowly while the bottle is rotated (Note 7). The contents are stored for approximately 4–5 days in a refrigerator (5°) and are shaken occasionally. During this time most of the solid dissolves, but a slight amount remains as a yellow sludge and the liquid assumes a yellow to amber color. The mixture is filtered, and the insoluble material is discarded. An excess of concentrated hydrochloric acid is added to the filtrate. The entire resulting mixture containing a white solid is extracted with three 200-ml. portions of ether. The ether extracts are combined, dried over anhydrous sodium sulfate, and filtered into a 1-l. flask. The ether is carefully removed by distillation using a hot-water bath to give a yellow oil which solidifies when cooled. The product is recrystallized from 500 ml. of benzene. The crystals are collected by filtration and washed with benzene until the filtrate is colorless. The air-dried product (Note 8) weighs 40–48 g. (69–83% based on *p,a,a*-tribromoacetophenone), m.p. 117–119° (Note 9). A second recrystallization from 500 ml. of benzene is sometimes necessary.

2. Notes

1. The use of ground-glass equipment is desirable but not necessary.
2. The preparation of *p*-bromoacetophenone is described in *Organic Syntheses*.² The compound is also available from Eastman Kodak Company.
3. Sometimes the initiation of the reaction is slow. The reaction may be started by heating the solution until the bromine is decolorized (approximately 45°), after which the reaction will proceed normally at 20°.
4. The checkers found that maximum yields of product were obtained when cooling was carried to the point where crystallization of the solvent commenced. The trace of crystalline solvent quickly melts during the filtering procedure.
5. These compounds are lachrymatory and should be kept away from the eyes.
6. An additional quantity of less pure material can be isolated from the glacial acetic acid mother liquid and alcohol filtrates by evaporation of the solvent. This, after recrystallization from ethanol, amounts to 15–30 g.
7. It is important that the reaction mixture be kept cold at this point. The amount of sludge and colored material increases as the temperature increases.
8. The last traces of benzene leave very slowly and if present lower the melting point. The product should be thoroughly dried in air or on a clay plate before the melting point is taken.
9. Under similar conditions, *p*-chloromandelic acid melting at 119–120° was obtained from *p*-chloroacetophenone in 54% yield and *p*-iodomandelic acid melting at 135–136° from *p*-iodoacetophenone in 21% yield.

3. Discussion

p-Bromomandelic acid has been prepared by the bromination of *p*-bromoacetophenone followed by alkaline hydrolysis;³ by the alkaline hydrolysis of the product formed by the addition of chloral to *p*-bromophenylmagnesium bromide;⁴ and by the condensation of bromobenzene and ethyl oxomalonate in the presence of stannic chloride followed by hydrolysis and decarboxylation.⁵ *p*-Bromomandelic acid is a valuable reagent in the analyses of zirconium and hafnium.⁶

References and Notes

1. Xavier University, Cincinnati, Ohio.
2. *Org. Syntheses Coll. Vol. 1*, 109 (1941).
3. Collect, *Bull. soc. chim. France*, [3] 21, 67 (1899).
4. Hebert, *Bull. soc. chim. France*, [4] 27, 45 (1920).
5. Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938).
6. Hahn, *Anal. Chem.*, **23**, 1259 (1951); Klingenberg and Papucci, *Anal. Chem.*, **24**, 1861 (1952).

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

bromobenzene (108-86-1)

Ethyl oxomalonate

stannic chloride (7646-78-8)

chloral (75-87-6)

p, α , α -Tribromoacetophenone (13195-79-4)

zirconium

hafnium

p-Bromoacetophenone (99-90-1)

p-Chloroacetophenone (99-91-2)

p-iodoacetophenone (13329-40-3)

p-bromophenylmagnesium bromide

p-Bromomandelic acid,
Mandelic acid, p-bromo (6940-50-7)

p-chloromandelic acid (492-86-4)

p-iodomandelic acid