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.

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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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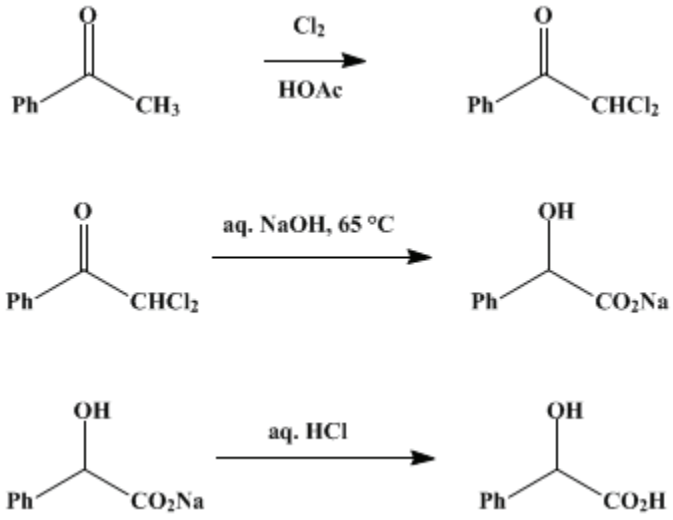
MANDELIC ACID



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Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

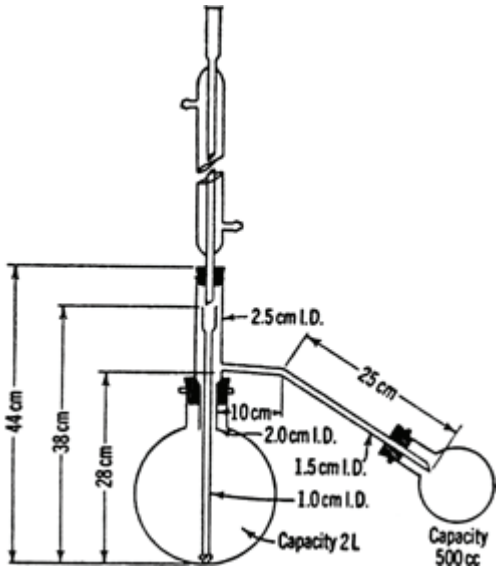
A. *Dichloroacetophenone*. A 3-l. round-bottomed flask is fitted with a three-holed rubber stopper through which are passed an inlet tube extending to the bottom of the flask, an outlet tube, and a thermometer. The inlet tube is connected to a cylinder of chlorine through a bubble counter consisting of a 500-ml. wash bottle which contains about 200 ml. of concentrated sulfuric acid. The outlet tube is connected with a gas trap in which the evolved hydrochloric acid is absorbed by running water. It is best to set up the apparatus under a good hood.

In the flask are placed 240 g. (2 moles) of acetophenone and 1 l. of glacial acetic acid. The thermometer is adjusted so that it extends considerably below the surface of the solution, and chlorine is admitted at such a rate that the temperature does not exceed 60° (Note 1). Chlorination is continued until an excess of the halogen has been absorbed. This requires about 5 hours; completion of the reaction is indicated by the development of a yellow color. The reaction mixture is poured over 6 l. of crushed ice in a 2-gal. jar. The mixture is stirred several times (Note 2) and allowed to stand until the ice has melted. The dichloroacetophenone, which separates as a heavy lachrymatory oil, is removed. The yield is 340–370 g. (90–97%). This product, containing only a few per cent of water and acetic acid, is pure enough for the preparation of mandelic acid. It may be purified by adding about 100 ml. of benzene, removing the water and benzene by distillation, and fractionally distilling the residual oil under reduced pressure. There is obtained 302–356 g. (80–94%) of a colorless oil boiling at 132–134°/13 mm. (142–144°/25 mm.).

B. *Mandelic acid*. In a 2-l. three-necked round-bottomed flask, fitted with an efficient mechanical stirrer, a dropping funnel, and a thermometer, is placed 156 g. (3.9 moles) of sodium hydroxide dissolved in 1.4 l. of water. The solution is warmed to 60° (Note 3), vigorous stirring is begun, and 200 g. (1.06 moles) of dichloroacetophenone (either crude or distilled) is added from the dropping funnel. The dichloroacetophenone is added slowly at first so that the temperature does not exceed 65°. The addition requires about 2 hours (Note 4). Stirring is continued for 1 hour longer while the temperature is maintained at 65° by means of a water or steam bath. After addition of 170 ml. of 12 *M* hydrochloric acid (Note 5), the solution is extracted with ether. The continuous extractor shown in Fig. 18 is very useful for this purpose. About 250–300 ml. of ether is used, and the extraction is continued until no more material is obtained. With this apparatus, about 130 g. of crude mandelic acid is recovered after 24 hours, and 150 g. after 48 hours. The volume of liquid in the larger flask must be great enough so that,

when 250–300 ml. of ether is used for the extraction, there will be a continuous overflow from the larger to the smaller flask; the latter serves as the "boiler."

Fig. 18.



The ether extracts are transferred to a 1-l. round-bottomed flask, the ether is removed by distillation, and the residue of crude mandelic acid is dried by warming it on a steam bath under the vacuum of a water pump. About 400 ml. of benzene is added, and the mixture is distilled until 100 ml. of distillate is collected. The acid in the residual mixture is brought completely into solution by the addition of 6–10 ml. of ethanol. The hot solution is then filtered through a warm Büchner funnel, and the filtrate is cooled overnight at 6°. The first crop of pure mandelic acid weighs 100–120 g. A second crop is obtained by evaporation of the mother liquor to about one-fourth its volume; this weighs 20–40 g. The total yield is 136–144 g. (85–90% based on the dichloroacetophenone, or 76–87% based on the acetophenone). The white crystalline product melts at 115–117° (Note 6).

2. Notes

1. According to Beilstein (**VII**, 283) trichloroacetophenone is obtained by chlorination of acetophenone at elevated temperatures.[1] However, at 60° less than 1% of trichloroacetophenone is formed.
2. Stirring results in a better separation of acetic acid from the oil and prevents the formation of an emulsion.
3. At lower temperatures, hydrolysis is slow.
4. If the temperature becomes much higher, side reactions occur and loss in yield and purity results. The heat of reaction is sufficient to maintain the required temperature.
5. If the reaction mixture is cooled at this point, some of the mandelic acid may crystallize. If this happens, the precipitate should not be filtered, as it is contaminated with sodium chloride.
6. The submitters report that when 1 kg. of acetophenone is used yields of 0.98–1.06 kg. of mandelic acid are obtained.

3. Discussion

Dichloroacetophenone has been prepared by chlorination of acetophenone with and without aluminum chloride;[2] by action of dichloroacetyl chloride upon benzene and aluminum chloride;[2] by action of hypochlorous acid upon phenylacetylene;[1] by heating trichloromethylphenylcarbinol;[3] and by chlorination of phenylacetylene in alcohol.[4]

Mandelic acid has been prepared by hydrolysis of mandelonitrile (prepared in turn from benzaldehyde and hydrogen cyanide or from benzaldehyde, sodium bisulfite, and sodium cyanide);[5] by action of water at 180° upon trichloromethylphenylcarbinol;[6] by action of potassium carbonate upon a

heated mixture of benzaldehyde and chloroform;[7] by action of warm, dilute alkali upon dibromoacetophenone;[8] by the action of warm, dilute sodium hydroxide upon phenylglyoxal;[9] by the hydrolysis of α-bromophenylacetic acid[10] or dimethyl α-cyano-α-hydroxybenzylphosphonate;[11] and by the hydrolysis of ethyl mandelate, prepared in turn by the catalytic reduction of phenylglyoxalate.[12]

α-C^{14}-Mandelic acid has been prepared from α-C^{14}-phenylglyoxal, and from α-C^{14}-α,α-dibromoacetophenone.[13] α-C^{13}-Mandelic acid has been prepared from α-C^{13}-α,α-dibromoacetophenone.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 572

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

α-C^{14}-Mandelic acid

α-C^{14}-phenylglyoxal

α-C^{14}-α,α-dibromoacetophenone

α-C^{13}-Mandelic acid

α-C^{13}-α,α-dibromoacetophenone

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

chloroform (67-66-3)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

Phenylglyoxal (1074-12-0)

mandelonitrile (532-28-5)

hypochlorous acid (7790-92-3)

Phenylacetylene (536-74-3)

dichloroacetyl chloride (79-36-7)

α-Bromophenylacetic acid (4870-65-9)

Ethyl mandelate (4358-88-7)

dichloroacetophenone (2648-61-5)

trichloroacetophenone (2902-69-4)

trichloromethylphenylcarbinol (2000-43-3)

dibromoacetophenone

dimethyl α-cyano-α-hydroxybenzylphosphonate

phenylglyoxalate