



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](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.

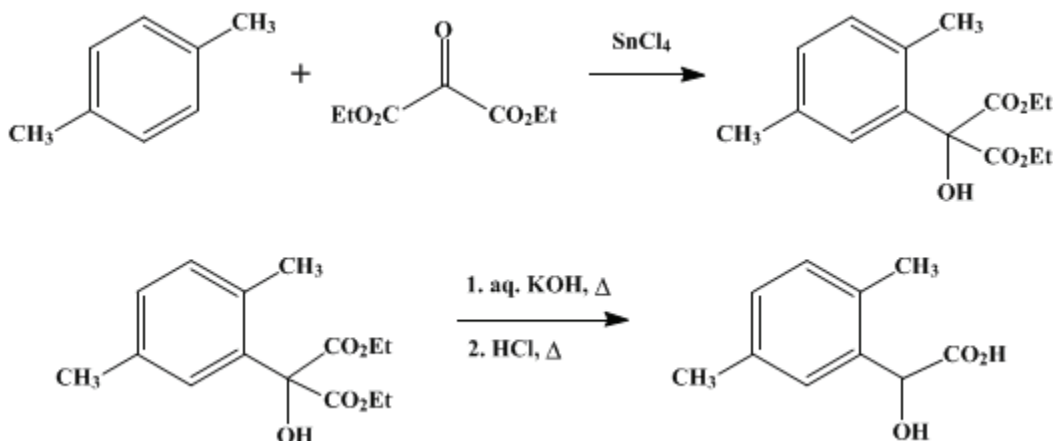
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries 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. 3, p.326 (1955); Vol. 25, p.33 (1945).*

## 2,5-DIMETHYLMANDELIC ACID

[Mandelic acid, 2,5-dimethyl-]



Submitted by J. L. Riebsomer and James Irvine.

Checked by H. R. Snyder and R. L. Rowland.

### 1. Procedure

A. *Ethyl 2,5-dimethylphenylhydroxymalonate*. One hundred and seventy-four grams (1 mole) of ethyl oxomalonate (Note 1) and 265 g. (2.5 moles) of *p*-xylene are mixed in a 1-l. three-necked flask equipped with a good stirrer, a dropping funnel, and a calcium chloride drying tube. Suitable precautions are taken to exclude moisture from the reaction mixture. While the mixture is cooled in an ice-water bath and stirred vigorously, 325 g. (1.25 moles) of anhydrous stannic chloride is added dropwise from the funnel. After the addition is complete, the cooling bath is removed and stirring is continued for 3 hours. The reaction mixture is poured with stirring into about 300 g. of cracked ice containing 50 ml. of concentrated hydrochloric acid. On standing this mixture separates into two layers. Two hundred milliliters of ether is added, and the ether layer is washed with 100-ml. portions of water until the wash water is free from chlorides. The ether solution is dried with anhydrous sodium sulfate and distilled. After removal of the ether and the excess of reagents (Note 2), the fraction boiling at 154–156°/5 mm. is collected. The yield of 2,5-dimethylphenylhydroxymalonic ester is 144.5–160 g. (51.5–57%).

B. *2,5-Dimethylmandelic acid*. A mixture prepared from 140 g. (0.5 mole) of 2,5-dimethylphenylhydroxymalonic ester and a cold solution of 140 g. of potassium hydroxide in 560 ml. of water in a 1-l. round-bottomed flask is warmed on a steam bath for 5 hours. The alkaline solution is cooled and extracted with one 100-ml. portion of ether to remove any material not soluble in alkali. The alkaline solution is acidified with 300 ml. of concentrated hydrochloric acid and then warmed on a steam bath and stirred for 2 hours (or until there is no further evidence that carbon dioxide is escaping). The mixture is cooled, the oily layer is extracted with ether, the ethereal solution is dried with anhydrous sodium sulfate, and the ether is distilled under partial vacuum (Note 3). The oily residue is crystallized from benzene. The yield of 2,5-dimethylmandelic acid melting at 116.5–117° is 55–63 g. (63–70%) (Note 4).

### 2. Notes

1. The ethyl oxomalonate must be of good quality. It has been found possible to use nitrogen peroxide (now available in cylinders from the du Pont Company) in the preparation of this reagent. The general conditions are the same as in the previous method in *Organic Syntheses*<sup>1</sup> except that the generating flask containing arsenious oxide and nitric acid is replaced with a cylinder of nitrogen peroxide. This method

is much more satisfactory.

2. The excess *p*-xylene can be recovered easily.

3. It is important to avoid long heating after removal of the ether. The mandelic acid tends to react with itself.

4. This general method has been applied to the synthesis of a variety of alkyl-substituted mandelic acids.<sup>2</sup>

### 3. Discussion

2,5-Dimethylmandelic acid has been prepared by the procedure described above;<sup>2</sup> and by the reaction between 2,5-dimethylphenylmagnesium bromide and chloral, followed by alkaline hydrolysis.<sup>3</sup>

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### References and Notes

1. *Org. Syntheses Coll. Vol. 1*, 266 (1941).
2. Ando, *J. Chem. Soc. Japan*, **56**, 745 (1935) [*C. A.*, **29**, 7960 (1935)]; Riebsomer, Irvine, and Andrews, *J. Am. Chem. Soc.*, **60**, 1015 (1938); *Proc. Indiana Acad. Sci.*, **47**, 139 (1938); Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938); Riebsomer, Stauffer, Glick, and Lambert, *J. Am. Chem. Soc.*, **64**, 2080 (1942).
3. Savarian, *Compt. rend.*, **146**, 297 (1908) [*C. A.*, **2**, 1443 (1908)].

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### Appendix

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

arsenious oxide

2,5-dimethylphenylhydroxymalonic ester

2,5-dimethylphenylmagnesium bromide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Mandelic acid (90-64-2)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

*p*-xylene (106-42-3)

Ethyl oxomalonate

stannic chloride (7646-78-8)

chloral (75-87-6)

2,5-Dimethylmandelic acid,  
Mandelic acid, 2,5-dimethyl-

nitrogen peroxide

Ethyl 2,5-dimethylphenylhydroxymalonate