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.

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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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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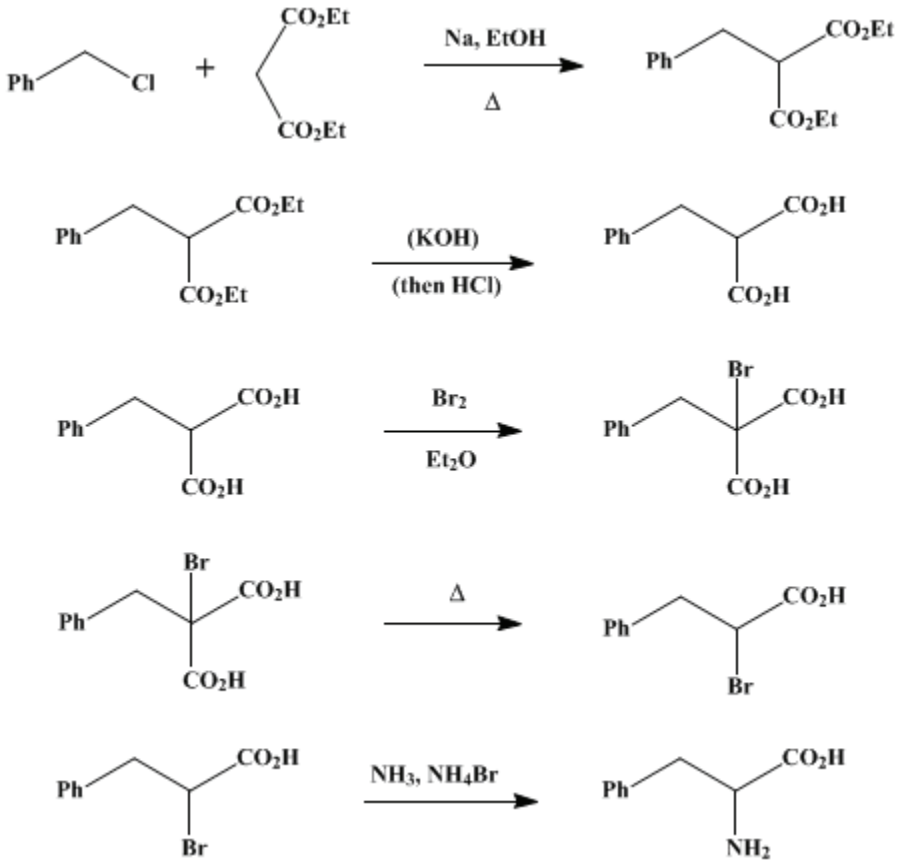
Organic Syntheses, Coll. Vol. 3, p.705 (1955); Vol. 21, p.99 (1941).

dl-PHENYLALANINE

[Alanine, phenyl-]



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1. Procedure

A. *Diethyl benzylmalonate*. To 2.5 l. of absolute ethanol in a 5-l. three-necked flask set on a steam cone and equipped with a mercury-sealed stirrer, reflux condenser, and a 500-ml. dropping funnel is added 115 g. (5 gram atoms) of sodium cut in small slices. When all the sodium has reacted, a calcium chloride tube is placed on the condenser and 830 g. (5.18 moles) of diethyl malonate is added through the separatory funnel in a steady stream. This is followed by the dropwise addition of 632 g. (5 moles) of benzyl chloride over a period of 2–3 hours. The mixture is refluxed, with stirring, until neutral to moist litmus paper (about 8–11 hours). The reflux condenser is then exchanged for a downward condenser, and the ethanol is distilled into another 5-l. three-necked flask equipped with a reflux condenser (Note 1). About 3 hours is required to remove the ethanol, and slightly more than 2 l. is recovered.

The residue is then treated with no more than 2 l. of water (Note 2) and shaken; if necessary, salt is added to make the ester layer separate sharply from the aqueous layer. The combined ester layers from two such runs are distilled from a 5-l. two-necked flask fitted with a well-wrapped 18-mm. Vigreux column. The fraction distilling at 145–155°/5 mm. is collected; it amounts to 1265–1420 g. (51–57%). The residue is chiefly diethyl dibenzylmalonate.

B. *α-Bromo-β-phenylpropionic acid*. Eight hundred and sixty grams of technical potassium

hydroxide is dissolved in 850 ml. of water in a 12-l. round-bottomed flask equipped with a stirrer and set on a large steam cone. While the solution is still hot, 1 kg. (4 moles) of diethyl benzylmalonate is added from a dropping funnel over a period of 1 hour. The removal of alcohol vapors is facilitated by placing a tube connected to the water pump in the mouth of the flask. Heating and stirring are continued for 3 hours, and more water is added, if necessary, to keep the mass from solidifying. The flask is then cooled and the contents poured into a crock surrounded by an ice bath and equipped with a stirrer. Five hundred grams of ice is added to lower the temperature; when it reaches 20°, technical hydrochloric acid is added at such a rate that the temperature does not rise. The addition is slow at first, but more rapid when the excess alkali has been neutralized. The solid monopotassium salt that separates is returned to solution by adding the acid more rapidly and stirring by hand. When the reaction mixture is acid to Congo red paper, an excess of 150 ml. of acid is added and the contents of the crock are transferred to a 12-l. round-bottomed flask fitted with a stopper containing a large stopcock which barely pierces the stopper, and a glass tube which reaches to the bottom of the flask. In this way the flask may be used as a large separatory funnel if the stopper is wired in tightly.

The benzylmalonic acid is extracted with four 1-l. portions of ether; the ether extracts are combined in a 5-l. flask and allowed to stand over 150 g. of calcium chloride overnight. The ether layer is then decanted into a 5-l. flask equipped with an efficient reflux condenser, mercury-sealed stirrer, and dropping funnel. Two hundred and twenty-five milliliters of dry bromine is dropped in at such a rate that the ether refluxes (Note 3). The time required is about 4 hours. After the complete addition of bromine, 1 l. of water is added through the dropping funnel at such a rate that the ether merely refluxes (Note 4).

The ether layer of bromobenzylmalonic acid is separated by decantation and the ether removed by distillation. The residue is then decarboxylated by heating to a temperature of 130–135° in a 3-l. flask in an oil bath for 5 hours.

C. *dl-Phenylalanine.* The crude bromo acid is divided into four portions and each portion is added to 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask. The flask is well shaken, a rubber stopper is wired in, and the mixture is allowed to stand for a week. The contents of the four amination flasks (Note 5) are then combined in a 12-l. flask, 20 g. of Norit is added, and the flasks are heated on a steam cone overnight. The ammonia which is evolved is conducted into a gas-absorption trap or merely led into water by a tube from the flask. The solution is filtered while still hot; on cooling most of the phenylalanine precipitates. This is filtered, washed with 250 ml. of methanol, and the filtrate evaporated under the pressure of a water pump until more crystals form. The solution is then cooled and an additional crop of phenylalanine obtained, which is also washed with methanol. The yield of crude product is 500 g., but it is slightly wet; if it is dried overnight in an oven at about 80°, it will weigh 460 g. This need not be done, however, as the yield of pure product is the same whether or not the crude product is dried.

The phenylalanine is recrystallized as follows: the crude product is dissolved in 9 l. of water heated to 95° on a steam cone, treated with 15 g. of Norit, and filtered. Three liters of alcohol is added and the solution cooled in the ice chest overnight. The yield of pure product amounts to 367 g. An additional 45 g. may be obtained by evaporating the mother liquor under reduced pressure until crystals separate, adding an amount of alcohol equivalent to one-third the volume of the concentrated mother liquor, and cooling. Additional material may be obtained by continuing to work down all mother liquors. The yield, 412 g., is 62.4% based on the diethyl benzylmalonate. The white crystals decompose at 271–273° (uncor.) in a closed capillary (Note 6).

2. Notes

1. The sodium required for the next run can be added to the second flask as the alcohol distils into it.
2. Usually 1.5 l. of water suffices, and it is not necessary to add salt.
3. To start the bromination 10 ml. of bromine is added and the solution stirred until decolorized. After the reaction has been started in this manner, it runs very smoothly. When large amounts of the amino acid are to be prepared, it is more convenient to double the portion used in the bromination step.
4. Care must be taken not to add the water too fast, as the reaction mixture will foam out of the flask.
5. The aminations are usually colored, and frequently the flasks contain small deposits of oil on the

bottom. This oil disappears in subsequent treatment.
6. The product thus obtained has the calculated amino nitrogen content.

3. Discussion

Methods of making *dl*-phenylalanine have been summarized [*Org. Syntheses* Coll. Vol. **2**, 489 (1943)]. The method described here is essentially the one originally described by Fischer.[2] For the preparation of large amounts of amino acids it is undoubtedly the cheapest and best procedure.

Additional preparative methods include the hydrolysis and decarboxylation of benzyl formamidomalonic ester,[3] benzylacetamidomalonic ester,[4] or benzylacetamidocyanoacetic ester.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 489

References and Notes

1. These directions are the result of the efforts of many men who have worked on the preparation of phenylalanine at the University of Illinois.
2. Fischer, *Ber.*, **37**, 3064 (1904).
3. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).
4. Albertson and Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).
5. Albertson and Tullar, *J. Am. Chem. Soc.*, **67**, 502 (1945).

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

benzyl formamidomalonic ester

benzylacetamidomalonic ester

benzylacetamidocyanoacetic ester

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

bromine (7726-95-6)

nitrogen (7727-37-9)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

ammonium hydroxide (1336-21-6)

diethyl malonate (105-53-3)

phenylalanine (63-91-2)

α-Bromo-β-phenylpropionic acid (42990-49-8)

Alanine, phenyl- (63-91-2)

diethyl dibenzylmalonate

Diethyl benzylmalonate (607-81-8)

benzylmalonic acid (616-75-1)

bromobenzylmalonic acid

DL-Phenylalanine (150-30-1)