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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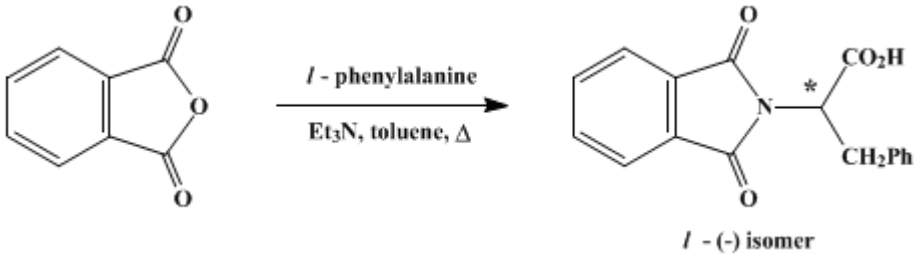
N-PHTHALYL-L-β-PHENYLALANINE

[2-Isoindolineacetic acid, α-benzyl-1,3-dioxo-, L-]



Submitted by Ajay K. Bose[1]
Checked by Max Tishler and George A. Doldouras.

1. Procedure

In a 300-ml. flask fitted with a water separator and a reflux condenser are placed 16.5 g. (0.1 mole) of L-phenylalanine (Note 1), 14.8 g. (0.1 mole) of finely ground phthalic anhydride, 150 ml. of toluene, and 1.3 ml. of triethylamine. The flask is heated on an oil bath or with an electric mantle so as to maintain a vigorous reflux (Note 2). Separation of water is rapid at the beginning but becomes slower with time and is virtually over in 1.5 hours.

After 2 hours the water separator and the reflux condenser are disconnected, and volatile material is removed from the mixture under reduced pressure and on a steam bath (Note 3). The solid residue is stirred with 200 ml. of cold water and 2 ml. of hydrochloric acid until all the lumps are broken (Note 4).

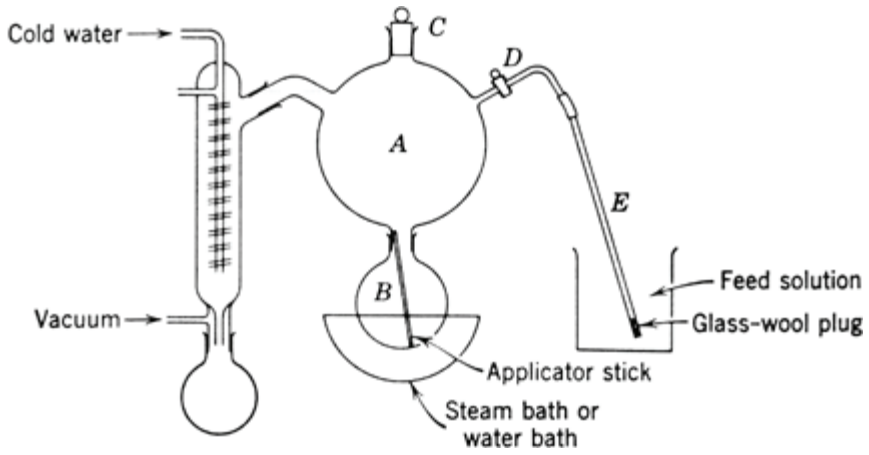
The mixture is filtered under suction, and the product is washed with three 50-ml. portions of cold water. After drying in an air oven the product weighs 27–28 g. (91.5–95%) and consists of a white crystalline powder, m.p. 179–183°, $[\alpha]_D^{25}$ −198 to −200° (in alc.) (Note 5).

This product can be recrystallized by dissolving 10 g. in 20 ml. of hot ethyl alcohol (95%), adding 14 ml. of water, and allowing the solution to cool slowly so that no oiling out takes place. Colorless needles, m.p. 183–185°, $[\alpha]_D^{25}$ −211 to −217° (in alc.) (Note 6), are obtained (first crop, 7.5–8.5 g., 83–90% recovery; further quantities can be recovered from the mother liquor).

2. Notes

1. Material (supplied by Nutritional Biochemicals Corp., Cleveland, Ohio) of $[\alpha]_D^{25}$ −32° (*c* = 1.98 in water) was used.
2. An applicator stick (available from drug stores) can be used very conveniently to ensure smooth boiling. If a boiling chip is used, it should be colored (Carborundum, for example) to make its separation from the product convenient.
3. This evaporation during which a solid separates is very conveniently carried out in a rotary vacuum evaporator (manufactured by Rinco Instrument Co., Greenville, Illinois). An equally convenient alternative arrangement for solvent stripping that is in use in some laboratories is shown in Fig. 1. The splash-head *A* permits rapid removal of solvent under reduced pressure. Any solid carried beyond the flask *B* by spattering is arrested in *A* and can be washed down into *B* by introducing a low-boiling liquid like acetone through the port *C*. The side arm *D* permits continuous feeding into the "stripper." If the feed tube *E* is fitted with a plug of glass wool, the feed solution can be automatically filtered from suspended solids such as drying agents. Another advantage of this stripper is that a conveniently small collecting flask *B* can be used for a feed solution that is very dilute and large in volume.

Fig. 1. Solvent stripper.



4. The purity of the product depends largely on the efficient breaking up of all lumps and the subsequent washing.
5. This material gives satisfactory elemental analysis and can be used without purification for further reactions.
6. The checkers observed a rotation of −211 to −217°, as against −207 to −212° reported by the submitter; Sheehan, Chapman, and Roth[2] report −212°.

3. Discussion

N-Phthalyl-L-phenylalanine has been prepared by the fusion of L-alanine with phthalic anhydride.[2]

The present method, based on a recent publication,[3] ensures a low temperature of reaction which precludes racemization and is more convenient than the fusion method for large-scale operation.

The method described here can be applied to other amino acids and on a larger scale. Thus β-alanine on a 1.5-mole scale gave *N*-phthalyl-β-alanine in 96% yield and L-alanine gave N-phthalyl-L-alanine in 91% yield, and glycine ethyl ester hydrochloride (using more than one molar equivalent of triethylamine) gave the ethyl ester of N-phthalylglycine in 96% yield.

References and Notes

1. Department of Chemistry, Stevens Institute, Hoboken, New Jersey.
2. J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).
3. A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

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

N-Phthalyl-L-β-phenylalanine

N-Phthalyl-L-phenylalanine

N-phthalyl-β-alanine

N-phthalyl-L-alanine

ethyl ester of N-phthalylglycine

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

L-alanine (56-41-7)

phthalic anhydride (85-44-9)

acetone (67-64-1)

toluene (108-88-3)

β-Alanine (107-95-9)

Glycine ethyl ester hydrochloride (623-33-6)

phenylalanine (63-91-2)

triethylamine (121-44-8)

2-Isoindolineacetic acid, α-benzyl-1,3-dioxo-, L-