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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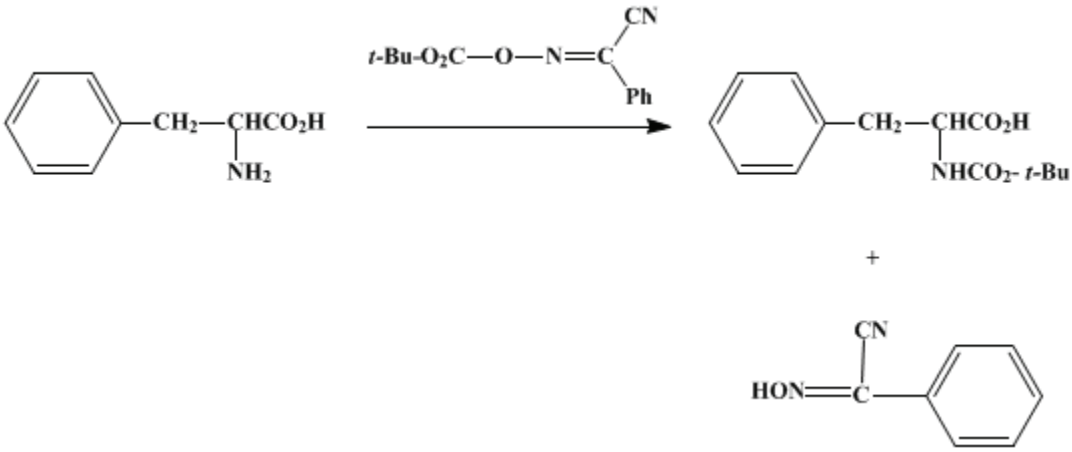
N-*tert*-BUTOXYCARBONYL-l-PHENYLALANINE

[L-Phenylalanine, *N*[(1,1-dimethylethoxy)carbonyl)]-]



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Checked by Mark A. Sanner, Thomas von Geldern, and Clayton H. Heathcock.

1. Procedure

To a stirred mixture of 16.51 g (0.1 mol) of L-phenylalanine in 60 mL of water and 60 mL of peroxide-free dioxane (Note 1) is added 21 mL of triethylamine. To the resulting solution is added 27.1 g (0.11 mol) of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Note 2). Solution is obtained during the first hour of stirring. After 3 hr (Note 3) the solution is diluted with 150 mL of water. The resulting turbid solution is extracted with at least four 200-mL portions of ethyl ether (Note 4). The aqueous layer is then acidified to pH 2.5 with cold 2.5 *N* hydrochloric acid to yield an oily layer. The mixture is extracted with three 100-mL portions of methylene chloride. The combined organic extracts are dried with anhydrous sodium sulfate. After filtration of the sodium sulfate, the filtrate is evaporated under reduced pressure at a bath temperature of 30°C. Hexane is added to the thick oil to turbidity. Crystallization occurs after cooling and stirring the mixture for a short time. More hexane is added in portions until no further crystallization occurs. A total of 200 mL of hexane is required. The mixture is allowed to stand for 1 hr. The white crystalline solid is collected by filtration, washed with three 100-mL portions of hexane, and dried under reduced pressure to yield 21.4–22.0 g (80–83%) of *tert*-butoxycarbonyl-L-phenylalanine, mp 86–88°C, $[\alpha]_D^{20}$ −3.6° (HOAc, *c* 1), $[\alpha]_{546}^{20}$ 29.9° [EtOH, *c* 1) (Note 5).

2. Notes

1. Peroxides are removed from dioxane by its passage through a column of neutral alumina.[2]
2. 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile is obtained from Aldrich Chemical Company, Inc., under the trademark "BOC-ON."
3. The reaction is allowed to continue until TLC (Whatman K1F, ethyl acetate–pyridine–acetic acid–water, 10:5:1:3) shows that the unprotected amino acid (R_f 0.4) is no longer present, as evidenced by negative ninhydrin spray.
4. It is imperative that all the by-product is removed at this point; otherwise it will contaminate the product, making crystallization difficult. Each ether extract is spotted on a Whatman K1F plate and the plate viewed under UV light to ascertain that all of the by-product has been extracted. The checkers found that six or seven ether extractions were required to remove the by-product completely.
5. The literature gives melting points ranging from 79–80°C to 84–86°C; the optical rotation is reported as $[\alpha]_D^{25}$ −0.8° (HOAc, *c* 4.957), $[\alpha]_D^{20}$ −4.8° (HOAc, *c* 1), $[\alpha]_{546}^{20}$ 30° (EtOH, *c* 1).
The spectral properties of *tert*-butoxycarbonyl-L-phenylalanine are as follows: ^{1}H NMR (CD_3OD) δ:

1.36 (s, 9 H, *t*-butyl), 2.87 (dd, 1 H, *J* = 14.9, H_β), 3.16 (dd, 1 H, *J* = 14.6, H_β), 4.36 (dd, 1 H, *J* = 9.6, H_α), 7.26 (s, 5 H, phenyl). In $CDCl_3$ solution, both carbamate rotamers may be seen in the ^1H NMR spectrum.

3. Discussion

Various reagents have been used for the introduction of the *tert*-butoxycarbonyl group, including *tert*-butyl *p*-nitrophenyl carbonate,[3] *tert*-butyl azidoformate[4] (no longer commercially available because of its toxic and potentially explosive nature), *tert*-butyl 2,4,5-trichlorophenyl carbonate,[5] di-*tert*-butyl dicarbonate,[6] and the reagent described herein, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile.[7] Using the same reagent, the crystalline BOC derivatives of the following amino acids have been prepared in these laboratories in the indicated yields: 7-aminoheptanoic acid (88%), DL-tyrosine (96%), 6-fluoro-DL-tryptophan (87%), 5-methyl-DL-tryptophan (95%), 5-bromo-DL-tryptophan (94%), 5-methoxy-DL-tryptophan (67%), 1-methyl-DL-tryptophan (82%), and 5-fluoro-DL-tryptophan (62%).

References and Notes

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

alumina
L-Phenylalanine, N[(1,1-dimethylethoxy)carbonyl)]-

hydrochloric acid (7647-01-0)

ether,
ethyl ether (60-29-7)

sodium sulfate (7757-82-6)

methylene chloride (75-09-2)

dioxane (123-91-1)

L-phenylalanine (63-91-2)

hexane (110-54-3)

triethylamine (121-44-8)

tert-Butyl azidoformate (1070-19-5)

2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (58632-95-4)

ninhydrin (938-24-9)

7-aminoheptanoic acid (929-17-9)

tert-butyl 2,4,5-trichlorophenyl carbonate (16965-08-5)

Di-tert-butyl dicarbonate (24424-99-5)

N-tert-Butoxycarbonyl-L-phenylalanine,
tert-butoxycarbonyl-L-phenylalanine (13734-34-4)

tert-butyl p-nitrophenyl carbonate (13303-10-1)

DL-tyrosine

6-fluoro-DL-tryptophan (7730-20-3)

5-methyl-DL-tryptophan (951-55-3)

5-bromo-DL-tryptophan (6548-09-0)

5-methoxy-DL-tryptophan (28052-84-8)

1-methyl-DL-tryptophan (26988-72-7)

5-fluoro-DL-tryptophan (154-08-5)