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of Organic Compounds

Working with Hazardous Chemicals

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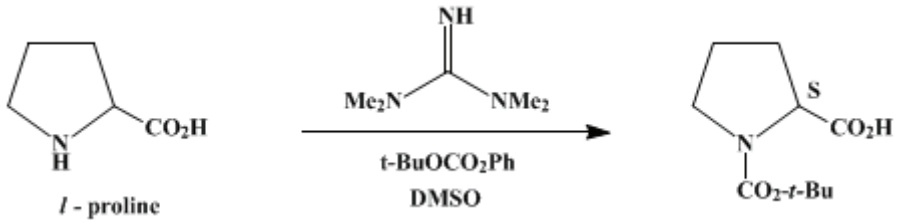
DOI:10.15227/orgsyn.053.0025

Organic Syntheses, Coll. Vol. 6, p.203 (1988); Vol. 53, p.25 (1973).

tert-BUTOXYCARBONYL-L-PROLINE

[1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (*S*)-]



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1. Procedure

A 1-l. Erlenmeyer flask (Note 1) equipped with a magnetic stirrer, and a thermometer is charged with 115 g. (1.00 mole) of L-proline (Note 2) and 500 ml. of dimethyl sulfoxide (Note 3). To the stirred suspension are added simultaneously, over 5 minutes, 115 g. (1.00 mole) of 1,1,3,3-tetramethylguanidine (Note 4) and 214 g. (1.10 moles) of *tert*-butyl phenyl carbonate (Note 5). The proline dissolves completely within a few minutes in an exothermic reaction, the temperature of which reaches a maximum of 50–52° after 10–15 minutes. After stirring for 3 hours, the clear reaction mixture is transferred to a 6-l. separatory funnel and shaken with 2.2 l. of water and 1.8 l. of diethyl ether (Note 6). The aqueous layer, after being washed with 500 ml. of ether, is acidified to pH 3.0 by the addition of 10% sulfuric acid (Note 7), which generally causes partial crystallization of the product. The acidic solution, including the solid, is extracted with three 600-ml. portions of a mixture of equal volumes of ethyl acetate and ether. The combined extracts are washed with three 25-ml. portions of water, dried over magnesium sulfate, filtered, and evaporated with a rotary evaporator at a bath temperature not exceeding 40°. After drying in a vacuum oven at 50°, the crude product weighs 202 g., m.p. 129–132°. It is recrystallized from 300 ml. of hot ethyl acetate, and clarified by filtration and the addition of 1 l. of petroleum ether (40–60°), yielding, after drying under vacuum at 50°, 179–193 g. (83–90%) of *tert*-butoxycarbonyl-L-proline, m.p. 132–134°, $[\alpha]_D^{25}$ −59.84° to −61.6° (*c* = 1, glacial acetic acid) (Note 8), (Note 9), and (Note 10).

2. Notes

1. A three-necked flask equipped with a U-tube may also be used for the reaction.
2. The submitters used L-proline obtained from Tanabe Seiyaku Company, Ltd., Osaka, Japan, and checked its purity by the method of Manning and Moore.[2] The L-proline used by the checkers was obtained from Ajinomoto Company, New York.
3. Dimethyl sulfoxide, Fisher Scientific Company, was used without further purification.
4. 1,1,3,3-Tetramethylguanidine, b.p. 159–160°, was used without further purification. The submitters obtained their material from Schuchardt, Munich, Germany, and the checkers obtained theirs from Pfaltz and Bauer, New York.
5. *tert*-Butyl phenyl carbonate furnished by Ega-Chemie KG, Steinheim, Germany, was used by the submitters. The checkers used material obtained from Aldrich Chemical Company, Inc.
6. The pH of the aqueous layer was 7.2. If the pH, as measured with a pH meter, is not between 7 and 8, it should be adjusted to within these limits by the addition of either 10% sulfuric acid or 1,1,3,3-tetramethylguanidine. The submitters worked up the reaction by the following alternate, but less convenient, method. The reaction mixture was poured into 1.25 l. of 1 *M* sodium hydrogen carbonate solution, 500 ml. of ether, and sufficient water (*ca.* 1 l.) to give two clear phases. The pH, which was 8.9, was adjusted to 8.0 by the addition, with stirring, of solid potassium hydrogen sulfate.
7. 10% Sulfuric acid (1.1 *M*) was prepared by diluting 25 ml. of concentrated sulfuric acid with 398 ml. of water. The submitters used solid potassium hydrogen sulfate for acidification to pH 3.0.

8. An additional 5 g. of product, m.p. 127–129°, may be obtained from the mother liquor
9. Some reported yields, melting points, and rotations are: 55%, 136–137°, and $[\alpha]_D^{25}$ −60.2° (2.011 in acetic acid)[3]; 96%, 134–136°, $[\alpha]_{578}^{18-25}$ −68.5° (*c* = 1, acetic acid)[4]; 95%, 132–134°, $[\alpha]_{578}$ −62.5° (acetic acid)[5]; 90%, 133–135°, $[\alpha]_D^{25}$ −60.4° (*c* = 2.2 in acetic acid)[6]; 93%, 134–135°, no rotation reported.[7]
10. ^{1}H NMR (dimethyl sulfoxide-d_6): δ 1.38 (s, 9H, 3CH_3), 1.92 (m, 4H, 2CH_2), 3.31 (t, 2H, CH_2N), 4.05 (t, 1H, C*H*N), 12.3 (s, 1H, CO_2H). Analysis calculated for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.81; H, 7.95; N, 6.44.

3. Discussion

Since their introduction by McKay and Albertson,[8] and Anderson and McGregor,[3] *tert*-butoxycarbonyl amino acids have been prepared by several different methods. The simplest procedure[6] requires working with large quantities of phosgene. Another very good method,[5] but one that has not found wide application, involves the use of *tert*-butoxycarbonylfluoride, which is not commercially available. At the present the most useful reagent has been *tert*-butoxycarbonylazide, for which good procedures[9,10] are available; the excellent method of Schnabel[4] and one more recently reported[7] are based on this reagent. Of the procedures for the preparation of *tert*-butoxycarbonylazide, one,[9] which is readily adaptable for large-scale operations, involves three steps and the other,[10] a two-step process, is more suitable for small-scale work.

Our procedure[11] represents a simplification in that *tert*-butyl phenyl carbonate, which is used as a starting material, is the first intermediate in the three-step synthesis[9] of *tert*-butoxycarbonylazide. This reagent is easy to prepare in quantity and is commercially available in bulk (Note 5). Further, 1,1,3,3-tetramethylguanidine is inexpensive and the experimental operations are extremely simple.

Proline dissolves readily in dimethyl sulfoxide. Some other amino which are less soluble require longer reaction times and, in some instances, other solvents.[11] These details and the scope of the reaction are illustrated in Table I.

TABLE I
OTHER BOC[a] AMINO ACIDS SYNTHESIZED BY THIS PROCEDURE

Compound	Solvent	Temperature, °	Time, Hr.	Yield, %	Remarks
Boc-Ala[b]	DMSO[c]	25	40	58	
Boc-Ala[b]	DMSO[c]	40	40	79	
Boc-Asn[d]	DMSO[c]	25	66	70	2 equiv. TMG[e]
Boc-Asp[f]	DMSO[c]	25	18	89	2 equiv. TMG
Boc-Cys(Bzl)[g]	DMSO[c]	25	40	62	CHA salt[h]
Boc-Cys (Bzl)[g]	DMSO[c]	40	40	78	CHA salt
Boc-Gln[i]	DMSO[c]	50	48	62	2 equiv. TMG, DCHA salt,[j] continuous extraction with ethyl acetate
Boc-Glu[k]	DMSO[c]	25	2.5	80	2 equiv. TMG
Boc-Ile[l]	DMSO[c]	40	72	72	
Boc-Leu[m]	DMSO[c]	25	48	73	Calc. as hemihydrate
Boc-Met[n]	DMSO[c]	25	24	86	81% solid +5% DCHA salt
Boc-Phe[o]	DMSO[c]	25	40	81	DCHA salt
Boc-Phe[o]	DMSO[c]	25	96	88	DCHA salt
Boc-Phe[o]	DMSO[c]	40	18	81	DCHA salt
Boc-Phe[o]	DMSO[c]	25	48	59	DCHA salt
Boc-Phe[o]	D—W[q]	25	48	5	DCHA salt
Boc-Pro[r]	DMSO[c]	25	2.5	90	
Boc-Pro[r]	DMF[p]	25	2.5	92	
Boc-Pro[r]	D—W[q]	25	21	84	

Boc-Thr[s]	DMSO[c]	25	67	66	DCHA salt
Boc-Val[t]	DMSO[c]	25	71	77	2 equiv. TMG, 65% solid +12% DCHA salt

[a]*tert*-Butoxycarbonyl. [b]L-Alanine. [c]Dimethylsulfoxide. [d]L-Aspargine. [e]1,1,3,3-Tetramethylguanidine. [f]L-Aspartic acid. [g]S-Benzyl-L-cysteine. [h]Cyclohexylamine. [i]L-Glutamine. [j]Dicyclohexylamine. [k]L-Glutamic acid. [l]L-Isoleucine. [m]L-Leucine. [n]L-Methionine. [o]L-Phenylalanine. [p]Dimethylformamide. [q]Dioxane-water 1:1. [r]L-Prolone. [s]L-Threonine. [t]L-Valine.

More recently, a few additional reagents have been found useful for the synthesis of Boc-amino acids. Among these are *tert*-butyl-4,6-dimethylpyrimidyl-2-thiol carbonate,[12] di-*tert*-butyl dicarbonate,[13] 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile,[14] and *tert*-butyl α-methoxyvinyl carbonate.[15] With the advent of a relatively simple method for the preparation of carbonyl chloride fluoride[16] *tert*-butoxycarbonylfluoride[17] is now more readily available.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 6, 207
- Org. Syn. Coll. Vol. 6, 418
- Org. Syn. Coll. Vol. 7, 70

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

petroleum ether

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

alanine (56-41-7)

potassium hydrogen sulfate (7646-93-7)

phosgene (75-44-5)

Glutamic Acid (56-86-0)

magnesium sulfate (7487-88-9)

Methionine (63-68-3)

phenylalanine (63-91-2)

proline,
L-proline (147-85-3)

isoleucine (73-32-5)

leucine (61-90-5)

threonine (72-19-5)

valine (72-18-4)

aspartic acid (56-84-8)

dimethyl sulfoxide (67-68-5)

cysteine (52-90-4)

1,1,3,3-tetramethylguanidine (80-70-6)

Butoxycarbonyl

Glutamine

tert-butoxycarbonylazide (1070-19-5)

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

tert-Butyl phenyl carbonate (6627-89-0)

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

1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (S)-,
tert-Butoxycarbonyl-L-proline (15761-39-4)

tert-butoxycarbonylfluoride

tert-butyl-4,6-dimethylpyrimidyl-2-thiol carbonate

tert-butyl α-methoxyvinyl carbonate