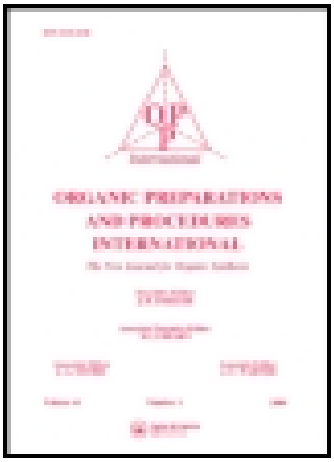


Organic Preparations and Procedures International: The New Journal for Organic Synthesis
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

AN IMPROVED SYNTHESIS OF tert-BUTYL N $^{\alpha}$-tert-BUTOXYCARBONYL-L-(S-TRITYL)CYSTEINATE

Elżb[idot]eta Masiukiewicz [a] & Barbara Rzeszotarska [a]
[a] Department of Organic Chemistry , University of Opole , Ul. Oleska 48, 45-052, Opole, POLAND
Published online: 09 Feb 2009.

To cite this article: Elżb[idot]eta Masiukiewicz & Barbara Rzeszotarska (1999) AN IMPROVED SYNTHESIS OF tert-BUTYL N $^{\alpha}$-tert-BUTOXYCARBONYL-L-(S-TRITYL)CYSTEINATE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 31:5, 571-572, DOI: 10.1080/00304949909355343

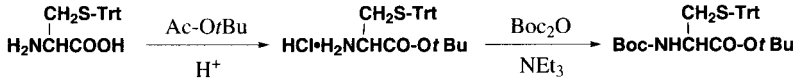
To link to this article: http://dx.doi.org/10.1080/00304949909355343

AN IMPROVED SYNTHESIS OF *tert*-BUTYL N^{α}-*tert*-BUTOXYCARBONYL-L-(*S*-TRITYL)CYSTEINATE

Submitted by (09/09/99) Elżbieta Masiukiewicz and Barbara Rzeszotarska

Department of Organic Chemistry
University of Opole
Ul. Oleska 48, 45-052 Opole, POLAND

The controlled synthesis of peptides requires that functional groups that are not directly involved in the amide bond-forming reaction be blocked. Acidic conditions[1] are preferred for the removal of protective groups since these conditions are less damaging to peptides. Therefore, it may be desirable that all protective groups be acid-sensitive, provided that the selective removal of either *N*- or *C*-protecting group is feasible.[2] Methods useful to this end are elaborated by testing on simple model compounds. One such useful model is the title compound. The literature refers its preparation to general procedures[2] and gives NMR spectra and elemental analysis as the only indicators of purity, while chromatographic criteria would be more appropriate for the compound that is to be used in chromatographic testing the methods of selective deprotection. Herein, we present a complete description of the preparation of Boc-Cys(Trt)-O*t*Bu[3] in high yield and of high purity.



H-Cys(Trt)-OH *HCl•H-Cys(Trt)-OtBu* *Boc-Cys(Trt)-OtBu*

H-Cys(Trt)-OH was esterified with *tert*-butyl acetate and $HClO_4$ as a catalyst.[4] The crude product was contaminated with about 5% H-Cys(*t*Bu)-O*t*Bu[5] and Trt-OH resulting from transeterification. While the former impurity could be removed by extraction with 0.5 M HCl, the latter could not be eliminated. The mixture was thus acylated with Boc_2O in the presence of triethylamine.[6] Since the crude acylated product contained other contaminants and was very soluble in all solvents, it could not be purified by simple crystallization and a chromatographic column had to be used. This procedure allows Boc-Cys(Trt)-O*t*Bu to be obtained as well-shaped crystals of 99.7% purity in 80% yield.

EXPERIMENTAL SECTION

Reactions were monitored and the products checked on silica gel plates (DC Alufolien Kieselgel, 0.25 Merck # 5553) in the following solvent systems (v/v): A = chloroform-methanol-acetic acid (95:5:3), B = chloroform-*n* hexane-acetic acid (10:10:1). HPLC analyses were carried out using a Beckman System Gold chromatograph, a 5 µl loop, an Alltech Alltima, C_{18}, 5 µ, 150 x 4.6 mm column, a flow rate of 1 mL/min and detection at 210 nm.

***tert*-Butyl L-(*S*-Trityl)cysteinate Hydrochloride (HCl·H-Cys(Trt)-O*t*Bu).**- To a vigorously stirred

suspension of H-Cys(Trt)-OH (10.0 g, 27.2 mmol) in *tert*-butyl acetate (160 mL), 70% $HClO_4$ (8 mL) was introduced dropwise. Stirring was continued at room temperature for 1 h and ethyl acetate (200 mL) and 1 M aqueous $NaHCO_3$ to pH 8.0 were added. The precipitated, unreacted H-Cys(Trt)-OH was filtered off (1.55 g, 4.3 mmol) and the aqueous layer was discarded. The organic phase was extracted with 0.5 M HCl (2 x 100 mL) and brine, dried and evaporated to give the product (9.79 g, 88% yield) as a colorless rigid foam. R_f: A - 0.48. HPLC: 0.1% trifluoroacetic acid-acetonitrile (30:70); HCl·H-Cys(Trt)-O*t*Bu (94%) tR = 2.85 min, Trt-OH (5%) tR = 5.35 min.

***tert*-Butyl N^{α}-*tert*-Butoxycarbonyl-L-(*S*-trityl)cysteinate (Boc-Cys(Trt)-O*t*Bu).**- To a solution of 94% HCl·H-Cys(Trt)-O*t*Bu (5.02 g, 10.3 mmol) in dioxane (30 mL), was added Boc_2O (3.64 g, 16 mmol) and followed by triethylamine (4.5 mL, 32 mmol), dropwise. After 15 h, triethylamine hydrochloride was filtered off and dioxane was evaporated; the residue was dissolved in ethyl acetate (30 mL) and extracted with 0.5 M HCl and brine and dried. After evaporation of ethyl acetate, the residue was dissolved in *n*-hexane, and applied to a silica gel column (ϕ 5 cm, Merck # 7736, 230 g) conditioned with *n*-hexane. The column was eluted under pressure in sequence with solutions of 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40% and 50% of chloroform in *n*-hexane (each 50 mL). The appropriate fractions (by TLC) were collected and evaporated; the residue was dissolved in *n*-hexane (10 mL) and left standing in a refrigerator for several days to furnish Boc-Cys(Trt)-O*t*Bu (4.2 g, 80% yield), homogenous by TLC, mp. 80-82° (uncorrected, a Boëtius heating block). R_f: A - 0.72. HPLC: water-acetonitrile (15:85), tR = 7.38 min, 99.7% purity.

Anal. Calcd. for $C_{31}H_{37}NO_4S$: C, 71.64, H, 7.18, N, 2.69. Found: C, 71.38, H, 7.37, N, 2.62

Acknowledgement.- The work was financially supported by a grant-in-aid from the Polish State Committee for Scientific Research (KBN). The support deserves our grateful thanks.

REFERENCES

1. P. Lloyd-Williams, F. Albericio and E. Giralt, *Chemical Approach to the Synthesis of Peptides and Proteins*, CRC Press, Boca Raton – New York, 1997.

2. F. S. Gibson, S. C. Bergmeier and H. Rapoport, *J. Org. Chem.*, **59**, 3216 (1994).

3. Abbreviations used: Boc = *tert*-butoxycarbonyl, Trt = trityl, Cys = L-cysteine, *t*-Bu = *tert*-butyl.

4. Š. Horvat, B. Grgas, N. Raos and Vl. Simeon, *Int. J. Peptide Protein Res.*, **34**, 346 (1989).

5. A. Chimiak, T. Kolasa and J. F. Biernat, *Z. Chem.*, **12**, 264 (1972); *Chem. Abstr.*, **77**, 152541e (1972).

6. E. Ponnusamy, U. Fotadar, A. Spisni and D. Fiat, *Synthesis*, 48 (**1986**).

****