



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.

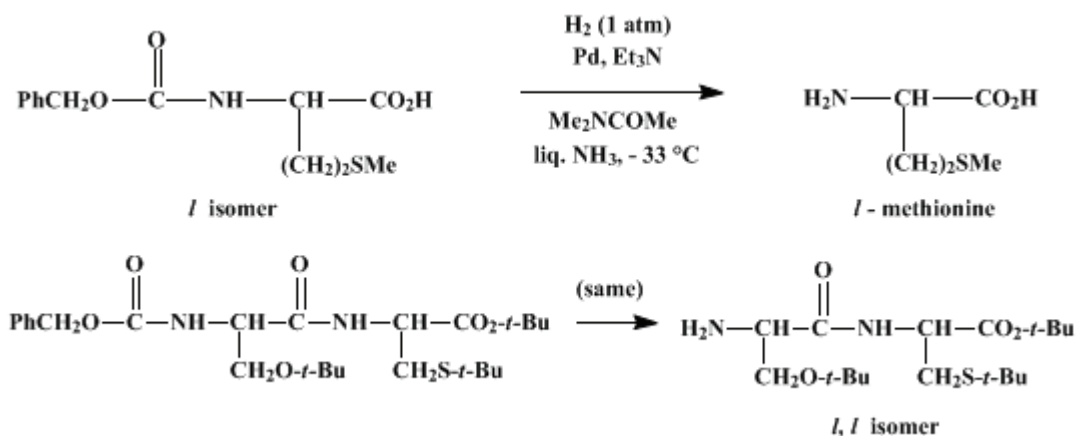
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

Organic Syntheses, Coll. Vol. 6, p.252 (1988); Vol. 59, p.159 (1979).

REMOVAL OF *N*^α-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES BY CATALYTIC HYDROGENATION IN LIQUID AMMONIA: *O*-*tert*-BUTYL-L-SERYL-*S*-*tert*-BUTYL-L-CYSTEINE *tert*-BUTYL ESTER



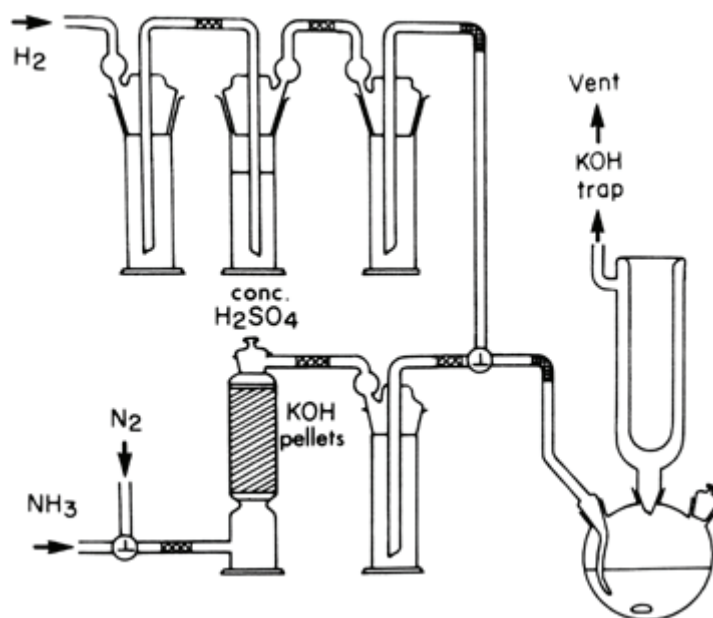
Submitted by Arthur M. Felix, Manuel H. Jimenz, and Johannes Meienhofer^{1,2}.
Checked by László Révész and G. Büchi.

1. Procedure

Caution! All operations described in these procedures must be carried out in a well-ventilated hood, since ammonia is highly toxic, hydrogen is extremely flammable, and palladium black is pyrophoric.

A. *L*-Methionine. A dry, 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar as illustrated in Figure 1. The reaction vessel is immersed in an acetone-dry ice bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and collected in the flask. The bath is removed to permit the reaction to proceed at the boiling point of ammonia (-33°), and a gentle stream of dry nitrogen (Note 2) is bubbled into the flask. A solution of 0.708 g. (0.80250 mole) of *N*-benzyloxycarbonyl-*L*-methionine (Note 3) in 10 ml. of *N,N*-dimethylacetamide (Note 4), 1.02 g. (1.40 ml., 0.0101 mole) of triethylamine (Note 5), and 1.25 g. of freshly prepared palladium black (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred under reflux for 5.5 hours to effect hydrogenolysis (Note 1). The hydrogen stream is discontinued, a flow of nitrogen is resumed, and the dry ice is removed from the reflux condenser, permitting rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8), and the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in water and filtered through a sintered funnel of medium porosity to remove the catalyst. The filtrate is evaporated to dryness, and the residue (354 mg., 95%) is crystallized from water-ethanol. The white crystalline product, after drying under reduced pressure at 25° , weighs 272–305 mg. (73–82%), m.p. $280\text{--}282^\circ$ (dec.) (Note 9), $[\alpha]_D^{25} +23.1^\circ$ ($c = 1$, aqueous 5 *N* hydrochloric acid) (Note 10).

Figure 1.



B. *O*-*tert*-Butyl-L-seryl-S-*tert*-butyl-L-cysteine *tert*-butyl ester. A dry, 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar, as illustrated in Figure 1. The reaction vessel is immersed in an acetone-dry ice bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and then collected in the flask. The bath is removed, and a gentle stream of nitrogen (Note 2) is bubbled into the flask. A solution of 200 mg. (0.392 mole) of *N*^α-benzyloxycarbonyl-*O*-*tert*-butyl-L-seryl-S-*tert*-butyl-L-cysteine *tert*-butyl ester (Note 11) in 4 ml. of *N,N*-dimethylacetamide (Note 4), 0.160 g. (0.220 ml., 0.00158 mole) of triethylamine (Note 5), and 200 mg. of palladium black freshly prepared from 333 mg. (0.00188 mole) of palladium(II) chloride (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred and hydrogenated at reflux temperature for 6 hours (Note 1). The hydrogen stream is discontinued, a stream of nitrogen is again passed into the flask, and the dry ice is removed from the reflux condenser to permit rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8) and evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml. of methanol (Note 12), and the suspension is filtered through a 5 × 25-mm. bed of Celite (Note 13) to remove the catalyst. The Celite bed is washed thoroughly with three 20-ml. portions of methanol. The filtrate is evaporated to dryness, and the residue is recrystallized from petroleum ether (b.p. 60–90°). The white crystalline product, after drying under reduced pressure at 25°, weighs 121–127 mg. (82–86%), m.p. 71–73° (Note 14), $[\alpha]_D^{25} -5.8^\circ$ ($c = 1$, methanol) (Note 15).

2. Notes

1. The condenser is filled with crushed dry ice (no solvent). More dry ice is added periodically as necessary throughout Parts A and B.
2. Anhydrous ammonia, prepurified nitrogen, and prepurified hydrogen were all purchased from Matheson Gas Products.
3. *N*-Benzyloxycarbonyl-L-methionine was obtained from Bachem, Inc., 3132 Kashiwa Street, Torrance, California 90505.
4. Spectrophotometric-grade *N,N*-dimethylacetamide was purchased from Aldrich Chemical Company, Inc., and stored over molecular sieves.
5. Sequanal-grade triethylamine, obtained from Pierce Chemical Company, Rockford, Illinois, was distilled under nitrogen from ninhydrin, which was also purchased from Pierce Chemical Company.
6. The catalyst is prepared^{4,5} with palladium(II) chloride and 97–100% formic acid, which were purchased from Engelhard Industries Division (Engelhard Minerals and Chemicals Corporation) and MC and B Manufacturing Chemists, respectively. A 10.4-ml. aliquot containing 2.08 g. (0.0117 mole) of palladium(II) chloride from a stock solution of palladium(II) chloride in 2 *N* hydrochloric acid (10 g.

per 50 ml.) is added to 104 ml. of boiling water in a 600-ml. beaker. A 0.51-g. (0.42 ml., 0.011 mole) portion of **formic acid** and 33 ml. of aqueous 10% **potassium hydroxide** are added to the boiling solution. The pH of the resulting slightly alkaline solution (pH \approx 8) is adjusted to 6–7 by adding **formic acid**, after which the mixture is allowed to boil for an additional 5 minutes. The catalyst is isolated by careful suction filtration. *Caution! The palladium catalyst is pyrophoric and must always be kept wet with water or methanol to prevent contact with air.*

To minimize the danger in handling palladium black, the submitters recommend that filtration, washing, and transfer of the catalyst be performed with a "syringe filter."⁶ This device was fashioned from a 10-ml. Plastipak syringe, purchased from Becton-Dickinson and Company, Rutherford, New Jersey, by cutting off the tip at the end of the cylindrical barrel and forcing a tight-fitting, porous disk of polypropylene into its place. The use of this "syringe filter" permits the removal of most of the solvent and the safe transfer of the catalyst to the flask with little danger of ignition or moisture absorption.

The catalyst is washed thoroughly with 100 ml. of water and with 200 ml. of absolute **methanol** to remove all traces of water, after which it is transferred to the flask under **nitrogen** with a minimal amount of absolute **methanol**. To be effective the catalyst must be pyrophoric, and extreme care must be taken during this operation to prevent ignition of the **methanol** or **ammonia**. The catalyst must not be allowed to become dry or to collect on the wall of the flask above the surface of the liquid **ammonia**.

7. Evaporation of the **ammonia** generally requires several hours. Toward the end of the evaporation, it is advantageous to immerse the flask in an acetone bath, taking care to avoid bumping.

8. **N,N-Dimethylacetamide** remains in the flask and is removed by rotary evaporation under reduced pressure with a water bath kept at a temperature lower than 35°. The submitters recommend that the evaporation be carried out directly in the same three-necked flask by stoppering the two side arms and adjusting the angle of the rotary evaporator.

9. The melting point is corrected [lit.,⁷ m.p. 280–281° (dec.)].

10. The literature⁸ reports $[\alpha]_D^{25} +23.2^\circ$ ($c = 1$, 5*N* **hydrochloric acid**). The product was analyzed by the submitters. Analysis calculated for C₅H₁₁NO₂S: C, 40.25; H, 7.43; N, 9.39; S, 21.49. Found: C, 40.14; H, 7.42; N, 9.50; S, 21.52. The product was homogeneous according to TLC on precoated silica gel G plates purchased from Analtech, Inc., Newark, Delaware, and developed with the following two solvent systems (solvents, volume ratios of solvents in the same order): **1-butanol–acetic acid–ethyl acetate–water**, 1:1:1:1, R_f 0.49; **1-butanol–acetic acid–pyridine–water**, 15:3:10:12, R_f 0.51.

11. The protected dipetide was prepared by the procedure described in the following paragraph using **N-benzyloxycarbonyl-O-tert-butyl-L-serine** purchased from Chemical Dynamics Corporation (P. O. Box 395, South Plainfield, New Jersey 07080), **tetrahydrofuran** distilled from **lithium aluminum hydride** [*Caution!* For a warning regarding this method for purifying tetrahydrofuran, see *Org. Synth., Coll. Vol. 5*, 976 (1973)], and **N-methylmorpholine** distilled from **ninhydrin**. **S-tert-Butyl-L-cysteine tert-butyl ester**⁹ was prepared as follows: To a suspension of 10 g. (0.082 mole) of **L-cysteine** in 75 ml. of dry **dioxane** in a 200-ml. pressure bottle cooled in an ice bath are added 10.0 ml. of concentrated **sulfuric acid** and 56 g. (95 ml., 1.0 mole) of **isobutylene**. The pressure bottle is stoppered and shaken at room temperature for 18 hours. The mixture is cooled to 0°, the pH is adjusted to 10 by adding 160 ml. of aqueous 2 *N* **sodium hydroxide**, and the product is extracted with three 100-ml. portions of **diethyl ether**. The ethereal solution is washed with three 80-ml. portions of aqueous 5% **sodium hydrogen carbonate** and three 80-ml. portions of water, dried over anhydrous **magnesium sulfate**, and concentrated to a volume of *ca.* 200 ml. The concentrate is stirred and cooled at 0° as 90.8 ml. (0.0908 mole) of 1 *M* **hydrogen chloride** in **ether** is added. The resulting mixture is stirred for several minutes, the precipitated hydrochloride is filtered, and the filter cake is washed with **ether**. The white crystalline product weighs 18.1 g. (81%) and is used without further purification. The submitters caution that the hydrochloride sublimes under reduced pressure. Recrystallization from **chloroform**–petroleum ether affords an analytical sample, double m.p. 187° and 219–222°, $[\alpha]_D^{25} +5.85^\circ$ ($c = 1$, **methanol**). Analysis calculated for C₁₁H₂₃NO₂S·HCl: C, 48.96; H, 8.96; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 49.07; H, 9.25; N, 5.13; S, 12.06; Cl, 13.07. The free base is obtained by dissolving the **hydrochloride** in aqueous 10% **sodium carbonate**, extracting the mixture with **ether**, and evaporating the ethereal solution under reduced pressure.

A dry, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a rubber septum, and a 200-ml., pressure-equalizing dropping funnel mounted with a T-shaped gas-inlet connected to both a nitrogen source and a bubbler serving as a gas exit. The flask is charged with a solution of 14.9 g. (0.0506 mole) of **N^α-benzyloxycarbonyl-O-tert-butyl-L-serine** in 100 ml. of **tetrahydrofuran** and purged

with nitrogen. The solution is stirred and cooled at -15° as 5.12 g. (5.67 ml., 0.0506 mole) of *N*-methylmorpholine and 6.91 g. (6.61 ml., 0.0506 mole) of isobutyl chloroformate are added rapidly through the septum with syringes. One minute after the addition is completed, a precooled (-20°) solution of 11.8 g. (0.0506 mole) of *S*-*tert*-butyl-L-cysteine *tert*-butyl ester in 100 ml. of tetrahydrofuran is added dropwise at -15° . The contents of the flask are stirred for 1 hour at -15° and for 3 hours at room temperature. The mixture is then evaporated to dryness under reduced pressure and dissolved in 150 ml. of ethyl acetate. The solution is washed with three 50-ml. portions of each of the following: 5% sodium hydrogen carbonate in water, water, 1 *M* citric acid in water, and water. The ethyl acetate solution is then dried over anhydrous magnesium sulfate, the solvent is evaporated, and the remaining solid is recrystallized from ethyl acetate–petroleum ether (b.p. 35 – 60°). The white crystalline product, after drying under reduced pressure at 25° , weighs 25.5 g. (98.6%), m.p. 94.5 – 95° , $[\alpha]_D^{25} -2.47^{\circ}$ ($c = 1$, methanol). TLC of the product on plates precoated with silica gel G and purchased from Analtech, Inc., Newark, Delaware, each showed a single spot when developed with the following three solvent systems (solvents, volume ratio of solvents in the same order): 1-butanol–acetic acid–ethyl acetate–water, 1:1:1:1, R_f 0.90; 1-butanol–acetic acid–water, 4:1:1, R_f 0.81; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, R_f 0.81. Analysis calculated for $C_{26}H_{42}N_2O_6S$: C, 61.15; H, 8.29; N, 5.49; S, 6.28. Found: C, 61.15; H, 8.52; N, 5.42; S, 6.44.

12. Other solvents including *N,N*-dimethylformamide and water may also be used to dissolve the products.

13. In some cases the catalyst was not entirely removed, and the filtrate contained trace amounts of palladium. In those instances the submitters evaporated the filtrate to a small volume and repeated the filtration using a large bed of Celite.

14. The melting point was taken on a Reichert hot stage microscope. This instrument is available from William J. Hacker and Company, Inc., P.O. Box 646, West Caldwell, New Jersey 07006.

15. The recrystallized product was analyzed by the submitters. Analysis calculated for $C_{18}H_{36}N_2O_4S$: C, 57.41; H, 9.63; N, 7.43; S, 8.51. Found: C, 57.60; H, 9.66; N, 7.37; S, 8.25. TLC ((Note 10)) run by the submitters showed a single spot for the product in each of three following solvent systems (solvents, volume ratio of solvents in the same order): chloroform–methanol–acetic acid, 85:10:5, R_f 1-butanol–acetic acid–water, 4:1:1, R_f 0.58; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, R_f 0.71.

3. Discussion

The protection of the amino terminus of a peptide with the benzyloxycarbonyl group combined with protection of the carboxyl terminus and all side-chain functions with *tert*-butyl-derived groups¹⁰ enables totally selective liberation of the terminal amino function by catalytic hydrogenolysis. This combination of protecting groups is currently considered "ideal" for peptide synthesis,¹¹ except for the rather serious limitation that catalyst poisoning has prevented its application to the preparation of peptides that contain cysteine, methionine, or other residues bearing divalent sulfur groups. The submitters have recently discovered¹² that catalyst poisoning is greatly diminished when liquid ammonia is used as solvent for palladium-catalyzed hydrogenation. This solvent enables quantitative cleavage of *N*^α-benzyloxycarbonyl groups on many protected peptides bearing *S*-protected cysteine residues. The method has been used successfully in syntheses of oxytocin¹³ and somatostatin.³

The present procedures illustrate this method with the regeneration of L-methionine and the preparation of the *tert*-butyl ester of *O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine³ from their respective *N*^α-benzyloxycarbonyl derivatives. No other procedures for the preparation of this protected dipeptide have been reported. These preparations and other peptide syntheses have served to establish the complete stability of the *S*-methyl substituent and various protecting groups including the *tert*-butyl ester (OBu^t), *tert*-butyl ether (Bu^t), *N*-*tert*-butyloxycarbonyl (Boc), *S*-*tert*-butyl (Bu^t), *S*-benzyl (Bzl), and *S*-acetamidomethyl (Acm) groups.¹⁴ Table I summarizes the results of hydrogenations carried out with sulfur-containing peptides having chain lengths varying from 6 to 13 amino acid residues, demonstrating the stability of various protecting groups to this procedure for hydrogenolysis. In each case the *N*^α-benzyloxycarbonyl (Z) group was removed quantitatively and the *tert*-butyl based protecting groups were unaffected. As a result of these findings, sulfur-containing amino acids may now be used in peptide synthesis by the "ideal" combination of aminoterminal benzyloxycarbonyl protection with *tert*-butyl-type blocking groups on all other functions.

TABLE I
REMOVAL OF *N*-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES

Peptide	Amount (g.) (mmole.)	Dimethylacetamide (ml.)	Triethylamine (mmole.)
$R = \begin{array}{ccccccc} \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & \\ \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & \end{array}$			
<i>a</i>			
$\text{Z-} \begin{array}{ccccccc} \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & \\ \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & \end{array}$	3.05 (2.54)	10.0	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & \\ \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & & \end{array}$	0.418 (0.272)	3.0	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Phe} & - & \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & & & \\ \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & & & & \end{array}$	0.263 (0.160)	3.5	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Asn} & - & \text{Phe} & - & \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & & & & & \\ \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & & & & & & \end{array}$	0.305 (0.170)	3.0	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Lys} & - & \text{Asn} & - & \text{Phe} & - & \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & & & & & & & & \\ \text{Boc} & & & & & & \text{Boc} & & \text{Bu}^t & & & & \text{Bu} & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & \end{array}$	0.368 (0.182)	3.0	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Cys} & - & \text{Lys} & - & \text{Asn} & - & \text{Phe} & - & \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & & & & & & & & & & \\ \text{Bu}^t & & \text{Boc} & & & & & & \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & \end{array}$	0.281 (0.129)	2.0	1.0
$\text{Z-} \begin{array}{ccccccc} \text{Gly} & - & \text{Cys} & - & \text{Lys} & - & \text{Asn} & - & \text{Phe} & - & \text{Phe} & - & \text{Trp} & - & \text{Lys} & - & \text{Thr} & - & \text{Phe} & - & \text{Thr} & - & \text{Ser} & - & \text{Cys} & - & \text{O} & \text{Bu}^t \\ & & & & & & & & & & & & & & & & & & & & & & & & & & & & \\ \text{Bu}^t & & \text{Boc} & & & & & & \text{Boc} & & \text{Bu}^t & & & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & \text{Bu}^t & & & & & & & & \end{array}$	0.178 (0.080)	1.3	1.0

a Protecting group abbreviations are as follows: *N*-benzyloxycarbonyl (Z), *N*-*tert*-butyloxycarbonyl (Boc), and *S*-*tert*-butyl (Bu^t).

b The reaction time was 5.0–6.0 hours in all entries.

Since the use of *N,N*-dimethylacetamide and triethylamine improved the rate and extent of cleavage of the *N*-benzyloxycarbonyl group in several difficult cases, these additives have been incorporated into the submitters' standard procedure and are included in the present procedures. Deprotection with this method has been carried out with as much as 25 g. of the protected peptide.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 6, 137](#)

References and Notes

1. Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
2. Paper VI in the series "Reactions in Liquid NH₃"; for paper V, see ref. ³.
3. A. M. Felix, M. H. Jimenez, T. Mowles, and J. Meienhofer, *Int. J. Pept. Protein Res.*, **11**, 329 (1978).
4. H. Willstätter and E. Waldschmidt-Leitz, *Ber. Dtsch. Chem. Ges.*, **54**, 113 (1921).
5. H. Wieland, *Ber. Dtsch. Chem. Ges.*, **45**, 484 (1912).
6. M. H. Jimenez, *Org. Prep. Proced. Int.*, **10**, 295 (1978).

7. "The Merck Index," 8th ed., Merck & Co., Inc., Rahway, New Jersey, 1968, p. 675.
 8. J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, Wiley, New York, 1961, p. 2125.
 9. A. Chimiak, T. Kolasa, and J. F. Biernat, *Z. Chem.*, **12**, 264 (1972).
 10. R. Schwyzer and P. Sieber, *Nature (London)*, **199**, 172 (1963).
 11. R. Schwyzer, *Naturwissenschaften*, **53**, 189 (1966); F. M. Finn and K. Hofmann, "The Synthesis of Peptides by Solution Methods with Emphasis on Peptide Hormones," in H. Neurath and R. L. Hill, Eds., "The Proteins," 3rd ed., Vol. 2, Academic Press, New York, 1976, pp. 105–253.
 12. J. Meienhofer and K. Kuromizu, *Tetrahedron Lett.*, 3259 (1974).
 13. K. Kuromizu and J. Meienhofer, *J. Am. Chem. Soc.*, **96**, 4978 (1974).
 14. A procedure for *S*-acetamidomethylation is described in *Org. Synth.*, **Coll. Vol. 6**, 5 (1988).
-

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

petroleum ether

palladium black

N^α-benzyloxycarbonyl-O-tert-butyl-L-serine

sulfuric acid (7664-93-9)

hydrogen chloride,
hydrochloric acid,
hydrochloride (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

formic acid (64-18-6)

nitrogen (7727-37-9)

1-butanol (71-36-3)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

palladium(II) chloride (7647-10-1)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

isobutylene (9003-27-4)

Methionine,
L-Methionine (63-68-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

benzyloxycarbonyl (Z)

triethylamine (121-44-8)

S-tert-Butyl (1605-73-8)

N,N-dimethylacetamide,
Dimethylacetamide (127-19-5)

cysteine,
L-cysteine (52-90-4)

ninhydrin (938-24-9)

isobutyl chloroformate (543-27-1)

N-methylmorpholine (109-02-4)
butyloxycarbonyl (Boc), tert-butyl ether

O-tert-Butyl-L-seryl-S-tert-butyl-L-cysteine tert-butyl ester,
tert-butyl ester of O-tert-butyl-L-seryl-S-tert-butyl-L-cysteine (67942-95-4)

N-benzyloxycarbonyl-L-methionine

N^α-benzyloxycarbonyl-O-tert-butyl-L-seryl-S-tert-butyl-L-cysteine tert-butyl ester

N-benzyloxycarbonyl-O-tert-butyl-L-serine

S-tert-Butyl-L-cysteine tert-butyl ester (45157-84-4)