

## Synthesis, Properties, and Use of $N^{\text{in}}$ -Boc-tryptophan Derivatives

Henry Franzén, Leif Grehn, and Ulf Ragnarsson

*Institute of Biochemistry, BMC, Box 576, S-751 23 Uppsala, Sweden*

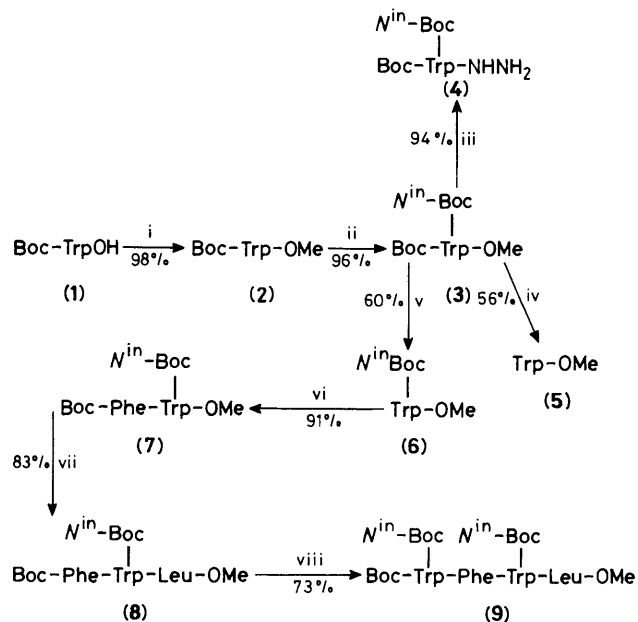
$N^{\text{in}}$ -Boc-protected tryptophan derivatives can be prepared with  $\text{Boc}_2\text{O}$ -4-dimethylaminopyridine in MeCN; their properties and utility are demonstrated in the synthesis of a tryptophan-containing tetrapeptide related to substance P.

We have recently reported on a mild, efficient method for the introduction of the t-butyloxycarbonyl (Boc) group in pyrroles and indoles<sup>1</sup> and now show that Boc can also serve as a suitable protection for the indole moiety in tryptophan in peptide synthesis. The protective groups hitherto employed for this purpose such as formyl<sup>2</sup> and 2,2,2-trichloroethoxycarbonyl<sup>3</sup> (Troc) are normally cleaved under alkaline conditions whereas benzyloxycarbonyl (Z)<sup>3</sup> is not easily removed from the indole nitrogen under conditions compatible with sensitive peptides.† Therefore  $N^{\text{in}}$ -Boc appears to be a valuable complement in this respect since it is readily removed with trifluoroacetic acid (TFA).

The methyl ester (2) was conveniently obtained from (1) using a standard method.<sup>4</sup> Treatment of (2) with  $\text{Boc}_2\text{O}$  (1.05 equiv.) and 4-dimethylaminopyridine (DMAP, 0.1 equiv.) in MeCN<sup>1</sup> gave the desired derivative (3) in almost quantitative yield. A larger excess of  $\text{Boc}_2\text{O}$  in this reaction gave rise to various side products. The fully protected (3) could be converted into the hydrazide (4) in high yield under normal conditions‡ for use in the Honzl-Rudinger azide

† Preliminary experiments indicate that Boc-Trp( $N^{\text{in}}$ -Boc)-OMe was partially destroyed by catalytic hydrogenation over a Pd-catalyst.

‡ Although 1-Boc-indoles are cleaved by strong bases (see A. C. Cheng, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, 1982, 47, 5258, Boc-Trp( $N^{\text{in}}$ -Boc)-OMe was successfully hydrolysed (NaOH, 1 equiv. in dioxane-water) to the corresponding acid without removal of the  $N^{\text{in}}$ -Boc group.



**Scheme 1.** Reagents: i,  $\text{Cs}_2\text{CO}_3$  then MeI-dimethylformamide; ii,  $\text{Boc}_2\text{O}$ , DMAP-MeCN; iii,  $\text{NH}_2\text{NH}_2\text{-MeOH}$ ; iv, TFA, 3 min, room temp.; v, 2.7 M HCl-dioxane, 3 h, room temp.; vi, Boc-Phe-OSu-DMF; vii,  $\text{NH}_2\text{NH}_2\text{-MeOH}$  then Leu-OMe, Honzl-Rudinger conditions; viii, 2.7 M HCl-dioxane, 3 h, room temp. then (4), Honzl-Rudinger conditions.

coupling reaction.<sup>5</sup> The removal of both Boc groups was readily effected by brief treatment with TFA and pure (5) was obtained in reasonable yield. In contrast, when the partially protected (2) was subjected to the same reaction conditions, substantial amounts of t-butylated byproducts were formed together with (5). The occurrence of such electrophilic alkylations seems to be in agreement with earlier findings.<sup>6</sup> During the TFA-mediated deprotection of 1-Boc-skatole, the 1-carboxy derivative could be isolated as the major product.<sup>1</sup> This compound is unstable in solution and decomposes slowly in water to give pure skatole. It is reasonable to believe that in this case the corresponding intermediate is formed from (3) under the influence of TFA. § Consequently, the presence of a deactivating substituent on the heterocyclic nitrogen is expected to suppress the reactivity of the aromatic ring system towards electrophiles.

Somewhat surprisingly, the selective deprotection of the *N*<sup>α</sup>-Boc group in (3) could be accomplished with 2.7 M HCl in dioxane (3 h, room temperature), thus affording pure (6) in satisfactory yield. Prolonged reaction time and/or a higher concentration of HCl gave mixtures of (5) and (6). The latter methyl ester was readily converted into the dipeptide (7) in good yield using an active ester procedure and this compound could be hydrazinolysed and further extended to (8) by an azide coupling reaction. Finally, a second selective *N*<sup>α</sup>-Boc

deprotection of (8) and an azide coupling with (4) to the resulting liberated amino derivative afforded (9) in acceptable yield. This fully protected peptide is a model compound for certain analogues of [p-Trp<sup>7,9</sup>]-substance P with potentially useful antagonistic properties.<sup>7</sup> We expect the corresponding stereoisomer of (9) to be a useful intermediate in the synthesis of such antagonists and their radiolabelled counterparts.

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§ Similar treatment of Z-Trp(*N*<sup>m</sup>-Boc)-OBzl (Bzl = benzyl) with TFA and immediate workup at low temperature avoiding excess base yielded the corresponding unstable *N*<sup>m</sup>-CO<sub>2</sub>H derivative (the characteristic <sup>1</sup>H n.m.r. *N*<sup>m</sup>-Boc peak at δ 1.65 disappeared and the indole-2H signal was shifted from δ 7.56 in Z-Trp-OBzl to δ 8.20).