Synthesis, Properties, and Use of N^{in}-Boc-tryptophan Derivatives

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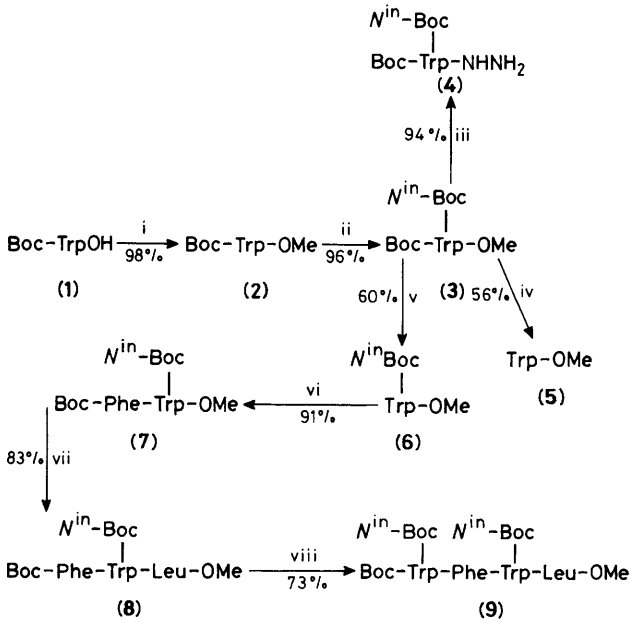
N^{in}-Boc-protected tryptophan derivatives can be prepared with Boc_2O–4-dimethylaminopyridine in MeCN; their properties and utility are demonstrated in the synthesis of a tryptophan-containing tetrapeptide related to substance P.

We have recently reported on a mild, efficient method for the introduction of the t-butyloxycarbonyl (Boc) group in pyrroles and indoles[1] 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[2] and 2,2,2-trichloroethoxycarbonyl[3] (Troc) are normally cleaved under alkaline conditions whereas benzyloxycarbonyl (Z)[3] is not easily removed from the indole nitrogen under conditions compatible with sensitive peptides.† Therefore N^{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.[4] Treatment of (**2**) with Boc_2O (1.05 equiv.) and 4-dimethylaminopyridine (DMAP, 0.1 equiv.) in MeCN[1] gave the desired derivative (**3**) in almost quantitative yield. A larger excess of Boc_2O 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



Scheme 1. *Reagents:* i, Cs_2CO_3 then MeI–dimethylformamide; ii, Boc_2O, DMAP-MeCN; iii, NH_2NH_2–MeOH; iv, TFA, 3 min, room temp.; v, 2.7 M HCl–dioxane, 3 h, room temp.; vi, Boc-Phe-OSu–DMF; vii, NH_2NH_2–MeOH then Leu-OMe, Honzl–Rudinger conditions; viii, 2.7 M HCl–dioxane, 3 h, room temp. then (**4**), Honzl–Rudinger conditions.

† Preliminary experiments indicate that Boc-Trp(N^{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^{in}-Boc)-OMe was successfully hydrolysed (NaOH, 1 equiv. in dioxane–water) to the corresponding acid without removal of the N^{in}-Boc group.

coupling reaction.[5] 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.[6] During the TFA-mediated deprotection of 1-Boc-skatole, the 1-carboxy derivative could be isolated as the major product.[1] 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^{α}-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^{α}-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 [D-Trp^{7,9}]-substance P with potentially useful antagonistic properties.[7] 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^{in}-Boc)-OBzl (Bzl = benzyl) with TFA and immediate workup at low temperature avoiding excess base yielded the corresponding unstable N^{in}-CO_2H derivative (the characteristic ^{1}H n.m.r. N^{in}-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).

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