

USE OF DI-*tert*-BUTYL PYROCARBONATE FOR THE SYNTHESIS  
OF N'-*tert*-BUTOXYCARBONYL-SUBSTITUTED HYDRAZIDES  
OF N-BENZYLOXYCARBONYL DERIVATIVES OF AMINO  
ACIDS AND PEPTIDES

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N-*tert*-Butoxycarbonylhydrazides (BOC-hydrazides) of N-acyl amino acids and peptides are widely used in the synthesis of natural peptides and their analogs [1, 2]. The advantage of this type of protection of the carboxy group is that after the elimination of the N'-BOC group, hydrazides of N-substituted peptides are obtained which are condensed by the azide method with other peptide fragments. This method permits large peptides to be assembled under conditions excluding racemization[2].

BOC-Hydrazides of N-acyl amino acids are obtained by the addition of BOC-hydrazine (carbazate) to N-acyl amino acids by the carbodiimide method [3] or by the mixed-anhydride method [4].

We have found that N'-BOC-hydrazides can be obtained by the *tert*-butoxycarbonylation of hydrazides of N-Z amino acids and peptides with di-*tert*-butyl pyrocarbonate (BOC<sub>2</sub>O) [5, 6]: Z-NHCHRCONH-NH<sub>2</sub> + (tert-BuOCO)<sub>2</sub>O → Z-NHCHRCONH-NHCOOBu-*tert* + CO<sub>2</sub> + *tert*-BuOH. This reaction takes place under mild conditions, and with a small excess of BOC<sub>2</sub>O the *tert*-butoxycarbonylation of the hydrazides takes place quantitatively. The yields of the BOC-hydrazides are determined only the the losses in isolation.

In 20 ml of dimethylformamide, 10 mmole of a hydrazide of a Z-substituted amino acid or peptide, 12 mmole of BOC<sub>2</sub>O, and ~0.5 ml of pyridine were mixed. The solution was stirred at room temperature for 2-3 h (until the spot of the initial hydrazide on TLC had disappeared) and was then mixed with 50 ml of 0.1 N HCl. The product was extracted with ethyl acetate (3 × 20 ml), the extract was washed with water, 2 N ammonia solution (3 × 20 ml) and brine, and was dried with MgSO<sub>4</sub>. After the vacuum distillation of the ethyl acetate, the residue was crystallized. The compounds obtained are given in Table 1.

TABLE 1. N'-BOC-Hydrazides of N-Z Amino Acids and Peptides

Amino acid or peptide	Yield, %	Mp, °C	Literature data		
			yield, %	mp, °C	reference
Gly	92	Oil	—	Macro	[3]
L-Phe	72	76—80	81	81—84	[4]
L-Pro*	52	67—70	89	164	[7]
L-Tyr	77	71—74	75	90—100	[7]
L-Val-L-Tyr	81	127—131	81	128—131	[7]
Gly-Gly	88	105—107	86	100—101	[8]
L-His-(N <sup>im</sup> BOC)†	82	65—70	—	—	—

\*C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>.

†C<sub>24</sub>H<sub>33</sub>N<sub>5</sub>O<sub>7</sub>.

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