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Transprotection in Solid Phase Peptide Synthesis: Easy Conversion of Fmoc Carbamates into Boc Carbamates

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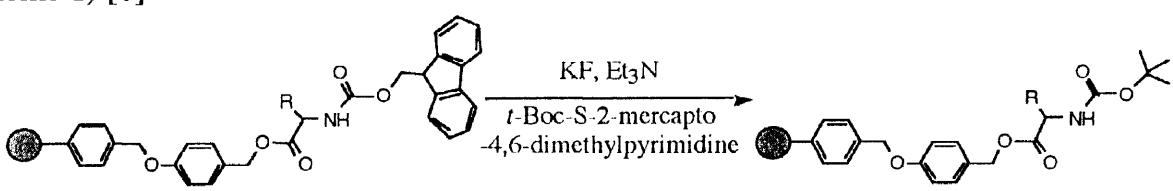
Abstract. A one-pot conversion of *N*-fluorenylmethoxycarbonyl (Fmoc) amino acids and dipeptides linked to Wang resin into the corresponding *N*-tert-butoxycarbonyl (Boc) derivatives was achieved in very high yields. The transformation was corroborated by cleaving of the Boc derivatives with trimethyltin hydroxide.

Keywords: Solid-phase synthesis; Amino acids and derivatives, peptides and polypeptides.

The scientific advances in the area of the synthesis of peptides and proteins have made the preparation of small and intermediate sized peptides molecules quite straightforward [1]. Among these advances, the advent of the solid phase peptide synthesis (SPPS) [2] is of outstanding importance. The most commonly used amino protecting groups in modern SPPS are *N*-fluorenylmethoxycarbonyl (Fmoc) and *N*-*tert*-butoxycarbonyl (Boc). Because of these protecting groups complement each other, conversion of Fmoc into Boc under mild conditions would be of great interest from the synthetic point of view. This is particularly important in the solid phase synthesis of the so-called "difficult" peptides where Boc protection has proved to be better than Fmoc protection after five or six steps, since acid deprotection may destroy undesirable β-sheet structures [3]. Moreover, this exchange is desirable considering that it is now possible to detach peptides from Wang resin in the presence of Boc amino protection under mild conditions using trimethyltin hydroxide (TMTOH)[4,5]. Also, the combination Fmoc-Boc transprotection / TMTOH cleavage would have interesting implications in the growing fields of solid phase organic synthesis (SPOS) and combinatorial chemistry. Here we wish to report the one–pot conversion of *N*-Fmoc amino acids and dipeptides linked to Wang resin into the corresponding *N*-Boc derivatives (Scheme 1) [6].



Scheme 1

We have found that this conversion can be carried out using two different procedures: i) potassium fluoride / *t*-Boc-S-2-mercapto-4,6-dimethylpyrimidine (Method A) [7], or ii) potassium fluoride / di-*tert*–butyl dicarbonate (Method B). Yields of *N*–Boc amino acids and

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dipeptides after separation from the resin with TMTOH, were very high (Table 1). No racemization was detected after comparison of the optical rotations of representative products with reported values.

Typical procedure. Solid phase transprotection of Fmoc group into Boc group. Method A: To a stirred suspension of Fmoc-AA-Wang resin (0.078 mmol) in DMF (1.5 mL) under nitrogen, KF (39 mg, 0.67 mmol) and Et_3N (40 μL, 0.234 mmol) were added at room temperature. Then, a solution of *t*-Boc-S-2-mercapto-4,6-dimethylpyrimidine [7] (58.1 mg, 0.284 mmol) in DMF (1 mL) was added. After stirring for 24 hours,§ the reaction mixture was filtered and washed successively with DMF, HCl 1N, 5% $NaHCO_3$, H_2O, MeOH, AcOEt, $CHCl_3$ and MeOH. The resin was then dried overnight at reduced pressure. Method B: To a stirred suspension of Fmoc-AA-Wang resin (0.099 mmol) in DMF (1.3 mL), under N_2 atmosphere, KF (58.95 mg, 1.014 mmol) and Et_3N (31 μL, 0.22 mmol) were added. The mixture was kept at room temperature and di-*tert*-butyl dicarbonate (28.37 mg, 0.13 mmol) was added. After stirring for 24 hours,§ the reaction mixture was filtered and washed as in Method A.

Table 1. One-pot conversion of *N*-Fmoc amino acid and dipeptides linked to Wang resin into the corresponding *N*-Boc derivatives.

Entry	Substrate	Product[a]	Yield(%), Method A[b]	Yield(%), Method B[b]
1	Fmoc-Ala-Wang resin	Boc-Ala-Wang resin	100	94
2	Fmoc-Leu-Wang resin	Boc-Leu-Wang resin	100	96
3	Fmoc-Ser(O^{t}Bu)-Wang resin	Boc-Ser(O^{t}Bu)-Wang resin	85	100
4	Fmoc-Boc-Lys-Wang resin	(Boc)$_2$-Lys-Wang resin	80	86
5	Fmoc-Cys(*p*-MeOBn)-Wang resin	Boc-Cys(*p*-MeOBn)-Wang resin	100	88
6	Fmoc-Phe-Wang resin	Boc-Phe-Wang resin	100	95
7	Fmoc-Ala-Leu-Wang resin	Boc-Ala-Leu-Wang resin	83	79
8	Fmoc-Pro-Phe-Wang resin	Boc-Pro-Phe-Wang resin	100	100
9	Fmoc-Ser(O^{t}Bu)-Phe-Wang resin	Boc-Ser(O^{t}Bu)-Phe-Wang resin	76	71

[a]Products were characterized by spectroscopic methods after removal of the amino acid or dipeptide from the resin by TMTOH[4,5].
[b]Overall isolated yields after TMTOH cleavage.

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§ Reaction time was determined by monitoring the disappearance of Fmoc carbamate measuring the dibenzofulvene-piperidine absorbance at 300 nm (see: Atherton E, Sheppard RC. Solid Phase Peptide Synthesis. IRL Press: Oxford, England, 1989:112-117).