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One-Pot Conversion of Fluorenylmethyl Carbamates into *tert*-Butyl Carbamates

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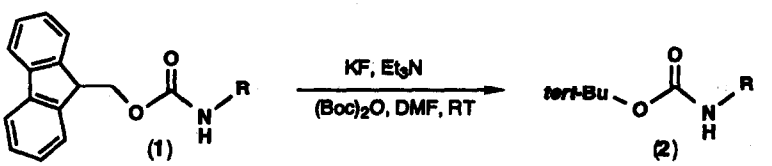
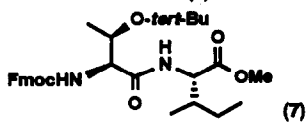
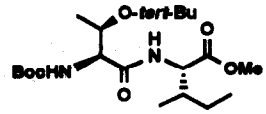
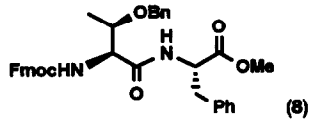
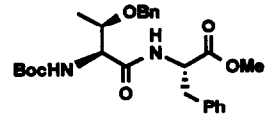
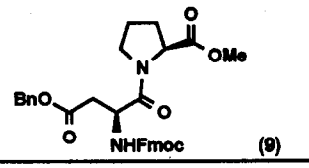
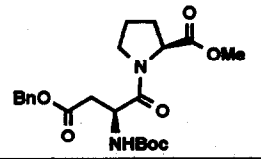
Abstract: N-Fluorenylmethoxycarbonyl groups may be efficiently converted into N-tert-butoxycarbonyl groups by potassium fluoride/Et_3N in the presence of Boc_2O.

The selection of a protecting group plays a major role in synthetic chemistry. The most useful amino protecting groups utilized in peptide chemistry are N-fluorenylmethoxycarbonyl (Fmoc), N-benzyloxycarbonyl (Z), and N-*tert*-butoxycarbonyl (Boc). These groups exhibit contrasting chemical stabilities to acids, bases, and hydrogenation. The Fmoc-amino acid derivatives exhibit complete acid stability and may be removed by base. They are also easily crystallized. N-Boc groups are stable to bases but removed with acids. The chemoselective exchange of these groups under mild conditions is of potential interest. The successful transformation of benzyl carbamates into *tert*-butyl carbamates[1,2] or the reverse transformation[3] are both known. However, the conversion of the Fmoc group into the Boc group has not been previously documented. Such an exchange could be synthetically useful as illustrated by two recent reports. A comparison of the Fmoc and Boc protecting groups in a solid phase peptide synthesis showed the Boc protection to be more advantageous in the final step. The reason given for this superiority was that the acid used in the deprotection also destroyed undesirable hydrogen bonding interactions. The basic protocol employed to remove Fmoc groups cannot achieve the same effect.[4] In another report, the previously difficult cyclization of a tetrapeptide was achieved by temporarily substituting all the amide nitrogens with Boc groups.[5] We now report the first application of potassium fluoride to the one-pot conversion of N-Fmoc protected amino groups (**1**) into the corresponding N-Boc protected derivatives (**2**).



As shown in **Table 1**, several fluorenylmethyl carbamates (**3-9**) were smoothly converted into *tert*-butyl carbamates in high yields. It should be noted that the various esters unstable in tetrabutylammonium fluoride (TBAF)/DMF,[6,7] are completely stable under the present milder reaction conditions. No racemization was reported in removing the esters[7] or in cleaving a peptide chain from a resin support with tetrabutylammonium fluoride.[6] In the present study racemization was not detected after comparison of the optical rotations of the products with authentic samples.

Table 1: One-Pot Conversion of Fluorenylmethyl Carbamates into *tert*-Butyl Carbamates[a]

Entry	Substrate	Time (h)	Product[b]	Yield (%)[c]
1	N-Fmoc-L-Met (3)	5	N-Boc-L-Met	86
2	N-Fmoc-L-Trp (4)	6	N-Boc-L-Trp	90
3	N-Fmoc-L-Ile-OMe (5)	5	N-Boc-L-Ile-OMe	93
4	N-Fmoc-L-Pro-OMe (6)	7	N-Boc-L-Pro-OMe	89
5	 (7)	10		85
6	 (8)	7		80
7	 (9)	10		84

[a]All reactions were carried out according to the general procedure described in the text. [b]All products were fully characterized by analytical methods. [c]Isolated yields.

General Procedure: To a stirred solution of N-fluorenylmethoxycarbonyl compound (0.14 mmol) in DMF (1.2 ml) was added, under nitrogen atmosphere, potassium fluoride (0.98 mmol) followed by Et_3N (0.30 mmol). The solution was kept at room temperature and di-*tert*-butyl dicarbonate (0.18 mmol) was added. After stirring for several hours, the reaction was diluted with ethyl acetate and washed with H_2O, 5% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography to afford the pure *tert*-butyl carbamate.

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