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TERT-BUTYL ESTERS OF N-PROTECTED AMINO ACIDS WITH TERT-BUTYL FLUOROCARBONATE (Boc-F)

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Summary : Tert-butyl fluorocarbonate (Boc-F) is efficiently used for the synthesis of tert-butyl esters of N-protected amino acids. The reaction proceeds at room temperature and under mild conditions in the presence of triethylamine and 4-dimethylamino-pyridine.

To date, described methods for the preparation of tert-butyl esters of N-protected amino acids are based on the use of isobutylene[1] in the presence of strong acids or other reagents for generation of the tert-butyl cation, in acidic conditions.[2] Alternately, conversion of the carboxylic acid to a mixed carboxylic-carbonic anhydride[3] followed by 4-dimethylamino-pyridine catalyzed addition of tert-butanol was investigated using isopropenyl chlorocarbonate.[4]

Here we report on the preparation of tert-butyl esters of N-protected amino acids *via* the tert-butyl anhydride generated *in situ* by the tert-butyl fluorocarbonate **1**.[5]

Tert-butyl esters of N-protected amino acids were prepared by Boc-F addition (1.5 eq.) to the N-benzyloxycarbonyl amino acid in the presence of triethylamine (1.5 eq.) and 4-dimethylamino-pyridine (0.2 eq.), in a CH_2Cl_2-tBuOH (1 : 1) solution (0.2 ml per mmol), at room temperature. After 4 h, the ester formed was easily purified by the usual workup. The presence of tert-butanol increased the yield of tert-butyl ester formation, by comparison with the results obtained in pure methylene chloride, as shown in the case of ZPheOtBu (from 73 to 91 % yield).

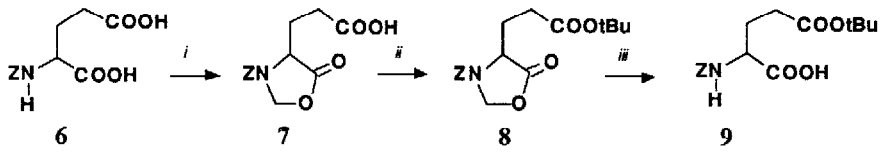
Table I. *Synthesis of tert-butyl ester of Z -amino acids with Boc-F*

	Amino ester	Yield (%)	mp°C (lit.)	$[\alpha]^{20}_D$ (lit., c, solvant)
2	Z-Phe-OtBu	91	78-79 (81-82)	- 7 (-9.9, 2, MeOH)
3	Z-Pro-OtBu	88	42-43 (44-45	-55 (-52 , 2, EtOH)
4	Z-Cys-(Bzl)-OtBu	92	54-56 (oil)	-25 (-30, 2, MeOH)
5	Z-Met-OtBu	96	oil	-35 (-27, 5.7, EtOH)
9	Z-Glu-(OtBu)	82	79-80 (80-82)	-8.9 (-9.4, 1, EtOH)

The usefulness of this method for the regioselective ω-tert-butylation of aspartic and glutamic acids is demonstrated in the following example (Scheme 1). The Z-glutamic oxazolidinone **7** was prepared in 91% yield following a previously described procedure.[6] The α-protected glutamic acid **7** was submitted to the BocF tert-butyl esterification to give the β-tert-butyl ester **8** in 95 % yield. Sodium hydroxide saponification of the oxazolidinone provided Z-Glu(OtBu) **9** in 82% overall yield, calculated from the starting Z-Glu(OH) **6**.

Furthermore, we demonstrated that the reaction proceeds without observable racemization, by using the previously described diastereomeric evaluation on ZAla-PheOtBu by ^1H NMR.[4]

Scheme 1. *Synthesis of Z-Glu(OtBu)OH*



6 7 8 9

i- 3 eq. trioxane, cat. TsOH, reflux toluene. ii- BocF, TEA, DMAP, CH_2Cl_2/tBuOH. iii- 1 eq. 1N NaOH, EtOH.

Tert-butyl fluorocarbonate (Boc-F) is a powerful agent for the N-tert-butyloxycarbonyl protection of amino acids. In the same way, the useful amino protection reagent di-tert-butyl dicarbonate (Boc_2-O) was successfully used for tert-butyl ester formation, but with lower yields, in our hands.[7] The present method also compares favorably with the alternative acidic cation transfer methodology (Table II).

The 4-dimethylamino catalyzed reaction of esterification with alkyl chlorocarbonates is a known general method.[3] Similarly, the mechanistic pathway of the BocF tert-butylation is supposed to proceed *via* a mixed carboxylic-carbonic anhydride as depicted in Scheme 2.

Table II. *Synthesis of Z-Phe-O^{t}Bu*

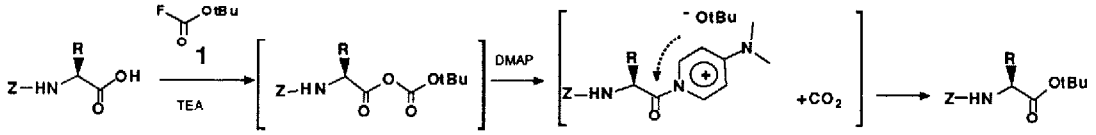
Reagent	Yield (%)
Boc-F/TEA/DMAP	91
Boc_2O/TEA/DMAP[a]	60
$Boc_2O/BF_3.EtO_2$[b]	60
$AcOtBu/BF_3.EtO_2$[c]	70
Isobutylene	75

(a) 1 eq. Z-Phe-OH, 2 eq. Boc_2O, 2 eq. TEA, 0.2 eq. DMAP, CH_2Cl_2/tBuOH (1 : 1).

(b) 1 eq. Z-Phe-OH, 2 eq. Boc_2O, 0.2 eq. $BF_3.EtO_2$

(c) 1 eq. Z-Phe-OH, 10 eq. AcO^{t}Bu, 0.2 eq. $BF_3.EtO_2$

Scheme 2. *BocF tert-butyl esterification.*



The ease of manipulation, mild conditions and high yields, are such that Boc-F appears to be a valuable reagent for the tert-butyl esterification of N-protected amino acids.

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