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Synthesis of 9-Fluorenylmethyl Esters Using 9-Fluorenylmethylchloroformate

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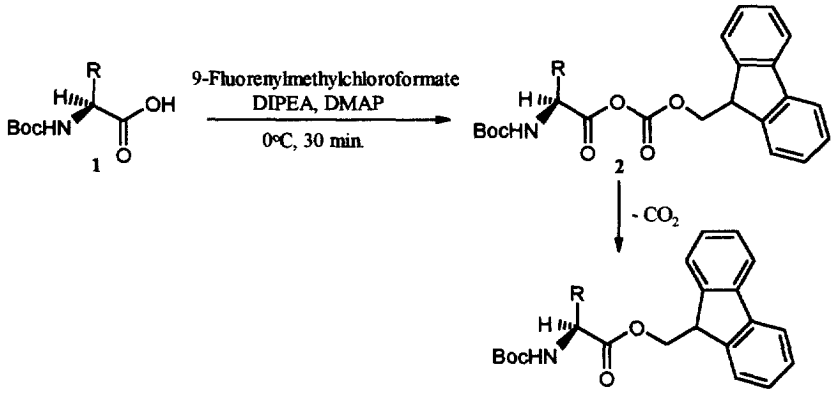
Abstract: 9-Fluorenylmethyl esters of amino acids were synthesized by reacting 9-fluorenylmethylchloroformate with *N*-protected amino acids in the presence of diisopropylethylamine (DIPEA) as base and 4-dimethylaminopyridine (DMAP) as catalyst.

Fluorenylmethyl (Fm) esters of *N*-protected amino acids can be used in solid phase chemistry because of their orthogonality with protecting groups such as Boc and their facile deprotection using a secondary amine in dimethylformamide [1]. Our aim was to synthesize such esters to be used for the synthesis of peptides from the *N* to *C* terminal on solid phase.

Fm esters have previously been synthesized by reacting *N*-protected amino acids with 9-fluorenylmethanol in the presence of dicyclohexylcarbodiimide/DMAP, [1] or with diazofluorene. [2] Alternatively, N-protected amino acids p-nitrophenyl esters have been transesterified in the presence of imidazole, [3] however prolonged reaction time (overnight) was required and some competing imidazole induced decomposition observed.

Alkyl and aryl chloroformates may be used to form esters in excellent yields under basic conditions (TEA). [4,5] Therefore we decided to investigate the use of 9-fluorenylmethylchloroformate for the synthesis of Fm esters.



Results show that the Fm esters **3** can be synthesized rapidly [6] (30 minutes) and in good yields (except for Boc-Val-OFm) by reacting *N*-protected amino acids **1** with the commercially available 9-fluorenylmethylchloroformate, in the presence of DIPEA and DMAP (see table 1). The reaction probably proceeds via the formation of a mixed carboxylic-carbonic anhydride **2** which produces the ester by decarboxylation [7]. Triethylamine was used alternatively as a base, in an attempt to improve the existing yields, but gave Boc-(L)Phe-OFm in 25% yield. It is known that the Fm esters are very sensitive to base, [1,7] which might explain why the esterification did not proceed well in this case. No racemization was observed, by analysis of mixtures of Boc-(L/D)Phe-OFm and Boc-(L/D)Phg-OFm [8], using normal phase chiral chromatography [9].

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In conlusion fluorenylmethyl esters of N-protected amino acids can be formed in good yields and high optical purity.

Table 1 : Fluorenylmethyl Esters of *N*-Protected Aminoacids

Amino Acid[a]	Yield[b] (%)	Mp[b] (°C)	ESI-MS (m/z)	$[\alpha]_D$[c]
Boc-(L)Pro-OFm	82	65-68	394	-17.95°
Boc-(L)Phe-OFm	67	125-127[d]	444	-0.97°
Boc-(L)Leu-OFm	74	53-54	410	-4.41°
Boc-(L)Ser(Bzl)-OFm	62	-	474	-0.35°
Boc-(L)His(Bom)-OFm	64	102-105	555	-1.07°
Boc-(L)Val-OFm	25	70-72	396	-5.58°
Boc-(D)Phe-OFm	84	125-127	444	+0.91°
Boc-(L)Phg-OFm	53	105-108	450	-42.8°
Boc-(D)Phg-OFm	58	102-105	450	+40.0°

[a] Boc : $(CH_3)_3OCO$-, Fm : $(C_6H_4)_2CHCH_2$-
[b] Yields, after crystallisation (EtOAc/hexane), are not optimized. CHN and ^1H and ^{13}C NMR analyses of the Fm esters were satisfactory (C : ± 0.22%, H : ± 0.16%, N : ± 0.11%). Melting points are uncorrected.
[c] Optical rotation analyses conducted at C = 1, in $CHCl_3$, at 25°C. Reference : (L)-menthol : $[\alpha]_D$ = -45.1° (C = 1, $CHCl_3$), sucrose : $[\alpha]_D$ = +66.8° (C = 1, $CHCl_3$).
[d] Lit. value : 125-126°C.

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6. To a solution of *N*-protected amino acid (about 0.02 moles) and DIPEA (1 eq.) in dry dichloromethane (80 ml) is added, at 0°C, a solution of 9-fluorenylmethylchloroformate (1.1 eq.) dissolved in DCM (20 ml). The mixture is stirred for 5 minutes before adding DMAP (0.1-0.15 eq.), then about 30 minutes at 0°C. Decarboxylation is observed throughout the reaction. Once the evolution of gas ceased, the reaction mixture is diluted with DCM and worked up using acid and base washes.
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9. Chiral chromatography was carried out at room temperature using a CHIRALCEL OD column (0.46 cm I.D. x 25 cm); Eluent: EtOH (0.1% DEA); Flow rate: 0.5-0.9 ml/min., Boc-(L)Phe-OFm: 11.5 min., Boc-(D)Phe-OFm: 16.8 min., Boc-(L)Phg-OFm: 11.7 min., Boc-(D)Phg-OFm: 12.2 min.