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PREPARATION OF PENTAFLUOROPHENYL ESTERS OF FMOC PROTECTED AMINO ACIDS WITH PENTAFLUOROPHENYL TRIFLUOROACETATE

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Summary: A high yield procedure for the preparation of pentafluorophenyl esters of N^{α}-9-fluorenylmethyloxycarbonyl protected amino acids is described. The procedure utilizes pentafluorophenyl trifluoroacetate.

The use of pentafluorophenyl esters (OPfp esters) as preformed active esters for coupling reactions has become common, especially in the area of solid-phase peptide synthesis. In a large number of these situations, the α-nitrogens of the amino acids are protected with a 9-fluorenylmethyloxycarbonyl group (Fmoc). The standard preparation of these activated esters has typically been achieved with a N,N-dicyclohexylcarbodiimide (DCC) mediated coupling of the Fmoc protected amino acid and pentafluorophenol[1]. This paper describes an alternate route to these pentafluorophenyl esters.

Although the preparation of *p*-nitrophenylesters commonly utilizes *p*-nitrophenyl trifluoroacetate[2], the use of pentafluorophenyl trifluoroacetate (1) is not widely described. Previous uses of 1 include preparation of the preformed active esters of N,N-dimethylvaline and N,N-dimethylphenylalanine[3] and preparation of a putative Dolastatin 3 intermediate[4]. Additionally, although pentafluorophenyl trichloroacetate (crystalline solid) has been used to prepare pentafluorophenyl esters[5], 1 reacts faster and is easier to remove via workup (hydrolytic lability and volatility).

The procedure makes use of a base-catalyzed transesterification reaction of pentafluorophenyl trifluoroacetate (Figure 1). The reagent 1 is a stable colorless liquid with a moderate boiling point (122°C). The use of this reagent provides better yields and greater convenience. Workup of the OPfp esters consists of washing with dilute aqueous acid and base. No recrystallization is necessary. Table 1 summarizes the physical constants of the derivatives prepared.

This new procedure with pentafluorophenyl trifluoroacetate is a very convenient method for preparing Fmoc-protected OPfp esters of amino acids. This procedure offers better yields then traditional methods while requiring less time, less trouble, and it still maintains the high standards of quality necessary for reagents used in solid-phase peptide synthesis.

Figure 1:

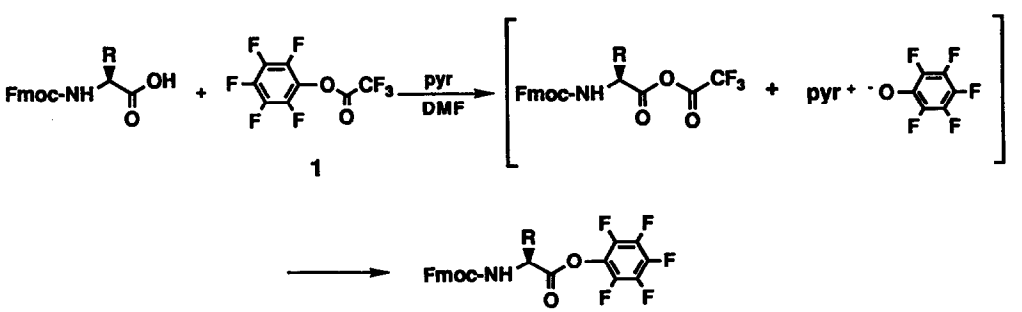

TABLE 1

Fmoc-amino acid-OPfp[a]	Yield	m.p.(°C)	R_f[b]	$[\alpha]_D^{25c}$	Purity[d]	^{1}H-NMR Solvent
Phe	99%	150-153	0.68	-20.8°	>99%	$CDCl_3$
Tyr(tBu)	99%	61-64	0.63	-13.8°	>99%	$CDCl_3$
Ile	99%	73-75	0.66	-13.1°	>99%	$CDCl_3$
Trp	96%	183-185	0.33	-42.6°	>99%	DMSO-d_6
Cys(Trt)	92%	71-73	0.77	+15.0°	>99%	$CDCl_3$
Lys(Boc)	98%	99-101	0.35	-14.1°	>99%	$CDCl_3$
Asp(OtBu)	99%	54-58	0.54	-2.5°	>99%	$CDCl_3$

[a]All Fmoc amino acids were purchased from Bachem Inc. (Torrance, Ca.) or Calbiochem Corporation (San Diego, Ca.) and used as received.
[b]TLC was performed using Hexane/EtOAc (3:1 v/v). All compounds gave a single spot when visualized by UV and staining with phosphomolybdic acid.
[c]All rotations were done in $CHCl_3$ with c=1.
[d]HPLC monitored at 254nm, using a CH_3CN gradient with 0.1% TFA, linear gradient of 30% to 100% CH_3CN over 28 minutes (flow rate 1.5 mL/min). Column: Vydac C_{18} (0.46cm x 25cm, 100Å, 5µm).

Preparation of 1: Pentafluorophenol (0.050 moles) and trifluoroacetic anhydride (0.075 moles) were stirred at 40°C overnight. The resulting liquid was distilled to a colorless liquid, b.p.: 122°C, density: 1.63g/mL, 88% yield. GC-MS indicated the desired material (trace of the starting phenol). A sample of 1 has shown no decomposition after 2 months storage at 4°C.

General preparation of OPfp esters: At room temperature the Fmoc protected amino acid (0.50 mmole) was dissolved in N,N-dimethylformamide (1mL). To this was added pyridine (0.55 mmole) followed by 1 (0.58 mmole). The reaction was allowed to stir for 45 minutes at room temperature (most appeared complete by TLC within 15 minutes). The solution was diluted with EtOAc (100mL), washed with 0.1 N aqueous HCl (3x100mL), washed with 5% aqueous $NaHCO_3$ (3x100mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to the desired white solid. All of the desired Fmoc amino acid OPfp esters had FAB-MS and PCI-MS data consistent with their structures, as well as the expected ^{1}H-NMR spectra ($CDCl_3$ or DMSO-d_6). The ^{1}H-NMR spectra often indicated trace amounts of EtOAc and H_2O (less than 1%).

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