THE PEPTIDES

Analysis, Synthesis, Biology

EDITED BY

SIDNEY UDENFRIEND
JOHANNES MEIENHOFER

Volume 9

Special Methods in Peptide Synthesis, Part C

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Part C

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The Peptides

Volume 9

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THE PEPTIDES

Analysis, Synthesis, Biology

Treatise Editors

S. UDENFRIEND AND J. MEIENHOFER

Volume 1
Major Methods of Peptide Bond Formation

Volume 2
Special Methods in Peptide Synthesis, Part A

Volume 3
Protection of Functional Groups in Peptide Synthesis

Volume 4
Modern Techniques of Conformational, Structural, and Configurational Analysis

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Special Methods in Peptide Synthesis, Part B

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Opioid Peptides: Biology, Chemistry, and Genetics

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Volume 9
Special Methods in Peptide Synthesis, Part C

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Preface

"The Peptides" is an open-ended treatise providing comprehensive and critical reviews of important developments in all areas of peptide research, including analysis, synthesis, and biology. These reviews are intended as a reference for the specialist, a guide for the novice, and a forum for all investigators concerned with peptides and proteins. In previous volumes on peptide synthesis attempts were made to present the current state of the methodology. Because of the dramatic increases in the number and efficiencies of commercial peptide synthetic instruments (including tea bags), most peptide syntheses are now carried out by solid-phase methods in automated instruments. However, this only makes it all the more important to be familiar with the latest chemical methods.

This volume contains five chapters, one chapter on the Fmoc protecting group, one chapter on the use of *N*-carboxy- and *N*-thio-carboxyanhydrides for peptide bond formation, two chapters on enzymatic synthesis, and the last chapter on strong acid deprotection of peptides. In the first chapter E. Atherton and R. C. Sheppard have reviewed the present state of peptide synthesis using the 9-fluorenylmethoxycarbonyl (Fmoc) amino protecting group. This system has the potential of becoming the most important protecting group for solid-phase synthesis in due time, because of its mild base cleavage. The preparation and use of *N*-carboxyanhydrides (NCAs) and *N*-thiocarboxyanhydrides (NTAs) for peptide bond formation are discussed in Chapter 2, by Thomas J. Blacklock, Ralph Hirschmann, and Daniel F. Veber. The opportunities and constraints of these systems suggest that they will be widely used in coming years. In Chapter 3 Hans-Dieter Jakubke presents a comprehensive discussion of enzymatic peptide synthesis. These methods have great potential for large-scale preparation of peptides and proteins. In Chapter 4, by John D. Glass, another aspect of enzymatic peptide synthesis is presented, i.e., enzymatic manipulation of protecting groups during peptide synthesis. The last chapter, by James P. Tam and R. B. Merrifield, provides an excellent discussion of strong acid deprotection of synthetic peptides, mechanisms and methods (see also Volume 5, Chapter 2).

Johannes Meienhofer

Contents

Chapter 5 *Strong Acid Deprotection of Synthetic Peptides: Mechanisms and Methods*

James P. Tam and R. B. Merrifield

Chapter 1

The Fluorenylmethoxycarbonyl Amino Protecting Group

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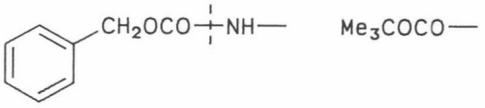
I. INTRODUCTION

In the 25 years following its introduction by Bergmann and Zervas in 1932, the benzyloxycarbonyl amino-protecting group became preeminent in peptide synthesis. The urethane structure (**1**) effectively reduced the nucleophilicity of the nitrogen atom in benzyloxycarbonyl amino acids. At the same time, it conferred substantial resistance to racemization of activated carboxyl derivatives. Cleavage by hydrogenolysis provided a ready means for its removal under very mild reaction conditions. This combination of properties—adequate protection, resistance to racemization, and ease of removal—is of paramount importance in protecting-group design. In more recent years, a number of other protecting groups have come to rival the archetypal benzyloxycarbonyl derivatives. Most have been based on urethane structures, which have similarly imparted adequate protection and resistance to racemization, but few have been cleavable under reaction conditions approaching the mildness of catalytic hydrogenolysis.

The most widely used of these newer groups has undoubtedly been the *t*-butoxycarbonyl function (**2**) of McKay and Albertson (1957). *t*-Butoxycarbonyl amino acids and peptides are cleaved by strong acids under reasonably mild conditions, and a number of similarly conceived groups have since been devised



(**1**) (**2**)

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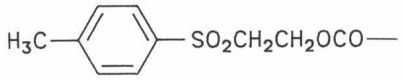
with varying degrees of acid lability. Much less attention has been paid to the development of base-labile derivatives. Kader and Stirling had shown in 1964 that urethanes containing suitably activated hydrogen atoms [e.g., the arylsulfonylethoxycarbonyl derivatives (**3**)] could be cleaved by base-catalyzed β-elimination, but rather strong aqueous alkaline conditions were required and no substantial application in peptide synthesis ensued. The corresponding alkyl derivatives (**4**) (Tesser and Balvaert-Geers, 1975) found greater application, notably in partially synthetic operations involving natural peptides or protein fragments, in part due to the favorable solubility properties imparted by **4.** The



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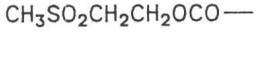

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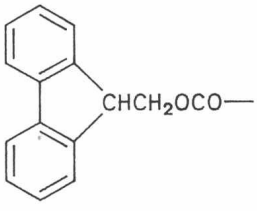
base-labile 9-fluorenylmethoxycarbonyl group (**5**) introduced by Carpino and Han in 1970 found no immediate use. Only passing mention appears in the literature in the 7 years following its first appearance, a period when acid-labile protecting groups steadily gained in importance. To a large extent this last was due to the introduction (Merrifield, 1963) and rapid growth in importance of solid-phase synthesis. Merrifield's solid-phase technique utilized Boc amino acids exclusively. Each cycle of amino acid addition included cleavage of this protecting group by treatment with acid, usually trifluoroacetic acid or anhydrous hydrogen chloride. Amino acid side chains were normally protected as various benzyl derivatives; these and the peptide–resin linkage (carboxy protecting group) were also cleaved by acidic reagents. Merrifield's solid-phase method was remarkably successful and clearly constitutes one of the most important developments in modern peptide synthesis. It was rapidly and widely applied to objectives of increasing complexity. As these synthetic targets became larger and more ambitious, however, it seemed possible that the rather vigorous acidic deprotection conditions necessarily involved might be restricting the scope of the method. Evidence was accumulating of substantial degradation of some assembled peptides by, for example, liquid hydrogen fluoride, frequently used in side-chain protecting-group cleavage and detachment from the solid support.



(5)

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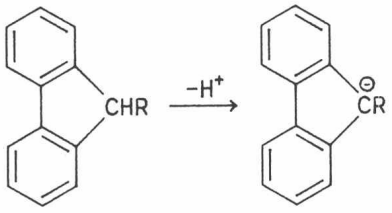
Motivated by this feeling, two laboratories (Chang and Meienhofer, 1978; Atherton *et al.*, 1978a) described independently in 1978 new protecting-group strategies for use in solid-phase synthesis that were considered to be much milder in character than the by now classical Boc–benzyl combination. Both laboratories used fluorenylmethoxycarbonyl (Fmoc) amino acids in place of the firmly established Boc derivatives. In the following 5 years, more than 60 publications appeared reporting applications of Fmoc amino acids, most but not all in relation to solid-phase synthesis.

The fluorenylmethoxycarbonyl group owes its base lability to the special characteristics of the dibenzocyclopentadiene structure (**6**). Resonance stabilization of the corresponding dibenzocyclopentadienide anion (**7**) imparts substantial

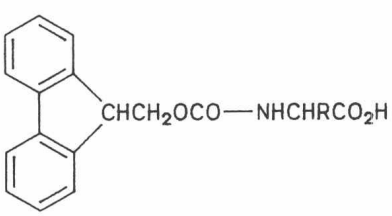


(**6**) (**7**)

lability to the 9-hydrogen atom. Hückel's rule for aromaticity is satisfied in **7.** Although mechanistic studies have apparently not been carried out on Fmoc amino acid or peptide derivatives, a kinetic study has shown that fluorenylmethanol itself undergoes base-catalyzed elimination by an Elcb mechanism (O'Ferrall and Slae, 1970). It is likely that the same mechanism holds for Fmoc derivatives. The rate-determining step would then be formation of the conjugate base analogous to **7.**

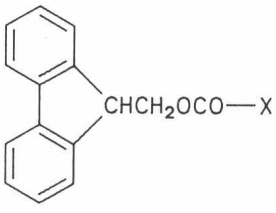
II. PREPARATION OF FLUORENYLMETHOXYCARBONYL AMINO ACIDS

Two reagents were described by Carpino and Han (1972) for the preparation of N_{α}-fluorenylmethoxycarbonyl amino acids (**8**). 9-Fluorenylmethyl chlorofor-

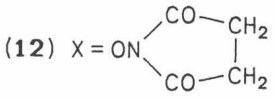


(**8**)

mate (**9**) is readily obtained from fluorenylmethanol [for an improved preparation see Carpino and Han (1973)] by reaction with phosgene. It is a stable, crystalline solid that keeps well at low temperatures in the absence of moisture. It reacts normally with amino acids in weakly alkaline solution, giving Fmoc derivatives in 88–97% yield (Carpino and Han, 1972). Only a few examples (glycine, alanine, β-alanine, phenylalanine, and tryptophan) were recorded by Carpino, but the method appears to be quite general and has been widely applied (Table I). Aqueous sodium carbonate is generally used as the alkaline medium, to which the chloroformate is added as a solution in dioxane. In our experience there is no merit in prolonging the contact time with this alkaline medium unnecessarily, and the reaction is best terminated as soon as thin-layer chromatography (tlc) shows that the starting amino acid has been nearly all consumed (usually within 1 hr). Carpino's alternative reagent, 9-fluorenylmethoxycarbonyl azide (**10**), may be prepared directly from the chloroformate by reaction with sodium azide or by way of the corresponding hydrazide (**11**). It reacts more sluggishly with amino acids, and the yield of Fmoc glycine reported (Carpino and Han, 1972) was lower (see Tessier *et al.*, 1983).



(**9**) X = Cl
(**10**) X = N_3
(**11**) X = $NHNH_2$



Some side products are commonly formed in the acylation reaction, and careful purification may be necessary to obtain homogeneous amino acid derivatives. Commercial Fmoc amino acids (especially Fmoc glycine) should be carefully examined by thin-layer chromatography for the presence of slower-running, ninhydrin-negative impurities. The presence of these has been noted by several authors (Fuller *et al.*, 1983; Sigler *et al.*, 1983; Tessier *et al.*, 1983; Lapatsanis *et al.*, 1983). In some cases the impurities present in crude samples of Fmoc amino acids have been isolated and identified as the corresponding Fmoc dipeptides. Traces of tripeptide derivatives have also been encountered. These oligomeric contaminants could arise through activation of the initially formed Fmoc amino acids by reaction with excess chloroformate. Such activation would be favored

Table I. List of Fmoc Amino Acids

Compound	Reagent used in preparation	Yield (%)	m.p. (°C)	$[\alpha]_D$ (Temp., °C)	Concentration	Solvent	Reference
Fmoc-AlaOH	Fmoc-Cl	97	143–144	−18.6 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-AlaOH	Fmoc-Cl	94	144–145	−3.5 (28.6)	2.5	EtOAc	Carpino and Han (1972)
Fmoc-AlaOH	Fmoc-OSu	96	142–143	−19.7 (20–25)	1	DMF	Lapatsanis *et al.* (1983)
Fmoc-AlaOH	Fmoc-N_3	75	146–147	−19.2	1	DMF	Tessier *et al.* (1983)
Fmoc-DL-AlaOH	Fmoc-Cl	88					Carpino and Han (1972)
Fmoc-AlaO-*t*Bu	Fmoc-Cl	68	84–85	+1.0 (25)	2.0	$CHCl_3$	Chang *et al.* (1980a)
Fmoc-Ala-OMPA[a]		54[b]	144–145				Alberico and Barany (1984)
Fmoc-ArgOH	Fmoc-Cl	89	145–160				E. Atherton and R. C. Sheppard, unpublished
Fmoc-Arg(Adoc)$_2$OH	Fmoc-Cl	80	152–154	+2.1[c] (18)	1.03	CH_3OH	E. Atherton and R. C. Sheppard, unpublished; Presentini and Antoni (1986)
Fmoc-Arg(Boc)OH	Fmoc-Cl	24[d]	170–171	−11.5 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-Arg(Mbs)OH	Fmoc-Cl	56	Amorphous	−6.6 (2.0)	0.74	DMF	E. Atherton and R. C. Sheppard, unpublished
Fmoc-Arg(Mds)OH	Fmoc-Cl	30	121–123				Atherton *et al.* (1983a)
Fmoc-Arg(Mtr)OH	Fmoc-Cl	60	118–120	+7.9 (18)	0.5	CH_3OH	Atherton *et al.* (1983a)
Fmoc-Arg(Pms)OH	Fmoc-Cl	73	125–127 (D)	+2.1 (18)	0.5	CH_3OH	Atherton *et al.* (1983a)
Fmoc-AsnOH	Fmoc-Cl	98	185–186	−11.4 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-Asn(Mbh)OH	Fmoc-Cl	72	182–184	+0.84 (18)	1	DMF	E. Atherton and R. C. Sheppard, unpublished
Fmoc-Asp(O-*t*Bu)OH	Fmoc-Cl	58	148–149	+9.1 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−20.3 (23–25)	1	DMF	
Fmoc-Asp(OBzl)OH	Fmoc-Cl	81	113–115	−3.5 (25)	1	CH_3OH	Kisfaludy and Schön (1983)
Fmoc-Asp(OH)OBzl	Fmoc-Cl	64	112–115	+4.0 (25)	1	CH_3OH	Kisfaludy and Schön (1983)
Fmoc-Cys(Acm)OH	Fmoc-Cl	75	150–154	−27.5 (18)	1	EtOAc	Atherton *et al.* (1985c)

(*continued*)

Table I. (*Continued*)

Compound	Reagent used in preparation	Yield (%)	m.p. (°C)	$[\alpha]_D$ (Temp., °C)	Concentration	Solvent	Reference
Fmoc-Cys(Acm)OH	Fmoc-Cl	81	Amorphous	−34.4 (25)	1	EtOAc	Kisfaludy and Schön (1983)
Fmoc-Cys(*t*Bu)OH	Fmoc-Cl	61	135–136	−1.9 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−23.2 (23–25)	1	DMF	
Fmoc-Cys(S-*t*Bu)OH	Fmoc-Cl	72	74–76	−84.6 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-Cys(Bzl)OH	Fmoc-Cl	90	125–126	−40.6 (25)	1	CH_3OH	Kisfaludy and Schön (1983)
Fmoc-Cys(Bzl)OH	Fmoc-Cl	96[e]	127–128	−30.0 (25)	2	DMF	Bodanszky *et al.* (1981b)
Fmoc-Glu(O*t*Bu)OH	Fmoc-Cl	71	76–77	+0.8 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-GlnOH	Fmoc-Cl	97	221–223	−17.0 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-Gln(Mbh)OH	Fmoc-Cl	59	177–178.5				E. Atherton and R. C. Sheppard, unpublished
Fmoc-GlyOH	Fmoc-Cl	88	173–176				Chang *et al.* (1980a)
Fmoc-GlyOH	Fmoc-Cl	88	174–175				Carpino and Han (1972)
Fmoc-GlyOH	Fmoc-N_3	60	174–175				Carpino and Han (1972)
Fmoc-GlyOH	Fmoc-N_3	78	176–178				Tessier *et al.* (1983)
Fmoc-GlyOH	Fmoc-OSu	68	175–176				Sigler *et al.* (1983)
Fmoc-GlyO*t*Bu	Fmoc-Cl	90	79–81				Carpino and Han (1972)
Fmoc-GlyOEt	Fmoc-Cl	91	109–110				Carpino and Han (1972)
Fmoc-Gly-OMPA[a]		50[b]	176–177				Albericio and Barany (1984)
Fmoc-His(Boc)OH-CHA[f]		62[g]	149–151	+15.2 (18)	1	DMF	E. Atherton and R. C. Sheppard, unpublished
Fmoc-His(BocTf)OH	Fmoc-Cl	10[h]	143–155	+14.7 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-His(Fmoc)OH	Fmoc-Cl	91[i]	161–163	−6.8 (18)	1	DMF	E. Atherton and R. C. Sheppard, unpublished
Fmoc-His(πBom)OH	Fmoc-Cl	41	160	+1.8 (20)	0.6	CH_3OH	Brown and Jones, unpublished
Fmoc-His(πBum)OH	Fmoc-Cl		175–176	−7.5	1	AcOH	Colombo *et al.* (1984)
Fmoc-His(Ppc)OH		37[g]	114–116	−2.5	1	CH_3OH	E. Atherton and R. C. Sheppard, unpublished

Fmoc-IleOH	Fmoc-Cl	82	145–147	−9.8 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−11.9 (23–25)	1	DMF	
Fmoc-LeuOH	Fmoc-Cl	91	153–154	−6.9 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−24.1 (23–25)	1	DMF	
Fmoc-LeuOH	Fmoc-Cl	90	155–156	−4.4 (28.3)	2.5	EtOAc	Carpino and Han (1972)
Fmoc-Lys(Boc)OH	Fmoc-Cl	99	123–124	+5.1 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−11.7 (23–25)	1	DMF	
Fmoc-Lys(Tfa)OH	Fmoc-Cl	67	140–141	−2.5 (18)	1	CH_3OH	E. Atherton and R. C. Sheppard, unpublished
Fmoc-Lys(Z)OH	Fmoc-Cl	81	108–110	−2.0 (25)	1	CH_3OH	Kisfaludy and Schön (1983)
Fmoc-MetOH	Fmoc-Cl	92	129–132	−0.3 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−28.3 (23–25)	1	DMF	
Fmoc-Met(O)OH[j]		56	164–166	−6.0 (18)	1	DMF	E. Atherton and R. C. Sheppard, unpublished
Fmoc-PheOH	Fmoc-Cl	97	181–183	−37.6 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-PheOH	Fmoc-Cl	92	183–185	+11.6 (28.6)	1.2	EtOAc	Carpino and Han (1972)
Fmoc-PheOH	Fmoc-OSu	91	178–179	−41.7 (20–25)	1	DMF	Lapatsanis *et al.* (1983)
Fmoc-DPheOH	Fmoc-Cl	83	176–181.5	+37.8 (24)	0.87	DMF	Smith *et al.* (1983)
Fmoc-PheOMPA[a]		54[b]	150–152				Albericio and Barany (1984)
Fmoc-PheOTcrom		89	102–107				Kemp and Hanson (1981)
Fmoc-ProOH	Fmoc-Cl	92	114–115	−39.0 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−33.9 (23–25)	1	DMF	
Fmoc-ProOH	Fmoc-OSu	86	116–117	−33.2 (20–25)	1	DMF	Lapatsanis *et al.* (1983)
Fmoc-SerOH	Fmoc-Cl	89	86–88	+14.9 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-SerOH	Fmoc-OSu	87	86–88	+14.8		EtOAc	Paquet (1982)
Fmoc-SerOH	Fmoc-OBt	64					Paquet (1982)
Fmoc-SerOBzl	Fmoc-Cl	87	97–98	+1.4 (23–25)	1	DMF	Chang *et al.* (1980a)
Fmoc-SerOBzl	Fmoc-OSu	87	97	+1.3		EtOAc	Paquet (1982)
Fmoc-SerOBzl	Fmoc-OBt	89					Paquet (1982)
Fmoc-SerOBzl	Fmoc-OPcp	50					Paquet (1982)
Fmoc-Ser(*t*Bu)OH	Fmoc-Cl	90	126–129	+25.4 (23–25)	1	EtOAc	Chang *et al.* (1980a)
				−1.5 (23–25)	1	DMF	

(*continued*)

Table I. (*Continued*)

Compound	Reagent used in preparation	Yield (%)	m.p. (°C)	$[\alpha]_D$ (Temp., °C)	Concentration	Solvent	Reference
Fmoc-Ser(*t*Bu)OBzl	Fmoc-Cl	90	70–71	−5.2 (23–25)	1	DMF	Chang *et al.* (1980)
Fmoc-Ser(Bzl)OH	Fmoc-OSu	79	118–119	+25.1 (20 or 25)	1	EtOAc	Lapatsanis *et al.* (1983)
Fmoc-SerOCH_3	Fmoc-OSu	80	127–129	−9.6 (20 or 25)	1	CH_3OH	Lapatsanis *et al.* (1983)
Fmoc-SerOCH_3	Fmoc-OSu	90	128	+4.0 (26)		EtOAc	Paquet (1982)
Fmoc-ThrOHDCHA	Fmoc-OSu	95	165	+9.8 (26)		DMF	Paquet (1982)
Fmoc-ThrOH	Fmoc-Cl	62	Amorphous	−4.8 (25)	1	CH_3OH	Kisfaludy and Schön (1983)
Fmoc-Thr(*t*Bu)OH	Fmoc-Cl	84	129–132	+15.5 (23–25) −4.5 (23–25)	1 1	EtOAc DMF	Chang *et al.* (1980a)
Fmoc-ThrOBzl	Fmoc-Cl	76	112–113	−6.3 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-Thr(*t*Bu)OBzl	Fmoc-Cl	72	69–70	+6.7 (23–25)	1	EtOAc	Chang *et al.* (1980a)
Fmoc-TrpOH	Fmoc-Cl	91	185–187	+6.4 (23.8)	1	EtOAc	Carpino and Han (1972)
Fmoc-TrpOH	Fmoc-Cl	81	165–166	+10.0 (23–25) −26.6 (23–25)	1 1	EtOAc DMF	Chang *et al.* (1980a)
Fmoc-DTrpOH	Fmoc-Cl	61	166.5	+26.8 (24)	1.08	DMF	Smith *et al.* (1983)
Fmoc-Tyr(*t*Bu)OH	Fmoc-Cl	58	150–151	+5.2 (23–25) −27.6 (23–25)	1 1	EtOAc DMF	Chang *et al.* (1980a)
Fmoc-Tyr(SO_3Bu)OH	Fmoc-Cl	49					Wünsch *et al.* (1981)
Fmoc-Tyr(Me)OH	Fmoc-Cl		161–162	−28.5 (22)	1	DMF	Sandberg *et al.* (1981)
Fmoc-TyrOBzl	Fmoc-OSu	86	152	−11.3 (26)		EtOAc	Paquet (1982)
Fmoc-TyrOCH_3	Fmoc-OSu	88	120–122	+3.4 (26)		EtOAc	Paquet (1982)
Fmoc-ValOH	Fmoc-Cl	82	143–144	+4.8 (23–25) −16.1 (23–25)	1 1	EtOAc DMF	Chang *et al.* (1980a)
Fmoc-ValOH	Fmoc-OSu	86	144	+4.6 (26)	1	EtOAc	Paquet (1982)
Fmoc-ValOH	Fmoc-OSu	87	142–143	−18.7 (20 or 25)	1	DMF	Lapatsanis *et al.* (1983)
Fmoc-ValOCH_3	Fmoc-OSu	90	95	−5.0 (26)		EtOAc	Paquet (1982)
Fmoc-ValOMPA[a]		62[b]	84–85				Albericio and Barany (1984)

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