Synthesis of Fmoc-β-Homoamino Acids by Ultrasound-Promoted Wolff Rearrangement[1]

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Dedicated to Prof. Dr. Klaus Burger on the occasion of his 60th birthday

Abstract: A highly efficient protocol for Arndt–Eistert chain elongation of the base-labile fluorenylmethoxycarbonyl (Fmoc) protected α-amino acids by Ag^+-catalyzed, ultrasound-promoted Wolff rearrangement of the corresponding α-diazo ketones at room temperature is described. The enantiomeric purity of the products was examined by capillary zone electrophoresis with chiral buffer systems.

Key words: Fmoc-β-homoamino acids, Wolff rearrangement, sonochemistry, capillary zone electrophoresis

The homologation of α-amino acids is an important strategy for the asymmetric synthesis of β-homoamino acids,[2] as well as addition of nitrogen nucleophiles to α,β-unsaturated esters,[3] enolate additions to imines, and hydrogenation reactions of β-enamino esters.

The Arndt–Eistert approach towards β-homoamino acids via Wolff rearrangement of diazo ketones derived from *N*-phthaloyl-,[4] *N*-tosyl-,[5] or *N*-Cbo/Boc-protected[6] α-amino acids has been utilized since the early 1950s.[7, 8] Recently, this protocol was reinvestigated thoroughly with respect to possible epimerization of the chiral center[9] and to the potential synthetic utility of the ketene intermediate.[10] The Wolff rearrangement of α-diazo ketones can be accomplished thermally, photochemically, or by metal ion (Ag^+) catalysis and has been shown to proceed with complete retention of the configuration.[9, 11] Epimerization (approximately 10%) occurs only in the case of carbamate-protected phenylglycine, presumably during carboxylic group activation.[9, 12]

There has been a growing interest in the structural features of peptides containing β-homoamino acids. However, only peptides containing β-alanine together with α-amino acids,[13] a few peptides containing exclusively or mainly β-homoamino acids[14] or poly[(α-alkyl)-β-L-aspartate]s[15] have been examined until now. Peptides containing β-homoamino acids are often characterized by lower rates of metabolic degradation.[8]

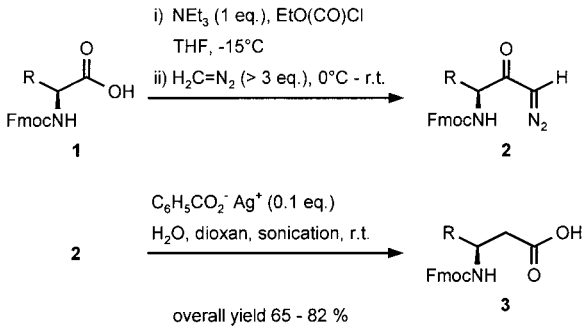
We have developed routes for the asymmetric synthesis of β-homoamino acids by Michael addition of homochiral amidocuprates to α,β-unsaturated esters and of α-deuterio β-homoamino acids or α-alkyl β-homoamino acids by tandem Michael addition/ester enolate trapping.[16] In the course of our investigation into secondary structure elements caused by the replacement of single α-amino acids by enantiomerically pure β-homoamino acids in physiologically active peptides, we required Fmoc-protected β-homoamino acids[17] for solid phase peptide synthesis (SPPS).[18] For simple derivatives, the chain elongation of α-amino acids according to the Arndt–Eistert procedure giving standard β-homoamino acids in only two steps nicely complements the synthetic repertoire.

Silver oxide catalysis usually involves a heterogeneous reaction at higher temperatures. This procedure has often been replaced by the Newman–Beal protocol6 consisting of a homogeneous, Ag^+-catalyzed decomposition, in the presence of several equivalents of a tertiary base, proceeding at considerably lower temperature.[9] A SET-initiated radical chain mechanism has been postulated.[19] Alternatively, a diazo ketone–$Ag(NEt_3)_n$ complex may be involved, which is formed upon deprotonation of the diazo ketone. The presence of a base has, therefore, often been assumed to be inevitable for the reaction progress.[19] However, the reaction results in low yield in the case of Fmoc-protected amino acids because of the eminent sensitivity of the Fmoc group towards basic conditions.

While this manuscript was in preparation, a publication described a base-free, silver ion catalyzed Wolff rearrangement of Fmoc-protected β-amino acids.[20] This reaction proceeds at elevated temperatures and the possible epimerization has been examined only in the case of (2*S*,3*S*)-isoleucine using ^{13}C NMR spectroscopy, which is intrinsically too insensitive for this purpose.[20]

The Ag^+/base-catalyzed reaction of simple diazo ketones (e.g. diazoacetophenone) is reported to be promoted substantially by sonication.[21] We found that a base-free, Ag^+-catalyzed Wolff rearrangement of **2** proceeds smoothly within minutes at room temperature on sonication using an ultrasound cleaning bath.

The Fmoc-protected α-amino acids are activated as mixed anhydrides using ethyl chloroformate. Reaction with a sufficiently high excess of diazomethane (approx. 3



Scheme

Table 1. Physical Data of Fmoc-Protected β-Amino Acids **3**

Compound[22]	CIP[23]	ee (%)	Yield[a] (%)	mp (°C)	$[\alpha]_D$ (°C, *c*, Solvent)	Molecular Formula[c]
Fmoc-D-β-HPhg-OH (**3a**) [Fmoc-D-β-Phe-OH]	*S*	80.5 CZE	70	184	–22.2 (24, 1.0, DMF)	$C_{24}H_{21}NO_4$ (387.44) · 0.5 H_2O
Fmoc-D-β-HPhe-OH (**3b**)	*R*		82 (Lit. 46[20])	127 (Lit. oil[20])	+26.9 (28, 0.6, MeOH)	$C_{25}H_{23}NO_4$ (401.46)
Fmoc-L-β-HPhe-OH (**3b**)	*S*	>99 CZE	76	125	–25.0 (28, 0.6, MeOH)	
Fmoc-L-β-HVal-OH (**3c**) [Fmoc-L-β-Leu-OH]	*R*		70 (Lit. 77,[20] 61[24])	157 (Lit. 153–154,[20] 154–155[24])	+8.0 (27, 0.5, MeOH)[b]	$C_{21}H_{23}NO_4$ (353.42) · 0.5 H_2O
Fmoc-L-β-HLeu-OH (**3d**)	*S*		77 (Lit. 79[20])	99 (Lit. 108–110[20])	–12.0 (26, 1.0, MeOH)	$C_{22}H_{25}NO_4$ (367.44)
Fmoc-L-β-HIle-OH (3e)	*R*		65 (Lit. 64[20])	138 (Lit. 99–l00[20])	+3.7 (28, 4.0, MeOH)	$C_{22}H_{25}NO_4$ (367.44) · 0.5 H_2O
Fmoc-L-β-HAsp(O-^{t}Bu)-OH (**3f**) [Fmoc-L-β-Glu(O-^{t}Bu)-OH]	*R*		80	88	+0.3 (28, 1.9, MeOH)	$C_{24}H_{27}NO_6$ (425.48)

[a] Overall yield starting from Fmoc-α-amino acids.
[b] $[\alpha]_D^{27}$ –17.9 (0.6, $CHCl_3$); Lit.[24] $[\alpha]_D^{27}$ –21.5 (0.46, $CHCl_3$).
[c] Elemental analysis C ± 0.49, H ± 0.47, N ± 0.40.

equiv) secures complete conversion into the diazo ketone, although it has been reported that the application of this protocol to Fmoc-protected substrates does not give satisfactory results.[20] The diazo ketones do not require further purification. Methyl esters of the starting material or other byproducts have not been observed by ^{1}H NMR spectroscopy. Sonication of the diazo ketone in 1,4-dioxane in the presence of silver benzoate and a suitable hetero nucleophile (water, alcohols, etc.) results in a clean formation of the β-amino acid derivative. The ^{1}H NMR spectra and HPLC profiles of the crude reaction mixtures reveal that no significant byproducts are formed. β-Amino acids obtained via this route can be used for peptide synthesis without further purification. Literature precedence[9] and the mild, base-free reaction conditions of our sonochemical procedure let us conclude that no substantial epimerization should occur (except for phenylglycine).

Nevertheless, we examined the degree of racemization using capillary zone electrophoresis (CZE) with chiral buffer systems. As expected according to previous findings,[9] considerable racemization (9–10%) is observed in the case of **3a** (Figure 2), because phenylglycine is prone to epimerization when the carboxy group is being activated as mixed anhydride. Figure 1 displays the separation of racemic **3a**.

Both enantiomers of β-homophenylalanine have been examined as representatives for the other Fmoc-protected β-

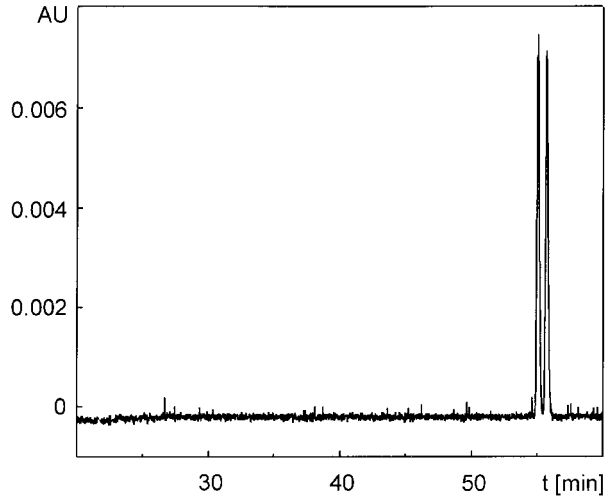


Figure 1. CZE analysis of racemic **3a**.

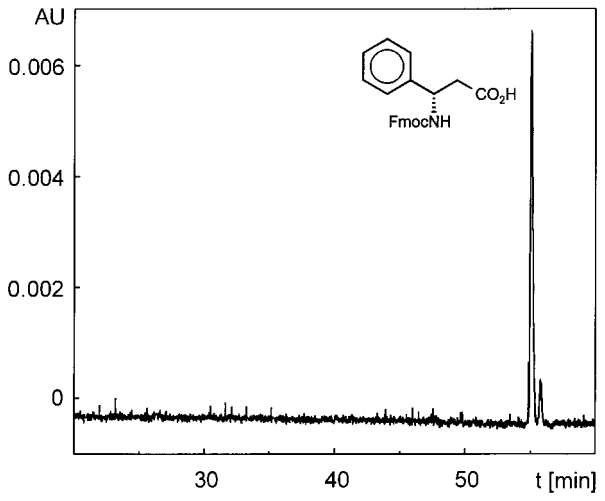


Figure 2. CZE analysis of of D-**3a**.

amino acid derivatives synthesized; they are obtained enantiomerically pure as shown in Figure 4 (L-**3b**). The trace given in Figure 3 arises from a sample obtained by arbitrarily mixing both enantiomers of **3b**. Further addition of D-**3b** to the mixture causes an increase in intensity of the first peak. Hence, D-β-homophenylalanine migrates faster than L-β-homophenylalanine. Therefore, even small quantities of the D enantiomer would inevitably have been detected on CZE of L-**3b**.

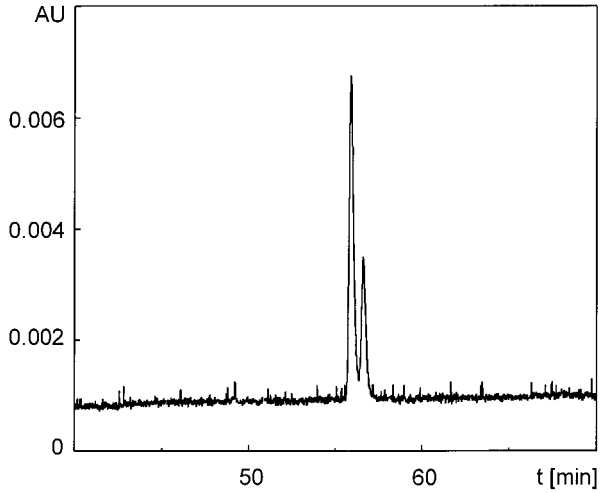


Figure 3. CZE analysis of scalemic **3b** (arbitrary DL mixture). The D enantiomer migrates faster than the L enantiomer.

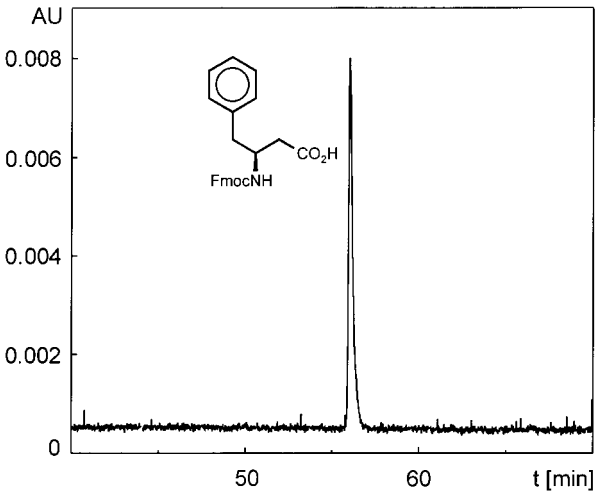


Figure 4. CZE analysis of L-**3b**.

An ultrasound cleaning bath Bandelin Sonorex RK 510 H was used for the sonochemically promoted Wolff rearrangement. Analytical TLC was performed using silica gel 60 F_{254} plates on aluminum foil; silica gel 60 (32–60 μm) was used for flash chromatography. The purity of the Fmoc-protected β-amino acids was checked by HPLC (MeCN/water/TFA gradient on RP-l8 column). Mps were determined with an apparatus according to Tottoli and are uncorrected. NMR spectra were recorded on Varian Gemini 200 or Gemini 2000 instruments, in acetone-d_6 at 200 MHz (^{1}H) and 50 MHz (^{13}C), at 297 K and were calibrated against internal standards (TMS and/or solvent). Optical rotation indices were obtained with a Polartronic-D polarimeter (Schmidt & Haensch); FT-IR spectra were recorded on an ATI Genesis spectrometer using KBr pellets, the data are given in wavenumbers (cm^{-1}). FAB mass spectra were recorded on a VG ZAB-HSQ and EI MS was done on a VG 12-250 instrument (70eV). Microanalyses were performed by the faculty's microanalytical laboratory on a Heraeus CHN-O-RAPID elemental analyzer. A Beckman P/ACE 2100 instrument with a fixed wavelength detector (214 nm, 5 Hz) was used for capillary zone electrophoresis. Racemic β-phenylalanine was commercially available (Aldrich).

Synthesis of Fmoc-Protected β-Homoamino Acids; General Procedure:

The Fmoc-protected α-amino acid derivative (5–l5 mmol) was dissolved in anhyd THF (5 mL/mmol). NEt_3 (1 equiv) and ethyl chloroformate (1 equiv) were added sequentially at –15 °C. Stirring was continued for 15 min at the same temperature, then the solution was warmed up to 0 °C. A solution of diazomethane (3 equiv, CAUTION) in Et_2O was added slowly at 0 °C. The slightly yellow solution was allowed to reach r.t. and was stirred for a further 3 h. Excess diazomethane was decomposed by dropwise addition of HOAc. The

Table 2. ^{1}H NMR Data for Fmoc-Protected β-Amino Acids **3**

Product	^{1}H NMR δ, J (Hz)
3a	2.80 (dd, J = 6.6, 15.5, 1H, H$^{\alpha}$), 2.91 (dd, J = 7.8, 15.5, 1H, H$^{\alpha}$), 4.13–4.31 (m, 3H, Fmoc CH_2, CH), 5.17 (dd, J = 6.6, 7.8, 1H, H$^{\beta}$), 7.20–7.42 (m, 9H, H_{ar}), 7.62 (m, 2H, H_a), 7.78 (m, 2H, H_{ar})
3b	2.55 (m, 2H, H$^{\alpha}$), 2.91 (m, 2H, H$^{\gamma}$), 4.1 4–4.31 (m, 4H, H$^{\beta}$, Fmoc CH_2, CH), 6.52 (br, 1H, NH), 7.16–7.45 (m, 9H, H_{ar}), 7.65 (m, 2H, H_{ar}), 7.86 (m, 2H, H_{ar})
3c	0.94 (d, J= 6.7, 6H, H$^{\delta}$), 1.88 (m, 1H, H$^{\gamma}$), 2.47 (dd, J= 8.0, 15.4, 1H, H$^{\alpha}$), 2.58 (dd, J = 5.5, 15.4, 1H, H$^{\alpha}$), 3.90 (m, 1H, H$^{\beta}$), 4.17–4.33 (m, 3H, Fmoc CH_2, CH), 6.43 (br d, J = 10.0, 1H, NH), 7.27–7.46 (m, 4H, H_{ar}), 7.68 (m, 2H, H_{ar}), 7.85 (m, 2H, H_{ar})
3d	0.95 (d, J= 6.7, 3H, H$^{\varepsilon}$), 0.97 (d, J = 6.7, 3H, H$^{\varepsilon}$), 1.38 (ddd, J = 4.5, 9.2, 13.7, 1H, H$^{\gamma}$), 1.60 (ddd, J = 4.4, 9.3, 13.7, 1H, H$^{\gamma}$), 1.75 (m, 1H, H$^{\delta}$), 2.50 (dd, J = 6.9, 15.4, 1H, H$^{\alpha}$), 2.56 (dd, J = 6.6, 15.4, 1H, H$^{\alpha}$), 4.13 (m, 1H, H$^{\beta}$), 4.26–4.37 (m, 3H, Fmoc CH_2, CH), 6.40 (d, J = 8.8, 1H, NH), 7.33–7.47 (m, 4H, H_{ar}), 7.72 (m, 2H, H_{ar}), 7.89 (m, 2H, H_{ar})
3e	0.92 (t, J = 6.8, 3H, H$^{\varepsilon}$), 0.93 (d, J = 6.4, 3H, CH_3), 1.22 (m, 1H, H$^{\delta}$), 1.57 (m, 1H, H$^{\delta}$), 1.66 (m, 1H, H$^{\gamma}$), 2.46 (dd, J = 8.0, 15.3, 1H, H$^{\alpha}$), 2.56 (dd, J = 5.0, 15.3, 1H, H$^{\alpha}$), 4.00 (m, 1H, H$^{\beta}$), 4.13–4.34 (m, 3H, Fmoc CH_2, CH), 6.46 (d, J = 8.8, 1H, NH), 7.25–7.44 (m, 4H, H_{ar}), 7.69 (m, 2H, H_{ar}), 7.85 (m, 2H, H_{ar})
3f	1.43 (s, 9H, O^{t}Bu), 2.57–2.67 (m, 4H, H$^{\alpha}$, H$^{\gamma}$), 4.22–4.41 (m, 4H, H$^{\beta}$, Fmoc CH_2, CH), 6.55 (br, 1H, NH), 7.27–7.45 (m, 4H, H_{ar}), 7.68 (m, 2H), 7.85 (m, 2H, H_{ar})

Table 3. ^{13}C NMR, IR, and MS Data for Fmoc-Protected β-Amino Acids **3**

Product	^{13}C NMR δ	IR ν (cm^{-1})	MS *m/z*
3a	41.31, 48.00, 52.86, 66.89, 120.72, 126.03, 127.32, 127.87, 128.00, 128.42, 129.23, 142.03, 143.47, 144.98, 156.31, 172.00	3420 (br), 1705	FAB: 410 $(M+Na)^+$, 388 $(M+H)^+$, 329, 307, 289, 178, 165, 154, 136
3b	38.62, 40.63, 47.75, 50.52, 66.43, 120.54, 125.88, 126.92, 127.67, 128.24, 128.92, 131.03, 139.31, 141.88, 144.91, 156.20, 172.55	3403 (br), 3341, 1703	FAB: 424 $(M+Na)^+$, 402 $(M+H)^+$, 307, 289, 191, 180, 179, 178, 165, 154, 136
3c	18.42, 19.44, 32.80, 37.30, 48.11, 54.41, 66.75, 120.82, 126.18, 127.97, 128.53, 142.17, 145.33, 156.90, 173.19	3404, 1700	EI: 353 $(M)^+$, 311, 267, 196, 179, 178, 165, 152, 139, 69, 42
3d	21.62, 23.14, 25.03, 40.24, 44.10, 46.88, 47.70, 66.18, 120.40, 125.75, 127.53, 128.10, 141.76, 144.88, 156.27, 172.43	3433 (br), 1704	FAB: 390 $(M+Na)^+$, 368 $(M)^+$, 191, 180, 179, 178, 165, 154, 136
3e	11.41, 14.94, 25.63, 36.08, 39.02, 47.67, 52.84, 66.31, 120.34, 125.77, 127.53, 128.10, 141.74, 144.90, 156.32, 172.90	3323, 1697, 1542	FAB: 390 $(M+Na)^+$, 368 $(M+H)^+$, 191, 180, 179, 178, 165, 146, 130
3f	28.59, 39.27, 41.01, 46.85, 48.43, 67.29, 81.29, 121.15, 126.48, 128.28, 128.85, 142.46, 145.48, 156.66, 171.15, 172.78	3404, 1700	FAB: 448 $(M+Na)^+$, 426 $(M+H)^+$, 392, 370, 179, 178, 165, 148

mixture was washed with sat. $NaHCO_3$, sat. NH_4Cl, and brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The resulting diazo ketone was dissolved in dioxane/water (5:1, v/v, 50 mL/mmol). After addition of silver benzoate (0.1 equiv) the mixture was sonicated using an ultrasound cleaning bath for ca. 30 min. The reaction progress could be monitored by TLC (EtOAc/petroleum ether l:1). When the reaction had reached completion, the solution was acidified to pH 2 with 1 M HCl and extracted with Et_2O (4 × 30 mL). The organic layers were pooled, dried ($MgSO_4$) and evaporated in vacuo. The resulting residue was purified by flash chromatography ($CHCl_3$/MeOH 20:1 + 1% HOAc).

The enantiomeric purity of the Fmoc-protected β-amino acid derivatives **3a,b** was determined by capillary zone electrophoresis. The sample was dissolved without using organic solvent in 60 mM SDS/25 mM borate buffer (pH 8.0) and injected by 2 s or 8 s pressure injection (equivalent to 1–5 nL). The separations were performed at 22 °C and 20 kV in a fused silica capillary (70/77 cm, 50 μm i.d.) using 60 mM sodium dodecyl sulfate (SDS), 50 mM borate buffer (pH 8.0), and 20 mM γ-cyclodextrin (for **3a**) or 30 mM γ-cyclodextrin (for **3b**).

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(22) Abbreviations: *HPhg* Homophenylglycine; *Phe* Phenylalanine; *HPhe* Homophenylalanine; *HVal* Homovaline; *Leu* Leucine; *HLeu* Homoleucine; *HIle* Homoisoleucine; *HAsp* Homoaspartic Acid; *Glu* Glutamic Acid. The Greek letter β indicates the position of the amino group, while the expression *homo* refers to the chain elongation by one carbon atom.
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