Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7659-7660, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01598-8

A Facile Conversion of Arginine into β-Homoarginine Dipeptides

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Abstract: *Irradiation of the arginine derived diazomethyl ketone 2 in the presence of amino esters gives the corresponding β-homoarginine dipeptide esters 3c-h in 45-76% yield.*

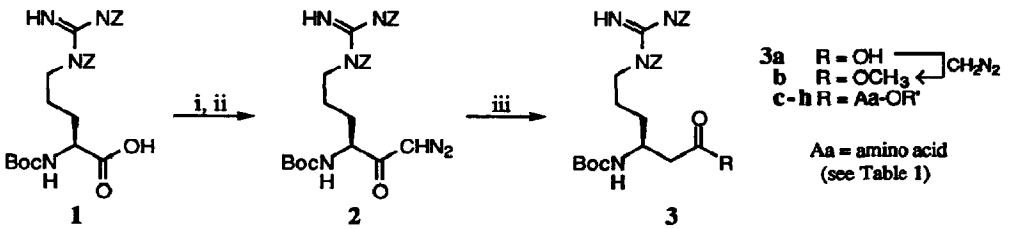
β-Amino acids are important constituents of natural products and have often been used as leads in the development of new therapeutics.[1] In the course of our investigations of arginine-containing enzyme inhibitors we searched for a route towards β-homoarginine peptides. Several synthetic routes to β-amino acids and peptides derived thereof have been devised.[2] Of these the most direct one is the Arndt-Eistert homologation of α-amino acids which gives the corresponding homologous β-amino acids or esters with retention of configuration.[3]

Here we report that this Arndt-Eistert methodology can also be applied for the preparation of β-homoarginine derivatives **3a-b** (Scheme 1). In particular, we observed that this homologation reaction - if performed in the presence of an amino ester - leads directly to the corresponding β-homoarginine dipeptide esters **3c-h**.

Conversion of the orthogonally protected arginine derivative **1**[4] into the diazomethyl ketone proved to be rather straightforward and gave **2** in 83% yield.[5,6] Crude **2** was used for the subsequent Wolff-rearrangement which, due to the base-labile nature of the δ-N benzyloxycarbonyl protecting group in arginine derivatives,[4] was carried out photochemically instead of by treatment with Ag_2O or with silver benzoate and triethylamine[7]. Thus, irradiation of a solution of diazomethyl ketone **2** and methanol in dioxane gave the β-homoarginine methyl ester **3b** in 65% yield. Alternatively, **3b** could also be prepared by trapping the intermediate ketene with water to give **3a** (55% yield), and subsequent reaction with diazomethane.[8]

Compound **3a** can be used in standard peptide coupling reactions in order to prepare β-homoarginine containing peptides. We reasoned, however, that direct peptide formation might be feasible by trapping the ketene derived from **2** with a second amino acid derivative. Indeed, photolysis of **2** in the presence of an amino ester yielded the corresponding β-homoarginine containing dipeptide esters **3c-h**.

Scheme 1



i) *i*-butyl chloroformate, Et_3N, CH_2Cl_2, -20 °C, 15 min.; ii) CH_2N_2, 5 °C, 22 h.; iii) H-R, CH_3CN, 22h, hv, 30 °C.

Thus, the dipeptides **3c-h** (Table 1) were prepared by irradiation (300 nm) of a 0.025 M solution of **2** in dry acetonitrile in the presence of 1.2 eq. of an amino ester hydrochloride and 1.2 eq. of triethylamine.[9] It is noteworthy that this reaction proceeds also with proline methyl ester, a secondary amine, to yield **3g**. In nearly all cases (except **3g**) a precipitate is being formed during the reaction; filtration gives an amorphous, colourless solid (35-68%) identified as pure dipeptide **3**. A second crop could be obtained after aqueous work-up of the filtrate and subsequent crystallization or chromatography.

Table 1. Dipeptides **3** Prepared by Irradiation of **2** in the Presence of Amino Esters (H-Aa-OR')

3	Aa	R'	Yield (%)[a]	Total (%)[b]	mp (°C)
c	L-valine	CH_3	42	66	138-139
d	L-tryptophan	CH_3	35	45	116-119
e	D-phenylalanine	CH_3	55	63	166-167
f	D-phenylalanine	CH_2Ph	- [c]	55	145-148
g	L-proline	CH_3	- [d]	59	84-86
h	β-alanine	CH_3	68	76	150-152

[a] Yield of dipeptide precipitated during reaction. [b] Total yield, after work-up of the filtrate and crystallization or chromatography. [c] Precipitate not isolated; the reaction mixture was worked-up and purified by chromatography. [d] No precipitate was formed.

In conclusion the Arndt-Eistert homologation in the presence of amino esters as nucleophilic reaction partners is a simple, direct and general method to prepare a large variety of homologous dipeptides including β-homoarginine containing ones.

REFERENCES AND NOTES

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4. Jetten, M.; Peters, C.A.M.; van Nispen, J.W.F.M. & Ouenhetjm, H.C.J. *Tetrahedron Lett.* **1991**, *32*, 6025-6028
5. All compounds were properly characterized by ^{1}H-, ^{13}C-NMR and FAB-HRMS.
6. **2**: mp 130-131 °C; Rf 0.45 (SiO_2; CH_2Cl_2/EtOAc, 12/1); ^{1}H-NMR ($CDCl_3$): δ 1.40 (s, 9H, Boc), 1.60-1.72 (m, 4H, β- + γ-H), 3.95 (bd, ^3J = 8.0 Hz, 2H, δ-H), 4.18 (m, 1H, α-H), 5.08 and 5.16 (AB system, 2H, J_{AB} = 12 Hz, OCH_2Ph), 5.22 (s, 2H, OCH_2Ph), 5.49 (bs, 1H, CHN_2), 5.61 (bd, 1H, ^3J = 8.0 Hz, α-NH), 7.25-7.42 (m, 10H, arom.), 9.29 (bs, 1H, ϖ-NH), 9.43 ppm (bs, 1H, ϖ'-NH). See also: Christiansen, J.; Young, G.T. *Pept. Proc. Eur. Pept. Symp. 16th* **1980**, 612-616.
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8. **3a**: viscous oil; Rf 0.52 (SiO_2; $CHCl_3$/MeOH, 32/1); ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 9H, Boc), 1.38-1.68 (m, 4H, γ- + δ-H), 2.42 (bs, 2H, α-H), 3.75-3.98 (m, 3H, β- + ε-H), 5.06 (bd, 1H, ^3J = 8.0 Hz, β-NH), 5.07 (bs, 2H, OCH_2Ph), 5.17 (bs, 2H, OCH_2Ph), 7.15-7.38 (m, 10H, arom.), 9.15-9.40 ppm (bs, 2H, ϖ- + ϖ'-NH).
3b: mp 89-91 °C; Rf 0.40 (SiO_2; CH_2Cl_2/EtOAc, 12/1); ^{1}H-NMR ($CDCl_3$): δ 1.28-1.70 (m, 4H, γ- + δ-H), 1.40 (s, 9H, Boc),2.39 (bd, 2H, ^3J = 6.7 Hz, α-H), 3.55 (s, 3H, OCH_3), 3.73-3.97 (m, 3H, β- + ε-H), 4.99 (bd, 1H, ^3J = 8.0 Hz, β-NH), 5.08 (bs, 2H, OCH_2Ph), 5.18 (bs, 2H, OCH_2Ph), 7.14-7.38 (m, 10H, arom.), 9.20 (bs, 1H, ϖ-NH), 9.37 ppm (bs, 1H, ϖ' NH).
9. The preparation of **3e** is typical: To a stirred solution of H-D-Phe-OMe.HCl (2.1 gr, 9.8 mmol) in dry CH_3CN (200 ml) and Et_3N (1.4 ml, 9.8 mmol) was added at room temperature a solution of **2** (8.2 mmol, about 80% pure) in dry CH_3CN (150 ml) under a nitrogen atmosphere. The reaction mixture was stirred and irradiated (300 nm) with 16 lamps of 12 Watt each; the temperature was kept at 30 °C. After a few minutes the evolution of N_2 was observed. The precipitate formed after 22 h of irradiation was filtered off, washed with ice-cold CH_3CN, and dried under reduced pressure giving pure **3e** in 55% yield. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution was washed with, subsequently, water, citric acid (1N), water and brine, dried (Na_2SO_4), filtrated, evaporated to dryness under vacuum, and crystallized from CH_3CN, yielding a second crop of 8%. Mp 166-167 °C; Rf 0.59 (SiO_2; CH_2Cl_2/EtOAc, 10/3); ^{1}H-NMR ($CDCl_3$): δ 1.38 (s, 9H, Boc), 1.33-1.64 (m, 4H, Arg γ- + δ-H), 2.26 and 2.73 (AB of ABX, 2H, J_{AB} = 16.0 Hz, Arg α-H), 3.71 and 3.10 (AB of ABX, 2H, J_{AB} = 14.8 Hz, Phe β-H), 3.50-3.80 (m, 3H, Arg β- + ε-H), 3.65 (s, 3H, OCH_3), 4.74-4.89 (X of ABX, 1H, Phe α-H), 5.07 and 5.15 (AB system, 2H, J_{AB} = 12.7 Hz, OCH_2Ph), 5.22 and 5.25 (AB system, 2H, J_{AB} = 13.3Hz, OCH_2Ph), 5.92 (bd, 1H, ^3J = 8.7 Hz, Arg β-NH), 6.62 (bd, 1H, ^3J = 8.6 Hz, amide-NH), 6.96-7.45 (m, 15H, arom.), 9.26 (bs, 1H, ϖ-NH), 9.37 ppm (bs, 1H, ϖ'-NH).

(*Received in UK* 14 *July* 1994; *revised* 18 *August* 1994; *accepted* 19 *August* 1994)