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Synthesis of α-N-Ethylamino Acids and their Derivatives

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Summary. A new synthesis of α-N-ethylamino acids starting from α-amino acids using hexafluoroacetone as protecting and activating agent is described. The hexafluoroacetone-protected N-ethylamino acid derivatives obtained are activated lactons. Therefore, they can be directly transformed without the need of an additional activation step with various nucleophiles into the corresponding carboxylic acid derivatives.

Keywords. Hexafluoroacetone; Amino acids; Oxazolidin-5-ones; Cuprates; N-Alkylation.

Introduction

N-Alkylamino acids are an important subclass of amino acids. The N-methyl species are natural occurring compounds found as free amino acids or as constituents of various peptides [1] like cyclosporine [2] and depsipeptides like dolastatin [3] and didemnin [4]. Several syntheses have been described for N-methylamino acids and their homologues [5]. Incorporation of N-alkylamino acids into peptides often improves the biological profile by increasing proteolytic stability, conformational rigidity, and lipophilicity.

Reaction of hexafluoroacetone (*HFA*) and α-amino acids results in a simultaneous protection of the carboxylic group and the adjacent amino group. Consequently, the carboxy group is activated towards nucleophiles [6], and the protected amino function is susceptible for monofunctionalization with highly electrophilic reagents like formaldehyde [6a].

Results and Discussion

In this paper we describe a preparatively simple access to N-ethylamino acids and some of their derivatives using hexafluoroacetone as protecting and activating reagent. Recently, we have shown that N-chloromethyl compounds **1**–**5** can easily be obtained *via* N-halomethylation of 2,2-*bis*-(trifluoromethyl)-oxazolidin-5-ones with paraformaldehyde and thionyl chloride [6a]. The highly reactive N-chloromethyl group is suitable for nucleophilic displacement reactions with hetero [6b] and carbon nucleophiles.

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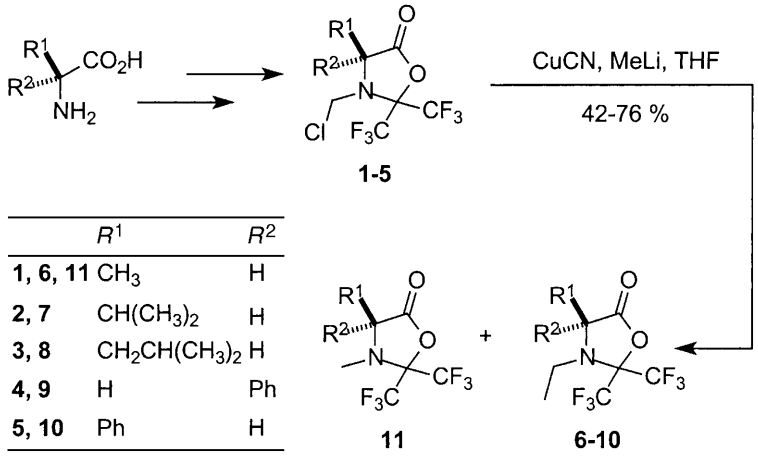
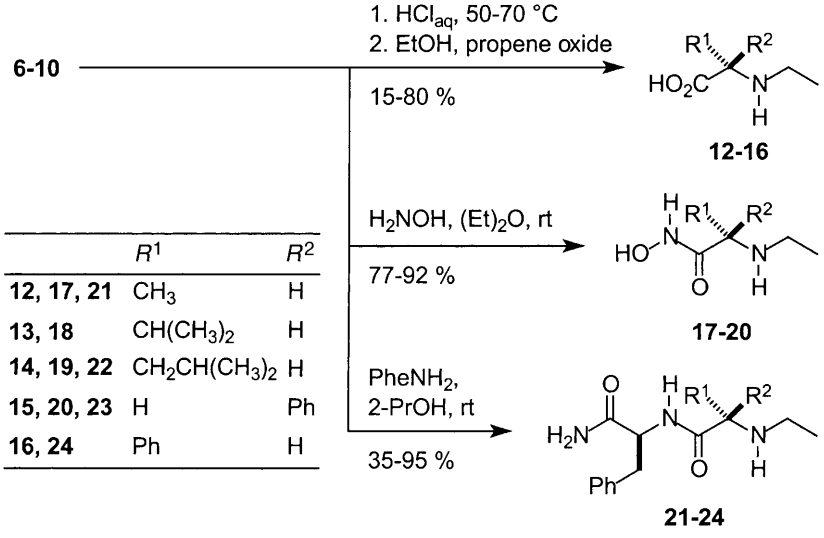


	R^1	R^2
1, 6, 11	CH_3	H
2, 7	$CH(CH_3)_2$	H
3, 8	$CH_2CH(CH_3)_2$	H
4, 9	H	Ph
5, 10	Ph	H

Scheme 1

From the reaction of **1** with cuprates generated from copper(I) cyanide and two equivalents of methyl lithium, a mixture of the N-ethyl-2,2-*bis*-(trifluoromethyl)-oxazolidin-5-ones **6** and 20–50% of the N-methyl compound **11** was obtained. Similar results were described for cuprate couplings with α-bromo glycine derivatives [7]. However, when a copper reagent prepared from copper(I) cyanide and only one equivalent of methyl lithium was used, we found that the N-ethyl compounds **6–10** were formed in high yields, and only traces of the N-methyl analogues **11** could be detected. The N-ethyl-2,2-*bis*-(trifluoromethyl)-oxazolidin-5-ones **6–10** are colorless, characteristically smelling, distillable liquids which are stabile at room temperature and can be stored under water-free conditions over months.

Since compounds **6–10** are activated esters, the unprotected N-ethylamino acid hydrochlorides are readily available by hydrolysis with diluted HCl. They are



	R^1	R^2
12, 17, 21	CH_3	H
13, 18	$CH(CH_3)_2$	H
14, 19, 22	$CH_2CH(CH_3)_2$	H
15, 20, 23	H	Ph
16, 24	Ph	H

Scheme 2

transformed into the free amino acids **12–16** upon treatment with propene oxide in ethanol. Amino-unprotected carboxylic acid derivatives are readily available from reaction with various nucleophiles in a one step procedure; *e.g.* hydroxamic acids **17–20** are formed on reaction with hydroxylamine, and dipeptide amides **21–24** are obtained by reaction with amino acid amides.

It is well documented that phenyl glycine derivatives are prone to recemization. Therefore, we tested the two enantiomeric N-ethyl-2,2-*bis*-(trifluoromethyl)-4-phenyloxazolidin-5-ones **9** and **10** whether they are suitable for analyzing the enantiomeric purity by HPLC. We found that oxazolidin-5-ones **9** and **10** are nicely separable on a chiral polysaccharide phase (CHIRALPAK). We recorded *ee*-values of 89% for **9** and 88% for **10** demonstrating that *L*- and *D*-phenyl glycine is partly racemized upon transformation of **4** and **5** into the N-ethyl compounds **9** and **10**. Further applications of 2,2-*bis*-(trifluoromethyl)-oxazolidin-5-ones for the determination of the enantiomeric purity of α-amino acids will be reported elsewhere.

Experimental

General comments

Solvents were purified and dried prior to use. Reagents were used as purchased. Melting points (uncorrected) were determined on a Boëtius heating table. Mass spectra were recorded on a VG 12–250 (Masslab) electron ionization spectrometer (EI-MS, EI = 70 eV) or by a VG ZAB-HSQ FAB (FAB-MS) spectrometer. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H (200 MHz), ^{13}C (50 MHz), and ^{19}F NMR (188 MHz) spectra were recorded on a Varian Gemini 2000 spectrometer. *TMS* was used as reference for ^{1}H and ^{13}C NMR spectra (internal), and CF_3CO_2H for ^{19}F NMR spectra (external). Flash chromatography was performed using silica gel (32–63 μm). *ee* values were analyzed by HPLC (Gilson 302 pump, a Gilson 231–401 autosampling injector and a Waters 481 UV detector at 220 nm) on a CHIRALPAK column (250 × 4.6 mm, DAICEL CHEMICAL Co., Ltd) at ambient temperature employing a mobile phase consisting of *n*-hexane/isopropanol/triethylamine = 99.7/0.2/0.1 vol% at a flow rate of 1 cm^3/min.

N-Ethyl-2,2-bis-(trifluoromethyl)-oxazolidin-5-ones **6–10** *(general procedure)*

Copper(I) cyanide (2.3 g, 26.2 mmol) was suspended in *THF* (50 cm^3) under an argon atmosphere. After cooling to −30°C, methyllithium (13.0 cm^3 2 *M* solution in $(Et)_2O$, 26.0 mmol) was added dropwise with stirring. The cooling bath was removed, and the mixture was allowed to warm up to 0°C. A pale yellow, clear solution resulted. The mixture was cooled again to −20°C, and the N-chloromethyl-2,2-*bis*-(trifluoromethyl)-oxazolidin-5-one dissolved in *THF* (10 cm^3) was added. The color changed to deep yellow. After stirring for 20 min at −20°C and additional stirring for 1 h after removal of the cooling bath a dark colored mixture resulted. For work-up, a NH_4Cl solution (30 cm^3) and Et_2O (100 cm^3) were added and vigorously stirred for 20 min. After separation, the organic phase was washed with NH_4Cl solution (2 × 30 cm^3) and water (3 × 30 cm^3). Drying over $MgSO_4$ and distillation gave **6–10**.

(4S)-3-Ethyl-2,2-bis-(trifluoromethyl-4-methyloxazolidin-5-one (**6**; $C_8H_9F_6NO_2$)

1 (5.0 g, 17.5 mmol) gave **6** (3.5 g, 76%) as a colorless, camphor-like smelling, oily liquid.

B.p.: 55–60°C/13.0 torr; $[\alpha]_D^{21} = 21$ ($c = 2$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.19$ (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.48 (d, $J = 7$ Hz, 3H, CH_3), 3.05 (m, 1H, CH_2), 3.25 (m, 1H, CH_2), 3.84 (q,

$J = 7$ Hz, 1H, NCH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.40$ (CH_3^{Et}), 18.39 (CH_3), 40.82 (CH_2), 54.67 (CH), 90.19 (m, CCF_3), 120.98 (q, $^1J_{CF} = 288$ Hz, CF_3), 122.22 (q, $^1J_{CF} = 294$ Hz, CF_3), 171.53 (CO) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -0.92$ (q, $^4J_{FF} = 8$ Hz, CF_3), 3.24 (q, $^4J_{FF} = 8$ Hz, CF_3) ppm; IR (film): $\nu = 1839\,cm^{-1}$; EI-MS: $m/z(\%) = 265$ (20, M^+), 250 (14), 218 (10), 196 (30), 168 (100), 140 (27), 70 (16), 69 (32), 56 (64).

(4S)-3-Ethyl-2,2-bis-(trifluoromethyl)-4-isopropyloxazolidin-5-one (**7**; $C_{10}H_{13}F_6NO_2$)

2 (5.5 g, 17.5 mmol) gave **7** (3.1 g, 60%) as a colorless, slightly rancid smelling, oily liquid.

B.p.: 82°C/16.0 torr; $[\alpha]_D^{21} = 33$ ($c = 2$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.99$ (d, $J = 7$ Hz, 3H, CH_3), 1.17 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.19 (d, $J = 7$ Hz, 3H, CH_3), 2.17 (m, 1H, CH), 3.05 (m, 1H, CH_2), 3.27 (m, 1H, CH_2), 3.71 (m, 1H, NCH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 13.67$ (CH_3^{Et}), 15.61 (CH_3), 17.86 (CH_3), 29.72 (CH), 40.88 (CH_2), 63.80 (NCH), 89.03 (m, CCF_3), 121.08 (q, $^1J_{CF} = 289$ Hz, CF_3), 122.68 (q, $^1J_{CF} = 296$ Hz, CF_3), 169.14 (CO) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) $\delta = -0.16$ (q, $^4J_{FF} = 8$ Hz, CF_3), 4.01 (q, $^4J_{FF} = 8$ Hz, CF_3) ppm; IR (film): $\nu = 1833\,cm^{-1}$; EI-MS: $m/z(\%) = 293$ (9, M^+), 251 (56), 250 (34), 222 (15), 182 (100), 154 (11), 56 (22).

(4S)-3-Ethyl-2,2-bis-(trifluoromethyl)-4-isobutyloxazolidin-5-one (**8**; $C_{11}H_{15}F_6NO_2$)

3 (5.6 g, 17.5 mmol) gave **8** (3.1 g, 58%) as a colorless, rancid smelling, oily liquid.

B.p.: 87°C/15.0 torr; $[\alpha]_D^{21} = 44$ ($c = 2$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 7$ Hz, 3H, CH_3), 0.97 (d, $J = 7$ Hz, 3H, CH_3), 1.18 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.66–1.73 (m, 2H, CH_2), 2.01 (m, 1H, CH), 3.06 (m, 1H, NCH_2), 3.24 (m, 1H, NCH_2), 3.79 (m, 1H, NCH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 13.81$ (CH_3^{Et}), 22.07 (CH_3), 23.99 (CH_3), 24.05 (CH), 40.36 (CH_2), 40.73 (CH_2), 56.83 (NCH), 90.03 (m, CCF_3), 121.08 (q, $^1J_{CF} = 288$ Hz, CF_3), 122.36 (q, $^1J_{CF} = 295$ Hz, CF_3), 171.02 (CO) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -0.50$ (q, $^4J_{FF} = 9$ Hz, CF_3), 3.48 (q, $^4J_{FF} = 9$ Hz, CF_3) ppm; IR (film): $\nu = 1837\,cm^{-1}$; EI-MS: $m/z(\%) = 307$ (25, M^+), 260 (11), 251 (39), 250 (100), 238 (26), 236 (18), 222 (54), 210 (44), 182 (49), 154 (19), 69 (22), 57 (18), 56 (54).

(4R)-3-Ethyl-2,2-bis-(trifluoromethyl)-4-phenyloxazolidin-5-one (**9**; $C_{13}H_{11}F_6NO_2$)

4 (6.1 g, 17.5 mmol) gave **9** (2.9 g, 50%) as a colorless, resinously smelling, oily liquid.

M.p.: 40°C; b.p.: 72°C/0.6 torr; $[\alpha]_D^{21} = -111$ ($c = 2$, CH_2Cl_2); *ee* = 89% (HPLC); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7$ Hz, 3H, CH_3), 3.09 (m, 1H, CH_2), 3.29 (m, 1H, CH_2), 4.69 (s, 1H, CH), 7.41 (m, 5H, arom. H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.10$ (CH_3), 42.56 (CH_2), 64.24 (CH), 90.16 (m, CCF_3), 121.24 (q, $^1J_{CF} = 289$Hz, CF_3), 122.52 (q, $^1J_{CF} = 295$ Hz, CF_3), 128.21, 129.69, 130.04, 136.01 (arom. C), 168.96 (CO) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -0.37$ (q, $^4J_{FF} = 8$ Hz, CF_3), 4.23 (q, $^4J_{FF} = 8$ Hz, CF_3) ppm; IR (film): $\nu = 1842\,cm^{-1}$; EI-MS: $m/z(\%) = 327$ (43, M^+), 312 (15), 280 (11), 258 (56), 251 (11), 250 (28), 231 (12), 230 (99), 222 (11), 191 (14), 182 (13), 132 (15), 124 (100), 118 (46), 110 (16), 107 (11), 105 (10), 104 (15), 91 (30), 90 (16), 89 (17), 79 (17), 77 (21), 69 (20), 59 (17).

(4S)-3-Ethyl-2,2-bis-(trifluoromethyl)-4-phenyloxazolidin-5-one (**10**; $C_{13}H_{11}F_6NO_2$)

5 (6.1 g, 17.5 mmol) gave **10** (2.4 g, 42%) as a colorless, odourless, oily liquid.

B.p.: 62°C/0.3 torr; $[\alpha]_D^{21} = 97$ ($c = 2$, CH_2Cl_2); *ee* = 88% (HPLC); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7$ Hz, 3H, CH_3), 3.09 (m, 1H, CH_2), 3.28 (m, 1H, CH_2), 4.68 (s, 1H, CH), 7.41 (s, 5H, arom. H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.22$ (CH_3), 42.63 (CH_2), 64.29 (CH), 90.22 (m, CCF_3), 121.16 (q, $^1J_{CF} = 287$ Hz, CF_3), 122.46 (q, $^1J_{CF} = 295$ Hz, CF_3), 128.15, 129.63, 129.98, 135.95 (arom. C), 168.83 (CO) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -0.38$ (q, $^4J_{FF} = 8$ Hz, CF_3), 4.22 (q, $^4J_{FF} = 8$ Hz, CF_3) ppm; IR (film): $\nu = 1843\,cm^{-1}$; EI-MS:

$m/z(\%) = 327$ (47, M^+), 280 (23), 258 (53), 231 (27), 230 (92), 132 (37), 131 (20), 124 (100), 118 (59), 110 (32), 107 (25), 105 (20), 104 (35), 96 (19).

Hydrolysis of N-ethyl-2,2-bis-(trifluoromethyl)-oxazolidin-5-ones **6–10** *(general procedure)*

Compounds **6–10** were dissolved in a mixture of dioxane (10 cm^3 for 2 mmol), water (2 cm^3 for 2 mmol) and concd. HCl_{aq} (1 cm^3 for 2 mmol). This mixture was stirred at 60°C. The reaction was monitored by ^{19}F NMR spectroscopy. The solvents were evaporated *in vacuo*, and the residue was dissolved in a small amount of EtOH and treated with propene oxide (0.5 cm^3 for 2 mmol). Filtration and washing of the precipitate with $(Et)_2O$ gave **12–16**.

(L)-N-Ethylalanine (**12**; $C_5H_{11}NO_2$)

6 (0.5 g, 1.9 mmol) gave **12** (150 mg, 67%) after 48 h at 50°C as colorless crystals.

M.p.: 295–297°C (closed glass capillary: Ref. [8]: 302–303°C, Ref. [9]: 211–215°C, Ref. [10]: 238–240°C; $[\alpha]_D^{21} = 10$ ($c = 2$, H_2O); ^1H NMR (200 MHz, D_2O): $\delta = 1.15$ (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.33 (d, $J = 7$ Hz, 3H, CH_3), 2.94 (q, $J = 7$ Hz, 2H, CH_2), 3.51 (q, $J = 7$ Hz, 1H, CH) ppm; ^{13}C NMR (100 MHz, D_2O): $\delta = 11.37$ (CH_3^{Et}), 15.71 (CH_3), 42.04 (CH_2), 58.05 (CH), 175.74 (CO) ppm; IR (KBr): $\nu = 3446$, 1586 cm^{-1}; FAB-MS: $m/z = 118$ (M^+).

(L)-N-Ethylvaline (**13**; $C_7H_{15}NO_2$)

7 (0.5 g, 1.7 mmol) gave **13** (35 mg, 15%) after 14 d at 50°C as a white powder.

M.p.: 239°C Ref. [11]: 235–238°C, Ref. [12]: 286–287°C (H_2O); $[\alpha]_D^{21} = 28$ ($c = 2$, 1 *N* HCl Ref. [11]: $[\alpha]_D = 28$ ($c = 1$, dil. HCl_{aq})); ^1H NMR (300 MHz, D_2O): $\delta = 1.06$ (d, $J = 7$ Hz, 3H, CH_3), 1.12 (d, $J = 7$ Hz, 3H, CH_3), 1.34 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 2.38 (m, 1H, CH), 3.19 (m, 2H, CH_2), 3.94 (d, $J = 4$ Hz, 1H, NCH) ppm; ^{13}C NMR (50 MHz, D_2O): $\delta = 10.76$ (CH_3^{Et}), 17.08 (CH_3), 18.36 (CH_3), 29.45 (CH), 43.41 (CH_2), 66.27 (NCH), 171.70 (CO) ppm; IR (KBr): $\nu = 3450$, 1581 cm^{-1}; FAB-MS: $m/z = 146$ (M^+).

(L)-N-Ethylleucine (**14**; $C_8H_{17}NO_2$)

8 (0.5 g, 1.6 mmol) gave **14** (200 mg, 80%) after 7 d at 60°C as a white, crystalline powder.

M.p.: 315–317°C (closed glass capillary; Ref. [13]: 260–266°C); $[\alpha]_D^{21} = 29$ ($c = 2$, 1 *N* HCl; Ref. [13]: $[\alpha]_D = 26$ (H_2O)); ^1H NMR (200 MHz, D_2O): $\delta = 0.81$ (d, $J = 5$ Hz, 6H, 2 CH_3), 1.16 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.56–1.76 (m, 3H, CH_2, CH), 3.00 (q, $J = 7$ Hz, 2H, NCH_2), 3.85 (m, 1H, NCH) ppm; ^{13}C NMR (50 MHz, D_2O): $\delta = 10.91$ (CH_2^{Et}), 21.13 (CH_3), 22.28 (CH_3), 24.50 (CH), 38.34 (CH_2), 42.27 (NCH_2), 58.52 (NCH), 172.14 (CO) ppm; IR (KBr): $\nu = 3434$, 1579 cm^{-1}; FAB-MS: $m/z = 160$ (M^+).

(D)-N-Ethylphenylglycine (**15**; $C_{10}H_{13}NO_2$)

9 (0.5 g, 1.5 mmol) gave **15** (200 mg, 73%) after 3 d at 50° as a white, crystalline powder.

M.p.: 264–265°C (Ref. [14]: 265–266°C); $[\alpha]_D^{21} = -156$ ($c = 2$, 1 *N* HCl; Ref. [14]: $[\alpha]_D = -163$ ($c = 1$, dil. HCl_{aq})); ^1H NMR (200 MHz, D_2O): $\delta = 1.12$ (t, $J = 7$ Hz, 3H, CH_3), 2.85 (m, 2H, CH_2), 4.50 (s, 1H, CH), 7.29–7.38 (m, 5H, arom. H) ppm; ^{13}C NMR (50 MHz, D_2O): $\delta = 10.81$ (CH_3), 41.92 (CH_2), 65.65 (CH), 128.85, 129.91, 130.28, 132.87 (arom. C), 173.00 (CO) ppm; IR (KBr): $\nu = 3435$, 1579 cm^{-1}; FAB-MS: $m/z = 180$ (M^+).

(L)-N-Ethylphenylglycine (**16**; $C_{10}H_{13}NO_2$)

10 (2.0 g, 6.1 mmol) gave **16** (800 mg, 73%) after 5 d at 60°C as white crystals.

M.p.: 257–258°C (closed glass capillary); $[\alpha]_D^{21} = 139$ ($c = 2$, 1 *N* HCl; Ref. [14]: $[\alpha]_D = 165$ ($c = 1$, HCl_{aq})); ^{1}H NMR (200 MHz, D_2O): $\delta = 1.11$ (t, $J = 8$ Hz, 3H, CH_3), 2.68–3.00 (m, 2H, CH_2), 4.50 (s, 1H, CH), 7.29–7.37 (m, 5H, arom. H) ppm; ^{13}C NMR (50 MHz, D_2O): $\delta = 10.83$ (CH_3), 41.94 (CH_2), 65.66 (CH), 128.87, 129.93, 130.29, 132.90 (arom. C), 172.99 (CO) ppm; IR (KBr): $\nu = 3431$, 1582 cm^{-1}; FAB-MS: $m/z = 180$ (M^+).

Aminolysis of N-ethyl-2,2-bis-(trifluoromethyl)-oxazolidin-5-ones **6–10** *with hydroxylamine (general procedure)*

N-Ethyl-2,2-*bis*-(trifluoromethyl)-oxazolidin-5-ones **6–10** (1.7 mmol) were dissolved in $(Et)_2O$ (5 cm^3). Hydroxyl amine (2.0 mmol, 132 mg 50% aqueous solution) was added, and the mixture was vigorously stirred at room temperature. The precipitate was filtered off, suspended in $(Et)_2O$ (7 cm^3), stirred for 24 h, and then filtered and dried *in vacuo* to give **17–20**.

N-(N^{α}-Ethyl-L-alanyl)-hydroxylamine (**17**; $C_5H_{12}N_2O_2$)

6 gave **17** (180 mg, 80%) as a white powder.

M.p.: 171°C; $[\alpha]_D^{21} = -3$ ($c = 2$, 1 N HCl); ^{1}H NMR (200 MHz, *DMSO-d_6*): $\delta = 0.94$ (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.04 (d, $J = 7$ Hz, 3H, CH_3), 2.37 (m, 2H, CH_2), 2.93 (q, $J = 7$ Hz, 1H CH) ppm; ^{13}C NMR (50 MHz, *DMSO-d_6*): $\delta = 10.98$ (CH_3^{Et}), 15.91 (CH_3), 41.80 (CH_2), 54.11 (CH), 167.19 (CO) ppm; IR (KBr): $\nu = 1616$ cm^{-1}; FAB-MS: $m/z = 133$ (M^+).

N-(N^{α}-Ethyl-L-valyl)-hydroxylamine (**18**; $C_7H_{16}N_2O_2$)

7 gave **18** (251 mg, 92%) as a white powder.

M.p.: 193°C; $[\alpha]_D^{21} = 27$ ($c = 2$, 1 *N* HCl); ^{1}H NMR (200 MHz, D_2O/1% DCl): $\delta = 0.79$ (d, $J = 7$ Hz, 3H, CH_3), 0.86 (d, $J = 7$ Hz, 3H, CH_3), 1.09 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 2.03 (m, 1H, CH), 2.86 (q, $J = 7$ Hz, 2H, CH_2), 3.38 (d, $J = 7$ Hz, 1H, CH) ppm; ^{13}C NMR (75 MHz, D_2O/1% DCl): $\delta = 10.55$ (CH_3^{Et}), 17.09 (CH_3), 18.36 (CH_3), 29.63 (CH), 42.67 (CH_2), 63.52 (CH), 164.60 (CO) ppm; IR (KBr): $\nu = 1618$ cm^{-1}; FAB-MS: $m/z = 161$ (M^+).

N-(N^{α}-Ethyl-L-leucyl)-hydroxylamine (**19**; $C_8H_{18}N_2O_2$)

8 gave **19** (228 mg, 77%) as a white powder.

M.p.: 192°C; $[\alpha]_D^{21} = 41$ ($c = 2$, 1 *N* HCl); ^{1}H NMR (200 MHz, D_2O): $\delta = 0.47$ (d, $J = 6$ Hz, 6H, 2 CH_3), 0.82 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.09–1.45 (m, 3H, CH_2, CH), 2.59 (q, $J = 7$ Hz, 2H, NCH_2), 3.28 (dd, $J = 5$, 4 Hz, 1H, NCH) ppm; ^{13}C NMR (50 MHz, D_2O): $\delta = 10.86$ (CH_3^{Et}), 21.04 (CH_3), 22.53 (CH_3), 24.46 (CH), 38.76 (CH_2), 42.08 (NCH_2), 57.30 (NCH), 165.92 (CO) ppm; IR (KBr): $\nu = 1615$ cm^{-1}; FAB-MS: $m/z = 175$ (M^+).

N-(N^{α}-Ethyl-D-phenylglycyl)-hydroxylamine (**20**; $C_{10}H_{14}N_2O_2$)

9 gave **20** (297 mg, 90%) as a white powder.

M.p.: 181°C; $[\alpha]_D^{21} = -130$ ($c = 2$, 1 *N* HCl); ^{1}H NMR (200 MHz, D_2O/1% DCl): $\delta = 1.10$ (t, $J = 8$ Hz, 3H, CH_3), 2.86 (m, 2H, CH_2), 4.79 (s, 1H, CH), 7.35 (m, 5H, arom. H) ppm; ^{13}C NMR (50 MHz, D_2O/1% DCl): $\delta = 10.70$ (CH_3), 42.05 (CH_2), 61.26 (CH), 128.75, 130.20, 130.44, 131.21, (arom. C), 165.53 (CO) ppm; IR (KBr): $\nu = 1640$ cm^{-1}; FAB-MS: $m/z = 195$ (M^+).

Syntheses of dipeptides **21–24** *(general procedure)*

L-Phenylalanine amide was dissolved in 2-PrOH, and **6–10** were added with stirring at room temperature. The completion of the reaction (12–24 h) was determined by ^{19}F NMR. If the product

crystallized from the reaction mixture, the precipitate was collected by filtration. The crystalline compound obtained was suspended in $(Et)_2O$ (20 cm^3), stirred for 24 h, and then filtered. If no crystallization occurred, the solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography.

N^{α}-Ethyl-L-alanyl-L-phenylalanine amide (**21**; $C_{14}H_{21}N_3O_2$)

6 (400 mg, 1.5 mmol) and *L*-phenylalanine amide (328 mg, 2.0 mmol) in 2-PrOH (2 cm^3) gave **21** (239 mg, 60%) after column chromatography (eluent: CH_2Cl_2/MeOH, 7:1) as white solid.

M.p.: 169°C; $[\alpha]_D^{21} = 21$ ($c = 2$, *DMSO*); ^{1}H NMR (200 MHz, *DMSO-d_6*): $\delta = 0.87$ (t, $J = 7$ Hz, 3H, CH_3^{Et}), 0.96 (d, $J = 7$ Hz, 3H, CH_3), 2.20 (q, $J = 7$ Hz, 2H, NCH_2), 2.78 (dd, $J = 14$, 9 Hz, 1H, CH_2), 2.90–3.05 (m, 2H, CH_2, CH), 4.49 (m, 1H, CH^{Phe}), 7.08 (s, 1H, NH), 7.11–7.26 (m, 5H, arom. H), 7.48 (s, 1H, NH), 7.91 (d, $J = 9$ Hz, 1H, NH) ppm; ^{13}C NMR (50 MHz, *DMSO-d_6*): $\delta = 15.72$ (CH_3^{Et}), 19.78 (CH_3), 38.88 (CH_2^{Phe}), 42.31 (CH_2), 53.66 (CH^{Phe}), 57.98 (CH), 127.17, 128.88, 130.26, 138.61 (arom. C), 173.88, 174.99 (CO) ppm; IR (KBr): $\nu = 1672$, 1641 cm^{-1}; FAB-MS: $m/z = 264$ (M^+).

N^{α}-Ethyl-L-leucyl-L-phenylalanine amide (**22**; $C_{17}H_{27}N_3O_2$)

8 (500 mg, 1.6 mmol) and *L*-phenylalanine amide (328 mg, 2.0 mmol) in 2-PrOH (3 cm^3) gave **22** (170 mg, 35%) after column chromatography (eluent CH_2Cl_2/MeOH, 8:1) as white solid.

M.p.: 143–145°C; $[\alpha]_D^{21} = 1$ ($c = 1$, *DMSO*); ^{1}H NMR (200 MHz, *DMSO-d_6*): $\delta = 0.75$ (d, $J = 6$ Hz, 3H, CH_3), 0.81 (d, $J = 7$ Hz, 3H, CH_3), 0.85 (t, $J = 7$ Hz, 3H, CH_3^{Et}), 1.09–1.17 (m, 2H, CH_2), 1.50 (m, 1H, CH), 2.15 (q, $J = 7$ Hz, 2H, NCH_2), 2.77 (dd, $J = 14$, 9 Hz, 1H, CH_2^{Phe}), 2.90 (dd, $J = 7$, 7 Hz, 1H, NCH), 2.99 (dd, $J = 14$, 5 Hz, 1H, CH_2^{Phe}), 4.53 (m, 1H, CH^{Phe}), 7.05 (s, 1H, NH), 7.14–7.22 (m, 5H, arom. H), 7.45 (s, 1H, NH), 7.95 (d, $J = 9$ Hz, 1H NH) ppm; ^{13}C NMR (50 MHz, *DMSO-D_6*): $\delta = 20.66$ (CH_3^{Et}), 28.00 (CH_3), 28.46 (CH_3), 29.72 (CH), 43.65 (CH_2), 47.07 (CH_2), 48.17 (CH_2), 58.43 (CH^{Phe}), 65.91 (CH), 131.86, 133.61, 134.97, 143.50 (arom. C), 178.79, 179.92 (CO) ppm; IR (KBr): $\nu = 3406$, 1656 cm^{-1}; FAB-MS: $m/z = 306$ (M^+).

N^{α}-Ethyl-D-phenylglycyl-L-phenylalanine amide (**23**; $C_{19}H_{23}N_3O_2$)

9 (500 mg, 1.5 mmol) and *L*-phenylalanine amide (328 mg, 2.0 mmol) in 2-PrOH (2 cm^3) gave **23** (350 mg, 72%) after filtration and washing with $(Et)_2O$ as colorless crystals.

M.p.: 173–175°C; $[\alpha]_D^{21} = -9$ ($c = 2$, *DMSO*); ^{1}H NMR (200 MHz, *DMSO-d_6*): $\delta = 0.95$ (t, $J = 7$ Hz, 3H, CH_3), 2.19–2.32 (m, 2H, NCH_2), 2.82 (dd, $J = 14$, 9 Hz, 1H, CH_2), 2.98 (dd, $J = 14$, 5 Hz, 1H, CH_2), 4.07 (s, 1H, CH), 4.47 (m, 1H, CH^{Phe}), 7.09–7.27 (m, 11H, arom. H, NH), 7.45 (s, 1H, NH), 8.17 (d, $J = 8$ Hz, 1H, NH) ppm; ^{13}C NMR (50 MHz, *DMSO-d_6*): $\delta = 15.89$ (CH_3), 38.62 (CH_2), 42.67 (NCH_2), 54.21 (CH^{Phe}), 66.85 (CH), 127.19, 128.04, 128.24, 128.94, 130.13 (2C), 138.55, 141.11 (arom. C), 172.75, 173.91 (CO) ppm; IR (KBr): $\nu = 1634$ cm^{-1}; FAB-MS: $m/z = 326$ (M^+).

N^{α}-Ethyl-L-phenylglycyl-L-phenylalanine amide (**24**; $C_{19}H_{23}N_3O_2$)

10 (500 mg, 1.5 mmol) and *L*-phenylalanine amide (328 mg, 2.0 mmol) in 2-PrOH (2 cm^3) gave **24** (310 mg, 95%) after filtration and washing with $(Et)_2O$ as colorless crystals.

M.p.: 161°C; $[\alpha]_D^{21} = 47$ ($c = 2$, *DMSO*); ^{1}H NMR (200 MHz, *DMSO-d_6*): $\delta = 0.94$ (t, $J = 7$ Hz, 3H, CH_3), 2.29 (q, $J = 7$ Hz, 2H, CH_2N), 2.81 (dd, $J = 14$, 9 Hz, 1H, CH_2), 2.99 (dd, $J = 14$, 5 Hz, 1H, CH_2), 4.06 (s, 1H, CH), 4.51 (m, 1H, CH^{Phe}), 7.10 (s, 1H, NH), 7.10–7.24 (m, 10H, arom. H), 7.47 (s, 1H, NH), 8.14 (d, $J = 9$ Hz, 1H, NH) ppm; ^{13}C NMR (50 MHz, *DMSO-d_6*): $\delta = 15.23$

(CH_3), 38.24 (CH_2), 41.96 (NCH_2), 53.31 (CH^{Phe}), 66.37 (CH), 126.49, 127.37, 127.57 (2C), 128.25, 129.56, 137.82, 140.25 (arom. C), 171.88, 172.96 (CO) ppm; IR (KBr): $\nu = 3292$, 1662 cm^{-1}; FAB-MS: $m/z = 326$ (M^+).

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