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Direct dialkylation of peptide nitriles. Application to the synthesis of 1-aminocyclopropane-1-carboxylic acid (Acc)-containing dipeptides

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Summary — Several 1-aminocyclopropane-1-carboxylic acid-containing dipeptides (Acc-CP) have been prepared by regioselective dialkylation of peptoids containing α-aminonitriles as C-terminal residues. Regioselective deprotonation of the aminomethylene center using a strong base and dialkylation by ethylene sulfate lead to cyclopropane peptide nitriles, without inducing racemization on the amino-acid α-position. Subsequent hydrolysis of the nitrile group affords Acc-CP.

cyclopropyl peptide / peptide C-alkylation / cyclopropane amino acid / 1-aminocyclopropanecarbonitrile

Résumé — Substitution directe de peptides nitriles. Application à la synthèse de dipeptides contenant l'acide 1-aminocyclopropane-1-carboxylique. Plusieurs dipeptides contenant l'acide 1-aminocyclopropane-1-carboxylique ont été obtenus par disubstitution régiosélective d'analogues dipeptidiques terminés par un α-aminonitrile. La déprotonation régiosélective de l'aminométhylène par une base forte, et sa disubstitution par le sulfate d'éthylène, conduisent à des peptide-nitriles cyclopropaniques sans entraîner de racémisation en position α de l'aminoacide. L'hydrolyse du groupement nitrile permet d'obtenir les dipeptides avec l'acide 1-aminocyclopropane-1-carboxylique terminal.

peptide cyclopropanique / C-substitution de peptide / aminoacide cyclopropanique / 1-aminocyclopropanecarbonitrile

Introduction

1-Aminocyclopropane-1-carboxylic acid-containing peptides (Acc-CP) [1] constitute a highly valuable class of conformationally constrained analogues for the medicinal chemist because the incorporation of a cyclopropane can induce drastic changes in the peptides properties, ie, stabilization of a specific conformation [2], or modification of the peptides chemical reactivity [3] whilst at the same time introducing only little steric hindrance. Thus, unsurprisingly, a fast-growing number of Acc-CPs have been prepared during the last decade, frequently providing analogues with promising pharmacological activities [4].

Until now, the synthesis of Acc-CP has been achieved, almost exclusively, by step-by-step coupling of the amino acids using liquid or solid phase peptide chemistry [5]. Although Acc is commercially available, the low reactivity of its amino and carboxyl groups [6] often demands the use of long coupling reaction times or of large excesses of reagent compared to non- or mono-substituted amino acids. Clearly, there is still a special need to synthesize these peptides in new ways.

During the course of our studies on the synthesis of cyclopropane amino acids, we have demonstrated the higher reactivity of α-aminonitriles compared to α-aminoesters [7] towards dialkylation with 1,2-dielectrophiles, and among the latter, the unusual efficiency of the 1,2-cyclic sulfates [8]. Combining our methodology with results from Seebach's group on the lack of racemization during the C-alkylation of glycine residues within peptides in the presence of a strong base (lithium diisopropylamide (LDA)) [9], we have designed a new strategy for the synthesis of Acc-CP based on the selective deprotonation of peptides containing aminoacetonitrile as the C-terminal residue with a strong base and using ethylene sulfate as a 1,2-dielectrophile. Subsequent transformation of the nitrile function into an ester is expected to lead directly to the desired Acc-CP (scheme 1). We herein disclose our preliminary results on this procedure.

Results and discussion

Choice of peptide nitriles

Peptides containing α-aminonitrile as the C-terminal residue were first synthesized in 1974 [10] and can be prepared in a similar way to ordinary peptides. In order to define the limits of our strategy, we synthesized four different dipeptide nitriles **1**–**4**, protected in each case

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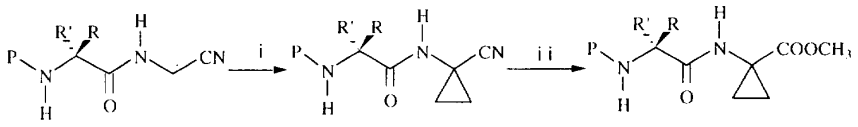

1: P = Boc, R = R′= H

2: P = Boc, R = R′ = CH_3

3: P = Boc, R= CH_2Ph, R′ = H

4: P = Boc, R = $CH(CH_3)_2$, R′ = H

1a: P = Boc, R = R′= H
1b: P= Z, R = R′ = H

2a: P = Boc, R = R′ = CH_3

3a: P = Boc, R = CH_2Ph, R′ = H
3a′: P = Boc, R = H, R′ = CH_2Ph
3b: P = Z, R = CH_2Ph, R′ = H

4a: P = Boc, R = $CH(CH_3)_2$, R′ = H
4b: P = Z, R = $CH(CH_3)_2$, R′ = H

1c: P = Z, R = R′ = H

3c: P = Z, R = CH_2Ph, R′ = H

4c: P = Z, R = $CH(CH_3)_2$, R′ = H

Scheme 1. Reagents and conditions: i) LDA (4.4 equiv), HMPA/THF (8.8 equiv), −78 °C, 10 min, *n*-BuLi (2.2 equiv), 60 min, ethylene sulfate; ii) a) TFA/CH_2Cl_2, b) $NaHCO_3$, Z-Cl, c) HCl/MeOH, d) 0.5 N aqueous HCl.

on the amine function by a *tert*-butoxycarbonyl (Boc) group in analogy with Seebach's results [9, 11] and chosen to determine the following: i) the regiospecificity of the dialkylation reaction (Boc-Gly-$NHCH_2CN$, **1**); ii) the importance of the steric hindrance at the α-position of the amino acid (Boc-Aib-$NHCH_2CN$, **2**); iii) the lack of racemization during the dialkylation step (Boc-(L)-Phe-$NHCH_2CN$, **3**); and iv) the importance of the steric hindrance at the β-position of the amino acid (Boc-(L)-Val-$NHCH_2CN$, **4**). Compounds **1**–**4** were prepared in 83–90% yields (**2** was prepared in 50% yield) by condensation of the selected *N*-protected amino acid (Boc-Gly, Boc-Aib, Boc-Phe and Boc-Val, respectively) with aminoacetonitrile using liquid phase peptide synthesis.

Evaluation of the regiospecificity of the reaction

We decided first to investigate the difference in reactivity towards cyclopropanation between an aminomethylene center adjacent to a nitrile or a carbonyl function within the same molecule. Double alkykation of **1** by ethylene sulfate 1,3,2-dioxothiolane-2,2-dioxide [8] furnished **1a**, after 5 h, in 55% yield (scheme 1). No trace of the product resulting from the (di)alkylation of the glycine methylene group was detected, thereby establishing the total regiospecificity of the reaction. These results confirm our previous observations [7, 12] and demonstrate once more that in our conditions the methylenes of aminonitriles behave differently to the methylenes neighboring carbonyl functions.

Study of the role of the amino-acid side chain

Having demonstrated the higher reactivity of a methylene adjacent to a nitrile group towards dialkylation, we decided to study the extent of possible steric hindrance close to the alkylation position and, more particularly, the influence of the amino-acid side chain during the reaction. Thus, we studied the case of a dipeptide nitrile composed of an amino acid disubstituted at its α-position. In the conditions described for the synthesis of **1a**, compound **2a** was obtained in 30% yield. Despite the conformational modifications possibly introduced by the Aib residue, we attributed this decrease of reactivity to the steric hindrance of the two methyl groups, these bulky groups probably precluding, in part, the approach of the dielectrophile.

Evaluation of the lack of epimerization

Aware of the lower reactivity induced by a α-disubstituted amino acid but encouraged by the results observed for the dialkylation of **1**, we decided to prepare a peptide nitrile containing a mono-substituted and optically pure amino acid. This would allow us to evaluate more precisely the role of the substituents at the amino acid α-position, and also provide a chiral compound thereby permitting us to evaluate the degree of epimerization during the course of the alkylation procedure. In order to avoid undesirable reactivity introduced by the amino acid side chain but get reasonable steric hindrance, we chose the (L)-Phe residue as a model amino acid. Hence optically pure **3** was prepared (in 83% yield) then subjected to the conditions used to synthesize **1a**. Compound **3a** was obtained in 50% yield (together with 10% of unreacted **3**). To demonstrate the optical integrity of **3a**, we also synthesized it by condensing Boc-(L)-Phe to 1-aminocyclopropane-1-carbonitrile [13] using conditions similar to those used for the synthesis of **1**–**4** (69% yield). Whatever the chemical pathway used, both compounds displayed similar optical rotation ($[\alpha]_D^{20} = -10.1$ (*c* 1.8, CH_2Cl_2)). Nevertheless, because of the low value of the optical rotation, we decided to confirm this result. Thus, we prepared a 50:50 mixture of **3a** and its enantiomer **3a′** starting from racemic Boc-Phe and 1-aminocyclopropane-1-carbonitrile. Although we were unable to separate the enantiomers by chiral HPLC, we successfully demonstrated the optical integrity of the *N*-deprotected derivative (TFA, CH_2Cl_2) of **3a** using Alexakis' elegant methodology [14]. This method allowed us to establish the optical integrity of **3a** to be at least 97%.

Further studies on the role of the amino acid side chain

The lack of racemization during the dialkylation procedure is established, and alkylation of monosubstituted peptides gives reasonable yields. We attempted to generalize our method by using Boc-(L)-Val, a common amino acid hindered at its β-position. Dialkylation of **4** (prepared in 84% yield) using our previously defined

conditions led to compound **4a** in 50% yield (together with 8% of unreacted **4**). This yield, similar to that observed for the synthesis of **3a**, showed that the nature of the amino acid alkyl side chain was of little importance for the cyclopropanation reaction.

Synthesis of the dipeptides

Several methods have been reported for the transformation of a nitrile group into an acid or ester function [15]. However, in our case the conditions had to be compatible with the presence of an amide bond and also non-racemizing. Model reactions showed that transformation of the nitrile function of a dipeptide nitrile into an imidate could be quantitatively achieved using anhydrous saturated hydrochloric methanol and subsequent hydrolysis of the imidate (dilute aqueous HCl) furnishing the corresponding dipeptide. However, since the first step would obviously concomitantly remove a Boc protecting group, we prepared the *Z*-analogues of our initial peptide nitriles and carried out their cyclopropanation using the conditions determined for the Boc derivatives. Unfortunately, these *Z*-derivatives turned out to be much less reactive towards dialkylation than their Boc counterparts. For example, Z-Gly-NH-CH_2-CN furnished the expected cyclopropyl peptide analogues in only 20% yield, while Z-Aib-NH-CH_2-CN was totally unreactive towards cyclopropanation, longer reaction times or higher temperature (−50 °C) leading only to degradative materials. Model reactions carried out using benzylbromide as a simple electrophile confirmed the higher reactivity of the Boc-protected peptides compared to their *Z*-analogues. Compounds **1**, **3** and **4** were mono-alkylated in 35–70% yields while, in the same conditions, the *Z*-derivatives were alkylated in only 10–25% yields. These results are in accordance with Seebach's hypothesis concerning the possible deprotonation of the *Z*-methylene protons and therefore the difficulty to alkylate amino acids of *Z*-protected peptides [11b]. Thus we returned to the Boc-protected peptide nitriles and prepared the *Z*-protected derivatives in 85–90% overall yield using a two-step deprotection-protection procedure: (a) 20% TFA/CH_2Cl_2; b) $NaHCO_3$, Z-Cl). Hence, we were able to obtain **1b**, **3b**, and **4b** which upon treatment with MeOH/HCl and then 0.5 N HCl aq furnished the expected diprotected peptides **1c**, **3c**, and **4c** respectively (70% yield) which could be isolated and fully characterized.

Conclusion

In summary, this report provides the first example of the synthesis of cyclopropyl peptides using the direct peptide alkylation method [9]. This methodology represents an attractive alternative synthesis for C-terminal cyclopropyl peptides that can be further lengthened. Although for peptides containing α-disubstituted amino acids slightly lower dialkylation yields are observed, in the best cases, this method provides Acc-CP easily and in 50–55% overall yield from an *N*-protected amino acid (three steps). Undeniably, to date, Acc-CPs are still more efficiently prepared by direct condensation of amino acids. However, this method also allows simple synthesis of conformationally constrained peptide nitrile analogues that are currently considered as peptide surrogates [16]. Moreover, following subsequent chemistry on the nitrile group, Acc-CPs provide an entry to methylketone peptide analogues that are pharmacologically active compounds [17, 18]. Furthermore, the use of substituted sulfates or other 1,2-dielectrophiles should lead to compounds that are more difficult to obtain using coupling peptide chemistry and also provide peptides whose amino acids are unstable. The detailed synthesis of these compounds will be reported shortly [19].

Experimental section

General procedures

Optical rotations were determined with a Perkin-Elmer 214 polarimeter. NMR spectra were recorded on a Bruker AC 300-P spectrometer. Chemical shifts were measured in ppm and given, for the ^1H NMR spectra, relatively to residual solvent traces ($CHCl_3$, δ = 7.26; DOH, δ = 4.6). For the ^{13}C NMR spectra, chemical shifts were given relative to $CDCl_3$ (δ = 77.7) or for the spectra recorded in D_2O relative to an external reference (dioxane, δ = 66.5). Mass spectra were obtained in chemical ionization mode by direct insertion (ionizing gas NH_3) on a Nermag R10-10 spectrometer. Thin-layer chromatography was performed on aluminium plates precoated with silica gel. Compounds were visualized by heating after dipping in a solution of phosphomolybdic acid (10–20%). Flash column chromatography was performed using Kieselgel 60 (250–450 mesh, SDS). Anhydrous Na_2SO_4 was used to dry organic solutions during workup. Microanalyses were performed at the ICSN, CNRS, Gif-sur-Yvette. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone and diisopropylamine was distilled under nitrogen from CaH_2 prior use. Hexamethylphosphoramide (HMPA) was distilled and kept over 3 Å molecular sieves.

*General procedure for dipeptide nitriles **1–4***

To an ice-cooled solution of *N*-protected amino acid (5 g) and 4-methylmorpholine (2.5 equiv) in dichloromethane (200 mL), was added dicyclohexylcarbodiimide (1 equiv) and 1-hydroxybenzotriazole (1 equiv). After 20 min, the white precipitate of dicyclohexylurea was filtered off and a mixture of aminoacetonitrile hydrochloride (1.1 equiv) and 4-methylmorpholine (2 equiv) in dichloromethane (75 mL) was added. The reaction was stirred for 18 h before being quenched with 1 N HCl (300 mL). The organic phase was collected, washed with brine (2 × 250 mL), dried and concentrated. The residue was chromatographed eluting with cyclohexane/EtOAc (3:1) to yield pure peptide nitriles.

*General procedure for cyclopropane dipeptide nitriles **1a–4a***

A solution of dipeptide nitrile (750 mg) in THF was slowly added to a solution of LDA (4.4 equiv) in THF/HMPA (8.8 equiv) prepared under a nitrogen atmosphere at −78 °C. The solution was stirred for 10 min and 2.5 M *n*-BuLi in hexanes (2.2 equiv) was added and the solution stirred for 1 h. A solution of ethylene sulfate (1.2 equiv) in THF was added and the solution stirred for 5 h at −78 °C before being quenched by addition of saturated NH_4Cl. After allowing the solution to warm to rt, the

organic phase was collected and the aqueous phase extracted with dichloromethane. The combined organic phases were dried and concentrated. HMPA was removed from the reaction mixture by a short flash chromatography (cyclohexane/EtOAc, 4:1) and final purification of the cyclopropane peptide nitriles was achieved by flash chromatography (cyclohexane/EtOAc, gradient of increasing polarity).

General procedure for cyclopropane dipeptides **1c**, **3c** *and* **4c**

Onto a solution of **1b**, **3b** or **4b** in dry methanol at 0 °C, a saturated anhydrous solution of MeOH/HCl was poured. The solution was stirred for 5 h and the volatile material removed under reduced pressure. A 0.5 N aqueous HCl solution was poured on the residue and the solution stirred for 18 h. The solution was extracted with dichloromethane. The organic phase was dried, concentrated and the dipeptides were isolated in pure form by crystallization (EtOAc).

• *{[N-(tert-Butoxycarbonyl)glycyl]amino}acetonitrile* **1**

Prepared in 89% yield using the general procedure, mp 112 °C (C_6H_{12}/EtOAc 2:1).

^{1}H NMR ($CDCl_3$): 7.05 (br s, 1H), 5.20 (br s, 1H), 4.15 (d, J = 5.8 Hz, 2H), 3.80 (d, J = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$): 170.5, 156.2, 116.1, 80.3, 43.8, 28.2, 27.3.

MS: m/z (%) 231 (100) [MNH_4^+], 214 (40) [MH^+], 175 (35).

Anal calc for $C_9H_{15}N_3O_3$: C, 50.68; H, 7.09; N, 19.71. Found: C, 50.52; H, 6.79; N, 19.61.

• *{[N-(tert-Butoxycarbonyl)dimethylglycyl]amino}acetonitrile* **2**

Obtained in 52% yield following the general procedure, mp 120 °C (C_6H_{12}/EtOAc 2:1).

^{1}H NMR ($CDCl_3$): 7.45 (t, J = 7.5 Hz, 1H), 5.40 (br s, 1H), 4.10 (d, J = 7.5 Hz, 2H), 1.35 (s, 6H), 1.30 (s, 9H).

^{13}C NMR ($CDCl_3$) 175.6, 155.0, 116.4, 80.7, 56.6, 28.1, 27.6, 25.4.

MS: m/z (%) 259 (100) [MNH_4^+], 242 (70) [MH^+], 203 (30), 186 (25).

• *{[N-(tert-Butoxycarbonyl)-L-phenylalanyl]amino}acetonitrile* **3**

Prepared in 83% yield using the general procedure, mp 142 °C (C_6H_{12}/EtOAc 2:1).

$[\alpha]_D^{20}$ = −11 (c = 2.1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.30–7.12 (m, 5H), 6.49 (br s, 1H), 4.91 (br s, 1H), 4.30 (m, 1H), 4.05 (m, 2H), 3.04 (d, J = 7.1 Hz, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$): 171.8, 155.5, 136.0, 129.2, 128.8, 127.1, 115.5, 81.7, 55.5, 38.1, 28.2, 27.2.

MS: m/z (%) 321 (9) [MNH_4^+], 304 (14) [MH^+], 248 (86), 204 (100), 120 (39).

Anal calc for $C_{16}H_{21}N_3O_3$: C, 63.33; H, 6.98; N, 13.86. Found: C, 63.22; H, 6.92; N, 13.87.

• *{[N-(tert-Butoxycarbonyl)-L-valyl]amino}acetonitrile* **4**

Prepared in 84% yield according to the general procedure, mp 93 °C (C_6H_{12}/EtOAc 2:1).

$[\alpha]_D^{20}$ = −27 (c = 1.3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.72 (br s, 1H), 5.40 (d, J = 7.1 Hz, 1H), 4.10 (m, 3H), 2.05 (m, 1H), 1.35 (s, 9H), 0.87 (s, 6H).

^{13}C NMR ($CDCl_3$): 172.6, 156.2, 115.9, 80.3, 59.8, 31.0, 28.2, 27.2, 19.1, 18.2.

MS: m/z (%) 273 (100) [MNH_4^+], 256 (5) [MH^+].

Anal calc for $C_{12}H_{21}N_3O_3 \cdot 1/2H_2O$: C, 56.5; H, 8.29; N, 16.46. Found: C, 56.83; H, 8.23; N, 16.43.

• *1-{[N-(tert-Butoxycarbonyl)glycyl]amino}cyclopropane-1-carbonitrile* **1a**

Prepared in 55% yield according to the general procedure, mp 151 °C (C_6H_{12}/EtOAc 2:1).

^{1}H NMR ($CDCl_3$): 7.25 (m, 5H), 7.02 (s, 1H), 5.53 (br t, 1H), 4.96 (s, 2H), 3.69 (d, J = 7.1 Hz, 2H), 1.37 (m, 2H), 1.12 (m, 2H).

^{13}C NMR ($CDCl_3$): 170.5, 156.8, 136.0, 128.5, 128.2, 127.9, 120.0, 67.2, 44.3, 20.2, 16.5.

MS: m/z (%) 257 (100) [MNH_4^+], 240 (14) [MH^+], 201 (10).

Anal calc for $C_{11}H_{17}N_3O_3 \cdot 1/2H_2O$: C, 53.2; H, 7.31; N, 16.93. Found: C, 52.99; H, 6.95; N, 16.93.

• *1-{[N-(tert-Butoxycarbonyl)dimethylglycyl]amino}-cyclopropane-1-carbonitrile* **2a**

Obtained in 30% yield following the general procedure, mp 132 °C (C_6H_{12}/EtOAc 2:1).

^{1}H NMR ($CDCl_3$): 7.45 (s, 1H), 5.20 (br s, 1H), 1.45 (m, 2H), 1.30 (s, 9H), 1.15 (m, 2H).

^{13}C NMR ($CDCl_3$): 176.0, 154.8, 120.2, 80.7, 56.5, 28.1, 25.2, 16.6.

MS: m/z (%) 285 (100) [MNH_4^+], 268 (10) [MH^+].

Anal calc for $C_{13}H_{21}N_3O_3 \cdot 1/4\ H_2O$: C, 57.44; H, 7.97; N, 15.46. Found: C, 57.56; H, 7.72; N, 15.69.

• *1-{[N-(tert-Butoxycarbonyl)-L-phenylalanyl]-amino}cyclopropane-1-carbonitrile* **3a**

Obtained in 50% yield according to the general procedure, mp 138 °C (C_6H_{12}/EtOAc 2:1).

$[\alpha]_D^{20}$ = −10.1 (c = 0.2, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.25–7.11 (m, 5H), 6.62 (s, 1H), 5.31 (d, J = 7.9 Hz, 1H), 4.23 (m, 1H), 2.92 (m, 2H), 1.36 (m, 11H), 0.95 (m, 2H).

^{13}C NMR ($CDCl_3$): 172.4, 155.6, 136.1, 129.2, 128.6, 127.0, 119.6, 80.6, 55.4, 38.5, 28.2, 20.0, 16.5.

MS: m/z (%) 347 (23) [MNH_4^+], 330 (27) [MH^+], 274 (100), 248 (26), 230 (73), 204 (40), 180 (81), 120 (23), 102 (23).

Anal calc for $C_{18}H_{23}N_3O_3$: C, 65.62; H, 7.04; N, 12.76. Found: C, 65.44; H, 6.91; N, 12.61.

• *1-{[N-(tert-Butoxycarbonyl)-L-valyl]amino}cyclopropane-1-carbonitrile* **4a**

Obtained in 50% yield according to the general procedure, mp 164 °C (C_6H_{12}/EtOAc 2:1).

$[\alpha]_D^{20}$ = −23 (c = 0.2, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.91 (s, 1H), 5.55 (d, J = 8.2 Hz, 1H), 3.85 (t, J = 8.2 Hz, 1H), 1.97 (m, 1H), 1.40 (m, 2H), 1.30 (s, 9H), 1.10 (m, 2H), 0.85 (m, 6H).

^{13}C NMR ($CDCl_3$): 173.5, 156.1, 119.7, 59.5, 31.1, 28.2, 20.1, 19.2, 19.0, 18.2, 16.6, 16.2.

MS: m/z (%) 299 (100) [MNH_4^+], 282 (50) [MH^+].

Anal calc for $C_{14}H_{23}N_3O_3 \cdot 1/2H_2O$: C, 57.9; H, 8.34; N, 14.48. Found: C, 57.88; H, 8.21; N, 14.48.

• *1-{[N-(Benzyloxycarbonyl)glycyl]amino}cyclopropane-1-carbonitrile* **1b**

Prepared in 20% yield according to the general procedure, mp 146 °C (C_6H_{12}/EtOAc 2:1).

^{1}H NMR ($CDCl_3$): 7.3–7.2 (m, 6H), 5.60 (br s, 1H), 4.95 (s, 2H), 3.7 (d, 2H), 1.35 (m, 2H), 1.12 (m, 2H).

^{13}C NMR ($CDCl_3$): 170.4, 156.8, 136.0, 128.5, 128.2, 127.9, 120.0, 67.2, 44.3, 20.2, 16.5.

MS: m/z (%) 291 (100) [MNH_4^+], 274 (17) [MH^+], 108 (22).

Anal calc for $C_{14}H_{15}N_3O_3 \cdot 1/2H_2O$: C, 59.55; H, 5.72; N, 14.89. Found: C, 60.27; H, 5.77; N, 14.49.

• *1-{[N-(Benzyloxycarbonyl)-L-phenylalanyl]amino}-cyclopropane-1-carbonitrile* ***3b***

Obtained in 33% yield according to the general procedure, mp 144 °C (EtOAc).

$[\alpha]_D^{20} = -3$ ($c = 0.2$, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.26–7.05 (m, 10H), 6.82 (s, 1H), 5.62 (d, $J = 6.2$ Hz, 1H), 4.99 (s, 2H), 4.31 (m, 1H), 3.00 (m, 2H), 1.48 (m, 2H), 0.95 (m, 2H).

^{13}C NMR ($CDCl_3$): 172.3, 156.3, 135.8, 129.3, 128.8, 128.6, 128.3, 127.9, 126.2, 119.6, 67.2, 55.9, 20.1, 16.5.

MS: m/z (%) 381 (100) [MNH_4^+], 364 (55) [MH^+], 327 (20), 273 (50), 230 (45).

Anal calc for $C_{21}H_{21}N_3O_3$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.12; H, 5.56; N, 11.89.

• *1-{[N-(Benzyloxycarbonyl)-L-valyl]amino}cyclopropane-1-carbonitrile* ***4b***

Obtained in 33% yield, mp 201 °C (EtOAc).

$[\alpha]_D^{20} = -18$ ($c = 1.25$, CH_2Cl_2).

^{1}H NMR (CD_3OD): 7.33 (m, 5H), 5.15 (s, 2H), 3.90 (m, 1H), 2.05 (m, 1H), 1.55 (m, 2H), 1.25 (m, 2H).

^{13}C NMR (CD_3OD): 174.0, 157.4, 136.5, 128.8, 128.5, 128.2, 120.2, 67.3, 60.2, 31.6, 20.4, 19.2, 18.0, 16.6, 16.2.

MS: m/z (%) 333 (80) [MNH_4^+], 316 (100) [MH^+], 182 (15).

Anal calc for $C_{17}H_{21}N_3O_3 \cdot H_2O$: C, 61.23; H, 6.95; N, 12.61. Found: C, 61.01; H, 6.41; N, 12.65.

• *1-{[N-(Benzyloxycarbonyl)glycyl]amino}cyclopropane-1-carboxylic acid methyl ester* ***1c***

Obtained as an amorphous solid in 70% yield according to the general procedure.

^{1}H NMR ($CDCl_3$): 7.25 (s, 5H), 6.95 (s, 1H), 5.65 (br s, 1H), 5.05 (s, 2H), 3.80 (d, $J = 5.7$ Hz, 1H), 3.65 (s, 3H), 1.5 (m, 2H), 1.05 (m, 2H).

^{13}C NMR ($CDCl_3$): 172.6, 170.5, 156, 136.0, 128.5, 128.2, 127.9, 67.1, 52.6, 44.5, 33.3, 17.5.

MS: m/z (%) 324 (100) [MNH_4^+], 307 (60) [MH^+], 279 (30), 241 (30), 180 (40).

Anal calc for $C_{15}H_{18}N_2O_5$: C, 58.80; H, 5.93; N, 9.16. Found: C, 58.53; H, 6.35; N, 8.76.

• *1-{[N-(Benzyloxycarbonyl)-L-phenylalanyl]amino}-cyclopropane-1-carboxylic acid methyl ester* ***3c***

Obtained in 60% yield according to the general procedure, mp 144 °C (C_6H_{12}/EtOAc 2:1).

$[\alpha]_D^{20} = -5$ ($c = 0.1$, CH_2Cl_2).

^{1}H NMR (acetone-d_6): 7.95 (s, 1H), 7.31 (m, 10H), 6.45 (d, $J = 8.5$ Hz, 1H), 5.06 (br s, 2H), 4.44, (m, 1H), 3.65 (s, 3H), 3.25 (dd, $J = 13.8$; 5.5 Hz, 1H), 2.99 (dd, $J = 13.8$; 8.6 Hz, 1H), 1.45 (m, 2H), 1.05 (m, 2H).

^{13}C NMR (acetone-d_6): 173.8, 173.4, 157.2, 139.1, 138.8, 130.8–127.8, 67.2, 57.5, 53.0, 39.5, 18.2, 18.0.

MS: m/z (%) 414 (25) [MNH_4^+], 397 (100) [MH^+], 353 (10), 263 (50), 225 (25).

Anal calc for $C_{22}H_{24}N_3O_5 \cdot H_2O$: C, 65.16; H, 6.22; N, 6.91. Found: C, 64.76; H, 6.06; N, 6.72.

• *1-{[N-(Benzyloxycarbonyl)-L-valyl]amino}cyclopropane-1-carboxylic acid methyl ester* ***4c***

Obtained as an amorphous solid in 86% yield according to the general procedure.

$[\alpha]_D^{20} = -8$ ($c = 0.2$, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): 7.3 (s, 5H), 6.65 (s, 1H), 5.40 (d, $J = 8.9$ Hz), 5.05 (s, 2H), 3.90 (dd, $J = 8.9$, 8.5 Hz), 3.55 (s, 3H), 2.05 (m, 1H), 1.50 (m, 2H), 1.05 (m, 2H), 0.94 (d, $J = 6.2$ Hz, 3H), 0.90 (d, $J = 7.3$ Hz, 3H).

^{13}C NMR ($CDCl_3$): 172.6, 170.5, 156, 136.0, 128.5, 128.2, 127.9, 67.1, 52.6, 44.5, 33.3, 17.5.

MS: m/z (%) 366 (90) [MNH_4^+], 349 (100) [MH^+], 215 (20).

Anal calc for $C_{18}H_{24}N_2O_5$: C, 62.04; H, 6.95; N, 8.04. Found: C, 61.98; H, 6.85; N, 8.33.

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