Synthesis of New Amino Acids with a 5-Imino-2,5-dihydro-3-furanyl Substituent at the Amino Group

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Abstract: Amino acids (glycine, β-alanine, γ-aminobutyric and ε-aminocaprylic acids, D,L-valine, and D,L-leucine) react under biomimetic conditions (H2O, NaOH, pH ~8.6–9.9, room temperature) smoothly with α,β-acetylenic γ-hydroxyacid nitriles to give a novel family of unnatural amino acids containing a 5-imino-2,5-di-hydro-3-furanyl substituent at the amino group, in 61–98% yield. As follows from a single-crystal X-ray analysis of 2-(5-imino-2,2-dimethyl-2,5-dihydro-3-furanyl)amino)acetic acid, the synthesized amino acids are zwitterions with a protonated imino group in the iminodihydrofuran moiety.

Key words: amino acids, acetylenes, nitriles, 2,5-dihydrofurans, nucleophilic addition

Amino acids play a pivotal role in all processes in living cells. They are the basic building materials for the synthesis of proteins, enzymes, peptide hormones, and other physiologically active compounds. Amino acids are also used in medicine for parenteral nutrition of patients with digestive system disorders, as well as for the treatment of liver diseases, anemia, burns (methionine), gastric ulcers (histidine), and neuropsychic diseases (glutaminic acid, γ-aminobutyric acid, etc.).1 As a result, amino acids are employed as building blocks for the synthesis of molecules with targeted biological activity.2 Synthetic amino acids (unnatural) may find application in the production of biomolecules for tissue engineering, as well as as markers for controlling the accuracy of drug transportation within organisms.3 Incorporation of unnatural amino acids in proteins might solve a number of basic problems of protein structure–property relationships. It also extends the possibilities for the synthesis of new proteins showing previously unknown features and of modifying the properties of known proteins and enzymes for a wide range of applications.4 Thus, the search for new types of amino acids is of paramount importance.

Of particular interest are amino acids with a dihydrofuran moiety in their structure; however, there is no information about such types of amino acids in the literature. The dihydrofuran motif is frequently found in numerous natural and biologically active compounds, e.g. in ascorbic,5 penicill, and tetronic acids and their thiol analogs,6 and in anti-AIDS drugs such as d4T [1-(2’,3’-dideoxy-γ-D-glycero-pent-2-enofuranosyl)thymine] and AZT [1-[4-azido-5-(hydroxymethyl)tetrahydro-2-furanyl]5-methylpyrimidine-2,4-(1H,3H)-dione].7 The dihydrofuran structure occurs in cardenolides8 (cardioactive steroid lactones) and in dysidiolide (the only known natural inhibitor of a protein phosphatase, cdc25A9), as well as in a great variety of other natural molecules including sesquiterpenes10 and pulvinic acid derivatives.11 In strigol and its analogs, the dihydrofuranone part is primarily responsible for the germination of seeds.12 Thus, the design of molecules which combine amino acid and dihydrofuran functionalities is an attractive area for organic synthesis.

In this paper, we report a general approach to the synthesis of amino acids containing the dihydrofuran moiety at the amino group. This approach involves a one-pot reaction of amino acids 1–6 [glycine (1), β-alanine (2), γ-aminobutyric acid (3), ε-aminocapronic acid (4), D,L-valine (5), and D,L-leucine (6)] with the α,β-acetylenic γ-hydroxyacid nitriles 7–10. The synthesis proceeds under biomimetic conditions (H2O, NaOH, pH ~8.6–9.9, room temperature, 4 h) to smoothly afford the amino acids 11–23 with a dihydrofuran moiety in 61–98% yield (Scheme 1).

Cyclization of the primary adducts A is assumed to be preceded by formation of the imino tautomers B with free rotation of the CH2CN group that facilitates ring closure, leading (through proton transfer in the intermediates C) to the end products 11–23. Spectroscopic analysis of amino acids 11–23 indicates the absence of a nitrile group (no signals at δ = 115–125 ppm in the 13C NMR spectra and no IR absorption at 2200–2260 cm–1), thus evidencing the lack of admixtures of the intermediates A and B in the final products. However, it cannot be excluded that, in solution, the amino acids 11–23 exist in tautomeric equilibrium with the alternative zwitterionic C.

It is understood that in the case of sodium hydroxide, the true catalysts are the sodium salts of the corresponding amino acids. Generally, in this reaction the role of a base is to increase the concentration of the non-zwitterionic form of an amino acid, which, unlike the zwitterionic form, is capable of nucleophilic addition of the amino
group to the triple bond. The influence of the synthesis conditions and the molecular structure of the starting compounds is shown in Table 1.

No reaction occurs in the absence of sodium hydroxide, while with an equimolar amount of sodium hydroxide (relative to acid) the yield is far from a maximum (70% for \(11\), Table 1) and 5-amino-2,2-dimethyl-3(2H)-furanone (24) is formed as a side product. The latter results from the nucleophilic addition of water to the starting acetylenic hydroxynitrile (Scheme 2).\(^{13}\)

As a rule, the best yields of products are attained for the less sterically constrained acetylenic hydroxynitrile (Table 1). Upon increasing the steric requirements in the acetylenic hydroxynitriles 7–10 in the reaction with glycine (1), the yield of amino acids (11 → 12 → 13 → 14) slightly decreases (Table 1). In ethanol (30–40 °C, 4 h) in the presence of sodium hydroxide, the reaction between amino acid 1 and acetylenic hydroxynitrile 7 leads to a 4:1 mixture of the corresponding amino acid 11 and (Z)-3-ethoxy-4-hydroxy-4-methyl-2-pentenenitrile (25) (Table 1), which is the adduct of ethanol to the triple bond of acetylenic hydroxynitrile 7 (Scheme 3).\(^{14}\)

The amino acids 11–23 are microcrystalline powders, soluble in water, slightly soluble in hot ethanol, and insoluble in diethyl ether, \(n\)-hexane, chloroform, acetonitrile, and dimethyl sulfoxide. \(^1\)H NMR, \(^{13}\)C NMR, and IR spectra of the amino acids 11–23 correspond to their structure (see experimental). The zwitterionic character of amino acid 11 (and presumably that of all the other new amino acids) follows from its single-crystal X-ray analysis (Figure 1).\(^{15}\)

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**Scheme 1** Synthesis of amino acids containing a dihydrofuran moiety at the amino group

**Scheme 2** Addition of water to the acetylenic hydroxynitrile 7

**Scheme 3** Addition of ethanol to the acetylenic hydroxynitrile 7

Figure 1 Molecular structure of 2-[[5-imino-2,2-dimethyl-2,5-dihydro-3-furanylamino]acetic acid (11)
The crystal structure of compound 11 is formed by one crystallographically independent molecule C₈H₁₂N₂O₃ (Figure 1) taking general position in the unit cell. The molecule has a practically planar conformation, except for the COO− moiety; the maximum deviation of atoms from the five-membered cycle plane is 1 pm [atom O(1)]. Deviations of N(6), N(7), and C(8) from this plane are 3, 0.5, and 16 pm, respectively. The torsion angle of C(9)−C(8)−N(7)−C(3) is 75.0(2)°, the dihedral angle formed by the plane of five-membered cycle and the C(9)−O(10)−O(11) moiety is equal to 58.9°, and the dihedral angle between the five-membered cycle and the C(3)−N(7)−C(8) fragment is 172.7°. Torsion angles of O(10)−C(9)−C(8)−N(7) and O(11)−C(9)−C(8)−N(7) are 152.0(1)° and 159.0(2)°, respectively. In the crystal structure of amino acid 11 all the molecules are bound by hydrogen bonds forming a supramolecular polymer structure of N(6)···H(6A)···O(10) and N(6)···H(6B)···O(10′) type, that is supported by the corresponding contacts [contact distances: N(6)···O(10), 276.4(2) pm; H(6A)···O(10), 185(2) pm; H(6B)···O(10′), 200(2) pm; angles: N(6)···H(6A)···O(10), 165.2°; N(6)···H(6B)···O(10′), 152.2°] and bonds, H(7)···O(11): 200(2) pm, angle N(7)−H(7)···O(11): 172(2)° (Figure 2) [sums of van der Waals radii are 310 pm (N···O) and 245 pm (O···H)].

The most important (and unusual) structural feature of the novel family of amino acids 11−23 is that they are zwitter-
ions with a protonated imino group in the 2,5-dihydrofuran moiety, thus meaning that the latter is conjugatively incorporated in the amino acid molecule (Scheme 4).

Such a long-range push–pull-type conjugation is expected to cause a number of special structural effects which can be manifested in an optoelectronic self-assembly behavior of the amino acids, as well as in their biological activity.

IR spectra were measured on a Specord IR 75 instrument. $^1$H and $^13$C NMR spectra were recorded on a Bruker DPX spectrometer. X-ray diffraction studies were carried out with an Enraf Nonius diffractometer at room temperature ($\theta$-scan mode, Cu-K$\alpha$ radiation, graphite monochromator). The crystal structure was solved by direct methods followed by Fourier synthesis using SHELXS-97. $^{18}$ Coordinates of hydrogen atoms were prepared according to a given procedure. $^{20}$ The reactions were monitored by TLC on alumina (CHCl$_3$–benzene–EtOH, 20:4:1).

Amino Acids 11–23: General Procedure

To a solution of an amino acid 1–6 (2 mmol) and NaOH (0.5–2.0 mmol) in H$_2$O (4 mL) was added an acetylenic hydroxynitrile (2.0 mmol). The mixture was stirred at r.t. for 4 h, stirring was stopped, and the H$_2$O was evaporated. The resulting residue was passed through neutral alumina (2–3 cm) using hot EtOH (50–60 °C) (50–70 mL) as eluent. The solvent was evaporated under reduced pressure to give the amino acid 11–23.

2-[(5-Imino-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]acetic Acid (11)

Yield: 0.346 g (98%); yellow microcrystalline powder; mp 270–275 °C.

IR (KBr): 3400, 3220 (NH, =CH), 1680 (C=O), 1630 cm$^{-1}$ (C=C).

$^1$H NMR (400.13 MHz, D$_2$O): $\delta$ = 1.44 (s, 6 H, 2 × CH$_3$), 3.65 (s, 2 H, CH$_2$), 4.79 (s, 1 H, =CH).

$^{13}$C NMR (101.61 MHz, D$_2$O): $\delta$ = 23.97 (CH$_3$), 36.19 (CH$_2$)$_2$, 49.80 (NHCH$_2$), 79.03 (C-1), 102.54 (=CH), 176.54 (C=NH), 177.21 (N=C=), 177.46 (COO$^-$).

Anal. Calcd for C$_8$H$_{12}$N$_2$O$_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.48; H, 6.32; N, 15.27.

2-[(2-Imino-1-oxaspiro[4.5]dec-3-en-4-yl)amino]acetic Acid (12)

Yield: 0.356 g (84%); light-yellow microcrystalline powder; mp 140–142 °C.

IR (KBr): 3396, 3220 (NH, =CH), 1660 (C=O), 1605 cm$^{-1}$ (C=C).

3-[(2-Imino-1-oxaspiro[4.4]non-3-en-4-yl)amino]propanoic Acid (13)

Yield: 0.242 g (61%); light-yellow microcrystalline powder; mp 248–253 °C.

IR (KBr): 3405, 3215 (NH, =CH), 1680 (C=O), 1605 cm$^{-1}$ (C=C).

$^1$H NMR (400.13 MHz, D$_2$O): $\delta$ = 1.11–1.17, 1.43–1.49 and 1.58–1.64 (m, 8 H, =CH$_2$), 176.72 (N=C=), 178.21 (COO$^-$).

Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_3$: C, 58.91; H, 7.12; N, 12.49. Found: C, 58.63; H, 7.12; N, 12.23.

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3-[1-Iodo-2-phenylthio]propanoic acid (21)
Yield: 0.217 g (74%); light-yellow microcrystalline powder; mp 220–225 °C.

IR (KBr): 3400, 3220 (NH, =CH), 1670 (C=O), 1605 cm–1 (C=C).
1H NMR (400.13 MHz, D2O): δ = 0.93 (t, J = 6.54 Hz, 3 H, CH(CH3)2), 1.48 (m, 2 H, CH2CH2C=O), 4.82 (s, 1 H, =CH).
13C NMR (101.61 MHz, D2O): δ = 16.55 (CH(CH3)2), 34.93 (CH2C=O), 77.32 (C(CH3)2), 92.37 (=CH), 175.72 (N–C=), 182.95 (COO–).

4-[2-Iodo-2-methyl-2,5-dihydro-3-furanyl]amino)butanoic acid (19)
Yield: 0.203 g (69%); yellow microcrystalline powder; mp 150–155 °C.
IR (KBr): 3304, 3210 (NH, =CH), 1680 (C=O), 1605 cm–1 (C=C).
1H NMR (400.13 MHz, D2O): δ = 0.60 (t, J = 7.12 Hz, 3 H, CH2CH3), 1.36 (s, 3 H, CH3), 1.68–1.69 (m, 3 H, CH2CH2C=O), 2.04 (t, J = 7.12 Hz, 2 H, CH2COO–), 3.09 (t, J = 6.85 Hz, 2 H, NHCH), 4.97 (s, 1 H, =CH).
13C NMR (101.61 MHz, D2O): δ = 16.52 (CH2CH3), 22.30 (CH2), 24.57 (NHCH2CH3), 30.27 (CH2CH2C=O), 44.92 (NHCH), 77.22 (C(CH3)2), 92.37 (=CH), 175.72 (C=NH), 176.53 (N–C=), 182.15 (COO–).
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References


(4) (a) Parsons, J. F.; Xiao, G.; Gilliland, G. L.; Armstrong, R. J. Am. Chem. Soc. 1998, 120, 120.52(3)°, \( V = 1757.2(6) \text{ Å}^3 \), \( b = 1757.2(6) \text{ Å} \), \( c = 9.194(2) \text{ Å} \), \( Z = 8, D_{\text{calcd}} = 1.39 \text{ g/cm}^3 \), reflections with \( |F_o| > 4\sigma(F_o) \) = 1498, parameters refined = 167, \( R = 0.031 \), CCDC 628146 (for 1) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


(15) Crystallographic data: monoclinic, space group C2/c, \( a = 20.712(4) \text{ Å}, b = 9.194(2) \text{ Å}, c = 10.712(2) \text{ Å}, \beta = 120.52(3)° \), \( V = 1757.2(6) \text{ Å}^3 \), \( Z = 8, D_{\text{calcd}} = 1.39 \text{ g/cm}^3 \), reflections with \( |F_o| > 4\sigma(F_o) \) = 1498, parameters refined = 167, \( R = 0.031 \), CCDC 628146 (for 11) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


