Tetrahedron 65 (2009) 9814–9818

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chemo-, regio- and stereospecific addition of amino acids to acylacetylenes: a facile synthesis of new *N*-acylvinyl derivatives of amino acids

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ARTICLE INFO

Article history:
Received 22 June 2009
Received in revised form 24 August 2009
Accepted 17 September 2009
Available online 22 September 2009

Keywords:
Amino acids
Acylacetylenes
N-Acylvinyl derivatives of amino acids
Nucleophilic addition

ABSTRACT

The one-pot reaction of natural amino acids (glycine, β-alanine, γ-aminobutyric and ε-aminocapronic acids, D,L-valine, D,L-leucine, anthranilic acid) with bielectrophilic acylacetylenes proceeds chemo-, regio- and stereospecifically in the presence of NaOH (45–50 °C, 4 h, EtOH–H_2O) to give (after treatment of the reaction mixture with aqueous HCl) *Z*-isomers of *N*-acylvinyl derivatives of amino acids in 87–94% yield.

1. Introduction

Amino acids play a pivotal role in all processes in living cells. They are the starting materials for the synthesis of hormones, vitamins, mediators, pigments, purine and pyrimidine bases and alkaloids. Also, amino acids are used as monomers in protein design. Amino acids are incorporated in many drugs[1] and are building blocks in the synthesis of biologically active compounds.[2] Therefore, the interest in various derivatives of amino acids as well as to the development of facile methods for their preparation remains an important challenge.

One of the promising approaches in this field is the synthesis of new amino acid derivatives containing a highly reactive enaminone moiety. Enaminones are versatile ambident synthetic intermediates,[3] which have been widely used in organic chemistry, for example, for the formation of the C–C bond,[4] in the synthesis of heterocycles,[4a,c,5] as bidentate ligands in complex synthesis[6] and pharmaceutical compounds.[6e,7] The combination of enaminone and amino acid in one molecule may result in a synergism of properties of these important chemical structures and substantially expand the fields of application of functionalized amino acids as effective building blocks for organic and medicinal chemistry.

The reaction of available acylacetylenes[8] with amino acids can be considered as a simple approach to the synthesis of amino acid derivatives bearing enaminone moiety. To our knowledge, the data on such a reaction are lacking in the literature. The only exception is nucleophilic addition of the ε-amino group of *N*-carbobenzyloxy lysine methyl ester to conjugated alkynones.[9]

2. Results and discussion

2.1. Synthesis

In the present work, we have developed a convenient method for the synthesis of amino acid derivatives containing an enaminone moiety. The method is based on the reaction of chemo-, regio- and stereospecific nucleophilic addition of natural amino acids **1**–**7** (glycine **1**, β-alanine **2**, γ-aminobutyric **3** and ε-aminocapronic **4** acids, D,L-valine **5**, D,L-leucine **6**, anthranilic acid **7**) to the β-carbon atom of the C≡C bond of 1-acyl-2-phenylacetylenes **8**, **9**. The reaction was carried out in the presence of NaOH (45–50 °C, 4 h, EtOH–H_2O system) followed by the subsequent treatment of the reaction mixture with aqueous HCl (−10 ÷ −5 °C, 15–20 min) to afford *N*-acylvinyl derivatives of amino acids **10a**–**n** of *Z*-configuration in 87–94% yield (Scheme 1, Table 1, entries 1–14). It is noteworthy that the reaction mixture should be treated with aqueous HCl at lowered temperature. Taking the reaction of glycine **1** with acylacetylenes **8**, **9** as an example, it was shown that the

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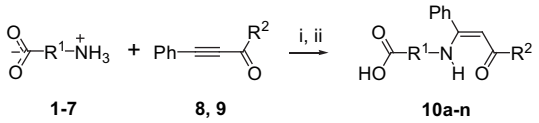
doi:10.1016/j.tet.2009.09.069



Scheme 1.

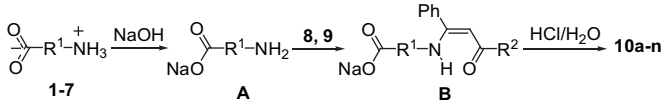
Table 1
Synthesis of amino acid derivatives **10a–n**[a]

Entry	Amino acid	R^1	Acylacetylene	R^2	Adduct	Yield[b] (%)
1	**1**	CH_2	**8**	Ph	**10a**	92
2	**1**	CH_2	**9**		**10b**	91
3	**2**	$(CH_2)_2$	**8**	Ph	**10c**	92
4	**2**	$(CH_2)_2$	**9**		**10d**	90
5	**3**	$(CH_2)_3$	**8**	Ph	**10e**	93
6	**3**	$(CH_2)_3$	**9**		**10f**	94
7	**4**	$(CH_2)_5$	**8**	Ph	**10g**	89
8	**4**	$(CH_2)_5$	**9**		**10h**	90
9	**5**	$(Me_2CH)CH$	**8**	Ph	**10i**	93
10	**5**	$(Me_2CH)CH$	**9**		**10j**	94
11	**6**	$(Me_2CH)CH_2CH$	**8**	Ph	**10k**	92
12	**6**	$(Me_2CH)CH_2CH$	**9**		**10l**	90
13	**7**		**8**	Ph	**10m**	87
14	**7**		**9**		**10n**	87
15	**1**	CH_2	**8**	Ph	**10a**	66[c]
16	**1**	CH_2	**9**		**10b**	67[c]

[a] Reagents and conditions: (i) **1–7** (2.5 mmol), **8**, **9** (2.5 mmol), NaOH (2.5 mmol), H_2O (5 mL), EtOH (5 mL), 45–50 °C, 4 h; (ii) 2 N HCl (2.5 mmol, 1.25 mL), −10 to −5 °C, 15–20 min.
[b] Isolated yield.
[c] In runs 15 and 16, the stage (ii) was carried out at room temperature to give side hydroxypropenones **11a**,**b** (yield ~20%).

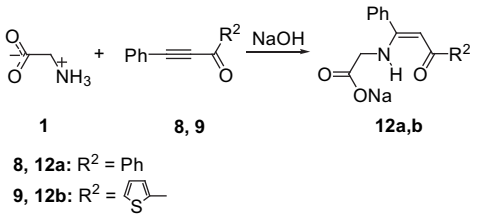
treatment of the reaction mixture at room temperature led to a lower yield of the products **10a**,**b** (up to 66–67%) and formation of 3-hydroxy-1,3-diphenyl-2-propen-1-one **11a** or 3-hydroxy-3-phenyl-1-(2-thienyl)-2-propen-1-one **11b**, respectively (yield ~20%) (Table 1, entries 15, 16).

The synthesis of amino acid derivatives **10a–n** was not realized in the absence of NaOH. The role of a base seems to be in the transformation of the zwitter-ionic form of the amino acid into the sodium salt **A**. Further, the free amino group of the salt reacts with acylacetylenes to deliver sodium salts **B**, which are treated with aqueous HCl to give *N*-acylvinyl derivatives of amino acids **10a–n** bearing a free carboxyl moiety (Scheme 2).



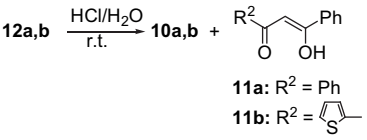
Scheme 2.

The formation of intermediate salts **B** was proved on the example of the reaction of glycine **1** with acylacetylenes **8**, **9**. The process was stopped at the stage of the formation of sodium salts **12a**,**b** of *N*-acylvinyl derivatives of glycine, which were isolated in 93% yield (Scheme 3).



Scheme 3. Reagents and conditions: 1 (2.5 mmol), 8, 9 (2.5 mmol), NaOH (2.5 mmol), H_2O (5 mL), EtOH (5 mL), 45–50 °C, 4 h.

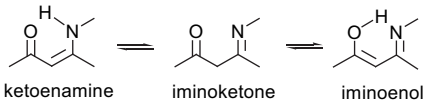
As expected, the treatment of salts **12a**,**b** with aqueous HCl at −10 to −5 °C led to the target compounds **10a**,**b** (yield 91–92%). When performed at room temperature, the reaction was accompanied by the formation of 3-hydroxy-1,3-diphenyl-2-propen-1-one **11a** or 3-hydroxy-3-phenyl-1-(2-thienyl)-2-propen-1-one **11b**, respectively (yield 19.5–20%); the yield of main products **10a**,**b** being ca. 67% (Scheme 4).



Scheme 4. Reagents and conditions: 12a,b (2.5 mmol), H_2O (5 mL), EtOH (5 mL), 2 N HCl (1.25 mL, 2.5 mmol), rt, 20 min.

2.2. Structure determination

The structure of compounds **10a–n** was not unambiguous, since theoretically the enaminone moiety might exist as three tautomers: ketoenamine (HN–C=CH–C=O), iminoketone (–N=C–CH_2–C=O) and iminoenol (–N=C–CH=C–OH)[3,10] (Scheme 5). X-ray diffraction analysis (for **10l**), NMR and IR spectroscopic techniques were applied to assign the structures of the compounds synthesized.



Scheme 5.

X-ray diffraction analysis of compound **10l** shows that it is present as the ketoenamine tautomer with *Z*-configuration of the enaminone fragment and *s-cis*-conformation of the enone moiety of the molecule (Fig. 1). The crystal structure of compound **10l** is formed by one crystallographically independent molecule $C_{19}H_{21}NO_3S$ (Fig. 1), taking a general position in the unit cell. The central fragment of the molecule O(1)C(6)C(7)C(8)N(9) is almost planar with a maximum deviation of the non-hydrogen atom from the plane being 0.04 Å [C(6) atom]. The intermolecular bond distances O(1)···H(9) and O(1)···N(9) are 2.12(3) and 2.755(3) Å, respectively and the angle O(1)···H(9)–N(9) equals 133(2)° (the sum of the van der Waals radii of the oxygen and hydrogen atoms is 2.72 Å[11]). These data are indicative of a probable intramolecular hydrogen bonding NH···O=C.

The bond distances in the central fragment of the molecule O(1)C(6)C(7)C(8)N(9) are O(1)–C(6) 1.265(3) Å, C(6)–C(7) 1.418(3) Å, C(7)–C(8) 1.377(3) Å, C(8)–N(9) 1.333(3) Å, respectively. A comparison of these values with the corresponding pure double or single bond distances[10] points to significant delocalization of

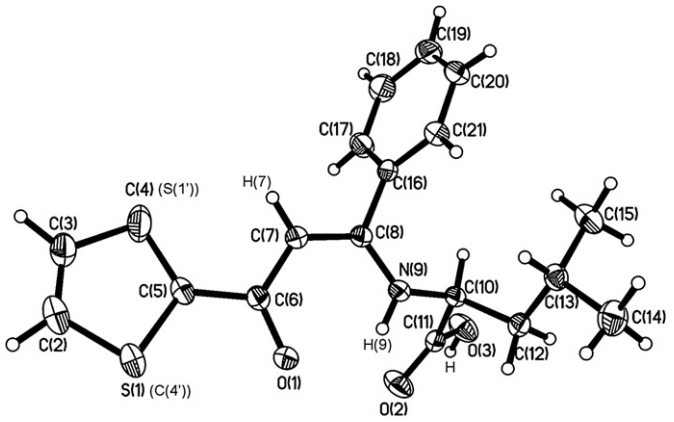


Figure 1. Molecular structure of 4-methyl-2-{[(*Z*)-3-oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}pentanoic acid **10l**.

electrons in the system O=C–C=C–NH, which is closed into a five-membered chelate cycle using the intramolecular hydrogen bond. The same picture was observed for 4-[(2-benzoyl-1-methyl)-vinyleneimino]butyric acid,[12] as well as for the enaminones coordinated with cations of two-valence metals.[6a–c]

In the ^{1}H NMR spectra of compounds **10a**–**n**, the chemical shifts of the vinyl protons and protons of the hydroxyl and amino groups are observed, while in the ^{13}C NMR spectra, typical signals of the carbon atom of the conjugated carbonyl group appear (see Experimental). Deshielding of amine proton (δ_{NH} 11.02–12.97 ppm) as well as its weak sensitivity towards dilution are indicative of the presence of intramolecular hydrogen bonding NH···O=C(R^2). In the IR spectra of compounds **10a**–**n** in the crystalline state, the ν(C=O) bands of the carboxyl groups are presented at 1691–1738 cm^{-1}, whereas the stretching vibrations of the COO$^-$ moiety of the initial amino acids are characterized by intensive bands in the region of 1400–1600 cm^{-1}. A wide absorption band with several peaks at 2500–3100 cm^{-1} corresponds to stretching vibrations of the associated OH and NH groups in these molecules. A band of stretching vibrations of the free NH group is not observed in the spectra of diluted solutions (CCl_4, $CHCl_3$, CH_2Cl_2; $C \sim 10^{-1}$–10^{-3} mol/L) that confirms the participation of this group in intramolecular hydrogen bonding NH···O=C(R^2). The high strength of the latter is also correlated with the decrease (up to ~1550 cm^{-1}) of the stretching vibration frequency of the carbonyl moiety in the spectra of compounds **10a**–**n**.

The spectroscopic parameters of compounds **10a**–**n** both in crystal (IR) and in solution (IR, NMR) were close to those found for compound **101**, indicating their similar structure.

3. Conclusion

In summary, a simple and convenient method for the direct synthesis of new *N*-acylvinyl derivatives of amino acids have been developed on the basis of the reaction of nucleophilic chemo-, regio- and stereospecific addition of natural amino acids to the triple bond of acylacetylenes. The amino acid derivatives synthesized are promising intermediates for the preparation of biologically active compounds, polydentate ligands for the design of metallocomplexes, and reactive building blocks for organic synthesis.

4. Experimental section

4.1. General

The IR spectra were recorded on a Specord 75-IR spectrophotometer from samples prepared as KBr pellets or solutions. The NMR spectra were measured from solutions in $CDCl_3$ or DMSO-d_6 on Bruker DPX-400 and AV-400 spectrometers (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C, and 40.53 MHz for ^{15}N) using hexamethyldisiloxane (^{1}H, ^{13}C) and nitromethane (^{15}N) as internal references. The assignments of ^{1}H and ^{13}C NMR spectra were performed by COSY, NOESY, HSQC, and HMBC experiments.

X-ray diffractions study of **10l** was carried out with an Enraf Nonius CAD-4 diffractometer at room temperature (ω-scan mode, Mo-K$_\alpha$ radiation, graphite monochromator). The crystal structure was solved by direct methods followed with Fourier synthesis using SHELXS-97.[13] All non-hydrogen atoms were refined using anisotropic full-matrix approximation using SHELXL-97.[14] Hydrogen atoms were determined experimentally. S(1) and C(4) atoms are disordered over two sites with occupancies 0.6 and 0.4. Crystallographic data: $C_{19}H_{21}NO_3S$, M=343.43, rhombic, space group $P2_12_12_1$, a=10.324(1) Å, b=11.614(2) Å, c=14.986(2) Å, V=1796.9(4) Å^3, Z=4, D_{cacld}=1.27 g·cm^{-3}, μ=0.196 mm^{-1}, reflections independent −2335, parameters refined −298, R=0.035 for 1700 reflections with [$F_0 > 4\sigma(F_0)$]. CCDC 725302 (for **10l**) 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.

Amino acids, sodium hydroxide are commercial products. Acylacetylenes **8**, **9** were prepared according to a given procedure.[8b]

4.2. General procedure for the preparation of *N*-acylvinyl derivatives of amino acids (10a–n)

The mixture of amino acids **1**–**7** (2.5 mmol), acylacetylenes **8**, **9** (2.5 mmol), sodium hydroxide (2.5 mmol), water (5 mL) and EtOH (5 mL) was stirred at temperature 45–50 °C for 4 h. The reaction mixture was cooled to −10 to −5 °C, 2 N HCl (2.5 mmol, 1.25 mL) was added, and the mixture was stirred for 15–20 min. Next, the temperature was increased up to room, water (30 mL) was added, the mixture was stirred for 1 h, the residue was filtered off, washed with water and dried in vacuo over $CaCl_2$. Synthesized adducts **10a**–**n** were purified by recrystallization.

4.2.1. 2-{[(Z)-3-Oxo-1,3-diphenyl-1-propenyl]amino}acetic acid ***10a*** Yield 647 mg (92%), pale yellow crystals, mp 116–122 °C dec (benzene–hexane); IR ν_{max} (KBr): 2514–3066 (NH, OH), 1736 (COOH), 1560 (C=O) cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 4.05 (br s, 2H, CH_2), 5.87 (s, 1H, CH=), 7.27–7.95 (m, 10H, Ar), 9.96 (br s, 1H, OH), 11.50 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 46.4 (CH_2), 94.8 (CH=); 127.3, 127.7, 128.3, 128.8, 129.9, 131.1, 134.9, 139.6 (Ar); 167.0 (=*C*Ph), 172.4 (COOH), 189.0 (C=O) ppm. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.88; H, 5.52; N, 5.12.

4.2.2. 2-{[(Z)-3-Oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}-acetic acid ***10b***. Yield 652 mg (91%), yellow–yellow crystals, mp 97–100 °C dec (benzene–hexane); IR ν_{max} (KBr): 2534–3062 (NH, OH), 1735 (COOH), 1562 (C=O) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 3.85 (br s, 2H, CH_2), 5.65 (s, 1H, CH=), 7.02–7.56 (m, 8H, Ar, HetAr), 11.07 (br s, 1H, NH); ^{13}C NMR δ ($CDCl_3$): 46.5 (CH_2), 93.6 (CH=); 127.4, 128.1, 128.9, 129.5, 131.7, 133.2, 135.3, 147.5 (Ar, HetAr); 165.6 (=*C*Ph), 171.2 (COOH), 181.1 (C=O) ppm. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.81; H, 4.59; N, 4.98; S, 11.32.

4.2.3. 3-{[(Z)-3-Oxo-1,3-diphenyl-1-propenyl]amino}propanoic acid ***10c***. Yield 680 mg (92%), pale yellow crystals, mp 168–172 °C dec (MeCN); IR ν_{max} (KBr): 2520–3056 (NH, OH), 1714 (COOH), 1568 (C=O) cm^{-1}; ^{1}H NMR δ (DMSO-d_6): 2.46 (m, 2H, CH_2), 3.31 (m, 2H, CH_2), 5.68 (s, 1H, CH=), 7.35–7.82 (m, 10H, Ar), 11.31 (br s, 1H, NH)., 12.40 (br s, 1H, OH) ppm; ^{13}C NMR δ (DMSO-d_6): 35.2 (CH_2), 49.6

(CH_2), 92.9 (CH=); 127.1, 128.0, 128.7, 129.0, 130.0, 131.2, 135.4, 140.1 (Ar); 166.4 (=*C*Ph), 172.9 (COOH), 187.0 (C=O) ppm. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.52; H, 5.97; N, 4.87.

4.2.4. 3-{[(Z)-3-Oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}propanoic acid ***10d***. Yield 680 mg (90%), yellow crystals, mp 150–156 °C dec (MeCN); IR ν_{max} (KBr): 2518–3045 (NH, OH), 1718 (COOH), 1535 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 2.69 (m, 2H, CH_2), 3.52 (m, 2H, CH_2), 5.64 (s, 1H, CH=), 7.03–7.57 (m, 8H, Ar, HetAr), 9.52 (br s, 1H, OH), 11.21 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 35.1 (CH_2), 40.6 (CH_2), 94.0 (CH=); 127.7, 127.9, 128.6, 128.8, 128.9, 130.4, 135.2, 146.1 (Ar, HetAr); 167.2 (=*C*Ph), 173.9 (COOH), 181.2 (C=O) ppm. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.81; H, 5.07; N, 4.69; S, 10.43.

4.2.5. 4-{[(Z)-3-Oxo-1,3-diphenyl-1-propenyl]amino}butanoic acid ***10e***. Yield 720 mg (93%), pale yellow crystals, mp 118–124 °C dec (MeCN); IR ν_{max} (KBr): 2519–3058 (NH, OH), 1723 (COOH), 1569 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.89 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 3.29 (m, 2H, CH_2), 5.76 (s, 1H, CH=), 7.27–7.89 (m, 10H, Ar), 9.46 (br s, 1H, OH), 11.42 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 25.8 (CH_2); 30.9 (CH_2); 43.9 (CH_2); 93.8 (CH=); 127.1, 127.7, 128.2, 128.6, 129.6, 130.8, 135.4, 140.0 (Ar); 167.2 (=*C*Ph), 177.1 (COOH), 188.4 (C=O) ppm. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.52; H, 6.44; N, 4.87.

4.2.6. 4-{[(Z)-3-Oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}butanoic acid ***10f***. Yield 740 mg (94%), yellow crystals, mp 119–123 °C dec (benzene–hexane); IR ν_{max} (KBr): 2507–3097 (NH, OH), 1733 (COOH), 1535 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.88 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 5.65 (s, 1H, CH=), 7.04–7.55 (m, 8H, Ar, HetAr), 9.23 (br s, 1H, OH), 11.05 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 25.7 (CH_2), 30.8 (CH_2), 43.9 (CH_2), 93.4 (CH=); 127.7, 127.7, 127.9, 128.6, 129.6, 130.2, 135.2, 146.1 (Ar, HetAr); 166.9 (=*C*Ph), 177.3 (COOH), 181.3 (C=O) ppm. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.59; H, 5.68; N, 4.60; S, 10.09.

4.2.7. 6-{[(Z)-3-Oxo-1,3-diphenyl-1-propenyl]amino}hexanoic acid ***10g***. Yield 750 mg (89%), pale yellow crystals, mp 104–108 °C dec (benzene–hexane); IR ν_{max} (KBr): 2580–3059 (NH, OH), 1719 (COOH), 1565 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.37 (m, 2H, CH_2), 1.58 (m, 4H, 2 CH_2), 2.31 (m, 2H, CH_2), 3.21 (m, 2H, CH_2), 5.72 (s, 1H, CH=), 7.24–7.86 (m, 10H, Ar), 9.63 (br s, 1H, OH), 11.41 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 24.3 (CH_2), 26.2 (CH_2), 30.4 (CH_2), 33.8 (CH_2), 44.6 (CH_2), 93.5 (CH=); 127.1, 127.7, 128.3, 128.6, 129.6, 130.8, 135.7, 140.3 (Ar); 167.2 (=*C*Ph), 178.5 (COOH), 188.4 (C=O) ppm. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.57; H, 6.51; N, 4.32.

4.2.8. 6-{[(Z)-3-Oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}hexanoic acid ***10h***. Yield 770 mg (90%), yellow wax-like solid; IR ν_{max} (KBr): 2500–3071 (NH, OH), 1731 (COOH), 1565 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.35 (m, 2H, CH_2), 1.55 (m, 4H, 2 CH_2), 2.28 (m, 2H, CH_2), 3.16 (m, 2H, CH_2), 5.58 (s, 1H, CH=), 6.99–7.50 (m, 8H, Ar, HetAr), 9.67 (br s, 1H, OH), 11.02 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 24.3 (CH_2), 26.2 (CH_2), 30.4 (CH_2), 33.8 (CH_2), 44.7 (CH_2), 93.1 (CH=); 127.7, 127.8, 128.6, 129.6, 130.1, 135.5, 147.0 (Ar, HetAr); 166.9 (=*C*Ph), 178.7 (COOH), 181.2 (C=O) ppm. Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.77; H, 6.35; N, 4.23; S, 9.14.

4.2.9. 3-Methyl-2-{[(Z)-3-oxo-1,3-diphenyl-1-propenyl]amino}butanoic acid ***10i***. Yield 750 mg (93%), yellow crystals, mp 174–177 °C dec (MeCN); IR ν_{max} (KBr): 2518–3060 (NH, OH), 1718 (COOH), 1569 (C=O) cm^{-1}; ^1H NMR δ (DMSO-d_6): 0.84 (d, 3H, CH_3), 0.94 (d, 3H, CH_3), 2.11 (m, 1H, CH), 3.84 (m, 1H, CH), 5.84 (s, 1H, CH=), 7.42–7.92 (m, 10H, Ar), 11.53 (br s, 1H, NH), 13.04 (br s, 1H, OH) ppm; ^{13}C NMR δ (DMSO-d_6): 17.2 (CH_3), 18.9 (CH_3), 31.2 (CH), 62.2 (CH), 93.5 (CH=); 126.9, 127.6, 128.3, 128.8, 129.8, 131.1, 134.8, 139.4 (Ar), 166.0 (=*C*Ph), 172.2 (COOH), 187.4 (C=O) ppm. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.57; H, 6.44; N, 4.47.

4.2.10. 3-Methyl-2-{[(Z)-3-oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}butanoic acid ***10j***. Yield 770 mg (94%), yellow crystals, mp 167–169 °C dec (MeCN); IR ν_{max} (KBr): 2527–3080 (NH, OH), 1726 (COOH), 1568 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.95 (d, 3H, CH_3), 1.06 (d, 3H, CH_3), 2.26 (m, 1H, CH), 3.94 (m, 1H, CH), 5.73 (s, 1H, CH=), 7.05–7.61 (m, 8H, Ar, HetAr), 9.59 (br s, 1H, OH), 11.18 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 17.9 (CH_3), 19.6 (CH_3), 32.1 (CH), 63.1 (CH), 95.1 (CH=); 128.2, 128.9, 129.2, 130.2, 131.0, 135.4, 146.9 (Ar, HetAr); 166.5 (=*C*Ph), 176.6 (COOH), 182.4 (C=O) ppm. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.39; H, 5.89; N, 4.47; S, 9.66.

4.2.11. 4-Methyl-2-{[(Z)-3-oxo-1,3-diphenyl-1-propenyl]amino}pentanoic acid ***10k***. Yield 780 mg (92%), yellow crystals, mp 140–146 °C dec (MeCN); IR ν_{max} (KBr): 2523–3073 (NH, OH), 1722 (COOH), 1567 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.68 (d, 3H, CH_3), 0.84 (d, 3H, CH_3), 1.73 (m, 3H, CH_2, CH), 4.03 (m, 1H, CH), 5.79 (s, 1H, CH=), 7.21–7.87 (m, 10H, Ar), 9.39 (br s, 1H, OH), 11.38 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 21.5 (CH_3), 22.8 (CH_3), 24.6 (CH), 42.5 (CH_2), 55.9 (CH), 94.7 (CH=); 127.3, 127.7, 128.2, 128.7, 129.8, 131.1, 139.3, 139.7 (Ar); 166.2 (=*C*Ph), 176.6 (COOH), 189.1 (C=O) ppm. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.57; H, 6.80; N, 4.32.

4.2.12. 4-Methyl-2-{[(Z)-3-oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}pentanoic acid ***10l***. Yield 770 mg (90%), yellow crystals, mp 138–142 °C dec (MeCN); IR ν_{max} (KBr): 2583–3107 (NH, OH), 1734 (COOH), 1569 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.73 (d, 3H, CH_3), 0.89 (d, 3H, CH_3), 1.73 (m, 3H, CH_2, CH), 4.04 (m, 1H, CH), 5.70 (s, 1H, CH=), 7.05–7.59 (m, 8H, Ar, HetAr), 10.40 (br s, 1H, OH), 11.03 (br s, 1H, NH) ppm; ^{13}C NMR δ ($CDCl_3$): 21.4 (CH_3), 22.8 (CH_3), 24.5 (CH), 42.4 (CH_2), 56.0 (CH), 94.6 (CH=); 127.7, 127.8, 128.6, 128.8, 129.9, 130.7, 135.1, 146.5 (Ar, HetAr); 166.0 (=*C*Ph), 177.0 (COOH), 182.0 (C=O) ppm; ^{15}N NMR δ ($CDCl_3$):=−269.4 ppm ($^1J_{NH}$ 90.5 Hz). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 65.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 65.39; H, 6.33; N, 4.01; S, 9.68.

4.2.13. 2-{[(Z)-3-Oxo-1,3-diphenyl-1-propenyl]amino}benzenecarboxylic acid ***10m***. Yield 750 mg (87%), yellow crystals, mp 193–197 °C dec (MeCN); IR ν_{max} (KBr): 2520–3059 (NH, OH), 1691 (COOH), 1559 (C=O) cm^{-1}; ^1H NMR δ (DMSO-d_6): 6.33 (s, 1H, CH=), 6.46–8.07 (m, 14H, Ar), 12.97 (s, 1H, NH), 13.36 (br s, 1H, OH) ppm; ^{13}C NMR δ (DMSO-d_6): 100.3 (CH=); 122.0, 123.3, 125.1, 127.8, 128.8, 129.0, 129.3, 130.4, 131.5, 132.2, 132.4, 136.5, 139.7, 141.1 (Ar); 158.6 (=*C*Ph), 168.0 (COOH), 188.8 (C=O) ppm. Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.82; H, 5.09; N, 4.22.

4.2.14. 2-{[(Z)-3-Oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}benzenecarboxylic acid ***10n***. Yield 760 mg (87%), yellow crystals, mp 176–180 °C dec (MeCN); IR ν_{max} (KBr): 2534–3080 (NH, OH), 1692 (COOH), 1557 (C=O) cm^{-1}; ^1H NMR δ (DMSO-d_6): 6.02 (s, 1H, CH=), 6.35–7.99 (m, 12H, Ar, HetAr), 12.89 (s, 1H, NH) ppm; ^{13}C NMR δ (DMSO-d_6): 100.4 (CH=); 122.2, 124.1, 124.5, 127.5, 128.0, 128.4, 129.2, 129.4, 131.1, 131.7, 132.1, 136.0, 141.3 (Ar, HetAr); 158.0 (=*C*Ph), 168.8 (COOH), 181.6 (C=O) ppm. Anal. Calcd

for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01; S, 9.18. Found: C, 68.97; H, 4.15; N, 4.29; S, 9.02.

4.3. Synthesis of sodium salts of *N*-acylvinyl derivatives of glycine (12a,b)

Typical procedure. The mixture of amino acid **1** (2.5 mmol), acylacetylene **8**, **9** (2.5 mmol), sodium hydroxide (2.5 mmol), water (5 mL) and EtOH (5 mL) was stirred at temperature 45–50 °C for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from the mixture EtOH–MeCN, 1:2.

*4.3.1. Sodium salt of 2-{[(Z)-3-oxo-1,3-diphenyl-1-propenyl]amino}-acetic acid **12a**.* Yield 700 mg (93%), white powder, mp 203–207 °C dec (EtOH–MeCN); IR ν_{max} (KBr): 3059 (NH), 1562, 1595 (C=O) cm^{-1}; ^1H NMR δ (DMSO-d_6): 3.33 (br s, 2H, CH_2), 5.63 (s, 1H, CH=), 7.27–7.86 (m, 10H, Ar), 11.31 (br s, 1H, NH) ppm; ^{13}C NMR δ (DMSO-d_6): 49.5 (CH_2); 91.3 (CH=); 126.6, 127.5, 128.1, 128.4, 129.7, 130.3, 136.2, 140.4 (Ar); 164.5 (=*C*Ph); 170.2 (COONa); 185.5 (C=O) ppm. Anal. Calcd for $C_{17}H_{14}NNaO_3$: C, 67.32; H, 4.65; N, 4.62; Na, 7.58. Found: C, 67.12; H, 4.95; N, 4.91; Na, 7.77.

*4.3.2. Sodium salt of 2-{[(Z)-3-oxo-1-phenyl-3-(2-thienyl)-1-propenyl]amino}acetic acid **12b**.* Yield 720 mg (93%), light-yellow powder, mp 184–188 °C dec (EtOH–MeCN); IR ν_{max} (KBr): 3085 (NH), 1543, 1596 (C=O) cm^{-1}; ^1H NMR δ (DMSO-d_6): 3.39 (br s, 2H, CH_2), 5.56 (s, 1H, CH=), 7.08–7.68 (m, 8H, Ar, HetAr), 10.97 (br s, 1H, NH) ppm; ^{13}C NMR δ (DMSO-d_6): 49.6 (CH_2); 91.1 (CH=); 127.3, 127.6, 128.1, 128.5, 129.4, 130.2, 136.1, 147.9 (Ar, HetAr); 164.3 (=*C*Ph); 170.1 (COONa); 179.2 (C=O) ppm. Anal. Calcd for $C_{15}H_{12}NNaO_3S$: C, 58.24; H, 3.91; N, 4.53; Na, 7.43; S, 10.37. Found: C, 58.53; H, 3.93; N, 4.79; Na, 7.77; S, 10.58.

4.4. Reaction of salts (12a,b) with the system HCl–H_2O at room temperature

Salt **12a**,**b** (2.5 mmol) was dissolved in a mixture of EtOH (5 mL) and water (5 mL), then 2 N HCl (2.5 mmol, 1.25 mL) was added, and the mixture was stirred for 20 min at room temperature. Next, water was added (30 mL) and the mixture was stirred for 1 h. The residue was filtered off, washed with water and dried in vacuo over $CaCl_2$. The crude was boiled in hexane (40 mL) for 10 min and the hot suspension was filtered. Insoluble fraction remained on filter was the corresponding adduct **10a**,**b** (yield 64–67%). Mother solution was cooled up to 5–10 °C, the residue precipitated was filtered to give the corresponding hydroxypropenone **11a**,**b**.

*4.4.1. (Z)-3-Hydroxy-1,3-diphenyl-2-propen-1-one **11a**.* Yield 112 mg (20%), colourless needles, mp 72–74 °C (lit.[15] mp 72–73 °C); IR ν_{max} (KBr): 3057 (OH), 1561 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 6.88 (s, 1H, CH=), 7.27–8.02 (m, 10H, Ar), 16.87 (s, 1H, OH) ppm; ^{13}C NMR δ ($CDCl_3$): 93.1 (CH=); 127.1, 128.7, 132.4, 135.6 (Ar); 176.5 (=*C*Ph); 185.7 (C=O) ppm. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.12; H, 5.36.

*4.4.2. (Z)-3-Hydroxy-3-phenyl-1-(2-thienyl)-2-propen-1-one **11b**.* Yield 112 mg (19.5%), colourless needles, mp 74–76 °C; IR ν_{max} (KBr): 3091 (OH), 1561 (C=O) cm^{-1}; ^1H NMR δ ($CDCl_3$): 6.66 (s, 1H, CH=), 7.14–7.93 (m, 8H, Ar, HetAr), 16.28 (s, 1H, OH) ppm; ^{13}C NMR δ ($CDCl_3$): 93.0 (CH=); 128.2, 128.6, 130.2, 132.1, 132.5, 134.4, 142.2 (Ar, HetAr); 180.7 (=*C*Ph); 182.8 (C=O) ppm. Anal. Calcd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.92. Found: C, 67.45; H, 4.55; S, 13.74.

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