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*Mendeleev Commun.*, 2012, **22**, 314–316
Mendeleev Communications

# Modification of γ-aminobutyric acid with acylacetylenes: stereoselective C-vinylation of the primary adducts and transformation to acylpyridines

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DOI: 10.1016/j.mencom.2012.11.012

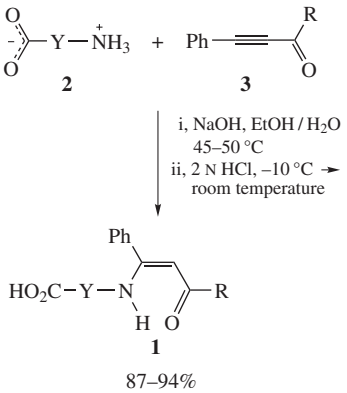
**Primary N–C adducts of γ-aminobutyric acid (GABA) to acylacetylenes undergo mild stereoselective C-vinylation by another acylacetylene molecule to afford (2*E*,4*Z*)-4-acyl-5-aminoalka-2,4-dien-1-one-type diadducts in 83–92% yields. The latter cyclize to acylpyridines in up to 89% yields with the C–N bond cleavage in the GABA moiety and elimination of γ-butyrolactone.**

Amino acids are the principal starting materials for the synthesis of hormones, vitamins, purine and pyrimidine bases, alkaloids and many other key biologically important substances.[1,2] One of the major trends in the drug design is the modification of essential amino acids with additional pharmacophoric groups into their molecules. A convenient approach in this line involves the reactions of nucleophilic addition of amino acids to activated acetylenes.[3]

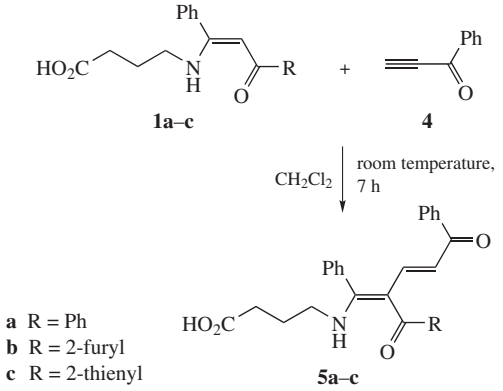
Recently,[4] we have synthesized a new family of unnatural amino acids **1** containing pharmacophoric enaminone function by mild stereoselective N-vinylation of essential amino acids **2** with acylacetylenes **3** (Scheme 1). Amino enones of type **1** are versatile ambident synthetic building blocks, which are widely used in organic sysnthesis.[5–8]

Aiming at the synthesis of new derivatives of γ-aminobutyric acid (GABA), a neurotransmitter in the central nervous system of humans, here we report on the reaction of selected mono-adducts **1a–c** with benzoylacetylene **4**, which under mild conditions ($CH_2Cl_2$, room temperature, 7 h) proceeds as regio- and *E*-stereoselective C-vinylation at the $C_{sp^2}$–H bond to afford diadducts **5a–c**, 4-{[(1*Z*,3*E*)-5-oxo-1,3-pentadienyl]amino}butanoic acids, in 83–92% yields (Scheme 2).

Adducts **5a–c** were isolated as free amino acids, however, not in expected zwitterionic forms. In the IR spectra of compounds **5a–c** in the crystalline state, the $\nu_{C=O}$ bands of the carboxylic groups are presented at 1728–1730 $cm^{-1}$, whereas the stretching vibration of the $COO^-$ moiety of the initial γ-aminobutyric acid




**Scheme 1**




**Scheme 2**

is characterized by intense band at 1580 $cm^{-1}$. Absorption bands of the carbonyl groups are observed in the region 1645–1647 $cm^{-1}$ [for the Ph–C(O)–CH=CH fragment] and 1593–1597 $cm^{-1}$ [for carbonyl moieties bounded by the intramolecular hydrogen bonding NH···O=C(R)] that is typical of similar α,β-unsaturated systems.[9] The structure of compounds **5a–c** was proved by $^1H$, $^{13}C$ and $^{15}N$ NMR spectroscopy.† In the $^1H$ NMR spectra, the signals

† IR spectra (KBr pellets) were recorded on a Bruker IFS25 spectrophotometer. NMR spectra ($CDCl_3$) were measured on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for $^1H$, 100.6 MHz for $^{13}C$, and 40.5 MHz for $^{15}N$) using HMDS ($^1H$, $^{13}C$) and nitromethane ($^{15}N$) as internal references. $^1H$–$^1H$ 2D homonuclear (COSY and NOESY) and $^1H$–$^{13}C$ 2D heteronuclear (HSQC and HMBC) experiments were used for the assignment of the carbon and proton resonances. The values of characteristic signals for $^{15}N$ atom were derived from 2D $^1H$–$^{15}N$ HMBC spectra.

*Synthesis of compounds* **5a–c**. A mixture of **1a–c** (1 mmol) and benzoylacetylene **4** (1.2 mmol) in $CH_2Cl_2$ (10 ml) was stirred at room temperature for 7 h. The crude product mixture was separated by column chromatography ($SiO_2$, EtOAc–hexane, 4:1).

*4-{[(1Z,3E)-2-Benzoyl-5-oxo-1,5-diphenylpenta-1,3-dienyl]amino}-butanoic acid* **5a**: yield 92%, yellow crystals, mp 40–42 °C. IR ($\nu$/$cm^{-1}$): 3250–2928 (NH, OH), 1730 (COOH), 1645 (C=O), 1594 (C=O). $^1H$ NMR, $\delta$: 1.84 (m, 2H, $CH_2$), 2.35 (m, 2H, $CH_2$), 3.15 (m, 2H, $CH_2$), 5.76 (d, 1H, O=C–CH=, $^3J_{HH}$ 15.6 Hz), 7.17–7.60 (m, 16H, Ar, =C–CH=), 9.45 (br. s, 1H, OH), 12.02 (br. s, 1H, NH). $^{13}C$ NMR, $\delta$: 25.5, 31.3, 44.6, 105.0, 117.0, 127.8, 127.9, 128.0, 128.4, 129.1, 129.4, 129.8, 130.6, 131.6, 132.8, 139.0, 141.6, 145.2, 169.9, 176.7, 189.1, 197.0. $^{15}N$ NMR, $\delta$: –253.9. Found (%): C, 76.84; H, 5.64; N, 3.01. Calc. for $C_{28}H_{25}NO_4$ (%): C, 76.52; H, 5.73; N, 3.19.

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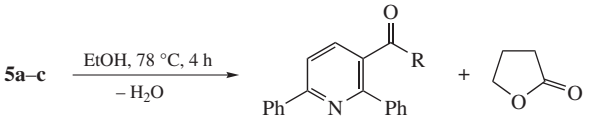
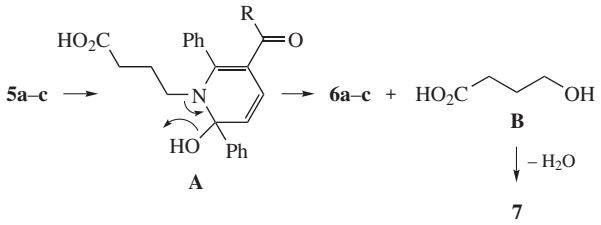
of the NH and OH functions (11.81–12.16 and 8.68–9.45 ppm, respectively) are detectable. The values of chemical shifts of hydrogen and nitrogen atoms in the amino acid counterpart of compounds **5a–c** are in good agreement with the spectral data of γ-aminobutanoic acid obtained under the conditions excluding the formation of zwitterionic forms.[10]

Compounds **5a–c** on heating in ethanol (78 °C, 4 h) underwent dehydrocyclization to give 3-acyl-2,6-diphenylpyridines **6a–c** (82–89% yields)‡ and γ-butyrolactone **7** (Scheme 3). Their structure was established ($^1$H NMR) by the characteristic pyridine doublets at 7.80–7.89 and 7.96–8.03 ppm ($^3J$ 7.4–8.1 Hz) and the $CH_2$-proton signals at 2.28, 2.48 and 4.35 ppm of γ-butyrolactone **7**.




**Scheme 3**

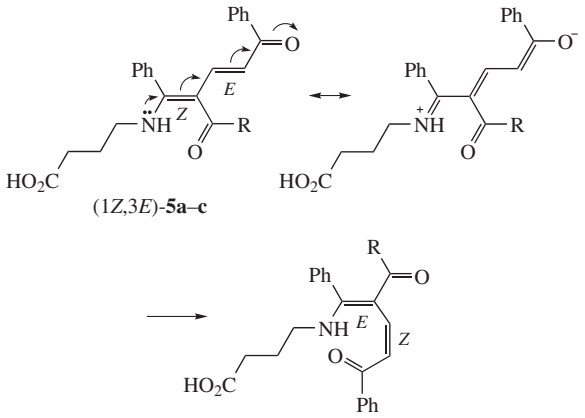
Noteworthy, the pyridine formation is accompanied by the unexpected cleavage of the C–N bond, unusual for GABA and generally for alkylamines. Apparently, the both processes are interrelated and proceed as outlined in Scheme 4. The dienone carbonyl group is intramolecularly attacked by the amino group to close dihydropyridine cycle **A**, which further is aromatized to acylpyridines *via* the elimination of 4-hydroxybutyric acid **B** (giving finally γ-butyrolactone **7**).




**Scheme 4**

For such a cyclization it is necessary that adduct **5**, initially of the *Z*,*E*-configuration, would accept the *E*,*Z*-configuration. This *E*/*Z*-isomerization is facilitated by the deep push-pull conjugation of the amino group with the dienone system up to the transfer of lone electron pair on the carbonyl oxygen. Owing to this, the free rotation around the loosen double bond becomes possible (Scheme 5). Significant decrease of the rotation barrier around the polarized double bond (up to 60–90 kJ mol$^{-1}$) has been observed for many push-pull ethylenes.[11]

In the primary adducts **1** the C–N bond cleavage in the γ-aminobutyric moiety did not take place even on prolonged (15 h) refluxing in EtOH. It follows unambiguously that for such bond cleavage, the presence of aminodienone system in the molecules is required.




**Scheme 5**

In conclusion, a facile and convenient approach to novel polyfunctional derivatives of GABA, representing a synthetic hybrid of pharmacophoric fragments of the amino acid, enaminones and chalcones,[12] has been developed. The compounds synthesized can also be considered as merocyanine analogues, 'donor–acceptor-substituted polyenes', which find applications in the design of new optoelectronic materials, information carriers, electroluminescent devices as well as probes and markers for chemical analysis, biology and medicine.[13]

*4-{[(1Z,3E)-2-(2-Furylcarbonyl)-5-oxo-1,5-diphenylpenta-1,3-dienyl]-amino}butanoic acid* **5b**: yield 83%, yellow crystals, mp 38–40 °C. IR (ν/cm$^{-1}$): 3127–2927 (NH, OH), 1728 (COOH), 1646 (C=O), 1597 (C=O). $^1$H NMR, δ: 1.85 (m, 2H, $CH_2$), 2.34 (m, 2H, $CH_2$), 3.14 (m, 2H, $CH_2$), 5.83 (d, 1H, O=C–CH=, $^3J_{HH}$ 15.4 Hz), 6.48 (dd, 1H, $H^4_{fur}$, $^3J_{HH}$ 3.4 Hz, $^3J_{HH}$ 1.5 Hz), 7.01 (dd, 1H, $H^3_{fur}$, $^3J_{HH}$ 3.4 Hz, $^4J_{HH}$ 0.8 Hz), 7.35–7.84 (m, 12H, Ar, $H^5_{fur}$, =C–CH=), 9.20 (br. s, 1H, OH), 12.16 (br. s, 1H, NH). $^{13}$C NMR, δ: 25.2, 30.8, 44.2, 111.7, 117.1, 117.5, 127.8, 128.0, 129.4, 129.9, 131.6, 133.0, 138.7, 143.9, 145.0, 152.7, 168.9, 176.5, 181.5, 189.3. $^{15}$N NMR, δ: –252.3. Found (%): C, 72.87; H, 5.44; N, 3.22. Calc. for $C_{26}H_{23}NO_5$ (%): C, 72.71; H, 5.40; N, 3.26.

*4-{[(1Z,3E)-5-Oxo-1,5-diphenyl-2-(2-thienylcarbonyl)penta-1,3-dienyl]-amino}butanoic acid* **5c**: yield 90%, yellow crystals, mp 42–44 °C. IR (ν/cm$^{-1}$): 3266–2930 (NH, OH), 1728 (COOH), 1647 (C=O), 1593 (C=O). $^1$H NMR, δ: 1.79 (m, 2H, $CH_2$), 2.27 (m, 2H, $CH_2$), 3.09 (m, 2H, $CH_2$), 5.90 (d, 1H, O=C–CH=, $^3J_{HH}$ 15.5 Hz), 7.02–7.78 (m, 14H, Ar, HetAr, =C–CH=), 8.68 (br. s, 1H, OH), 11.81 (br. s, 1H, NH). $^{13}$C NMR, δ: 25.4, 31.2, 44.4, 105.0, 117.1, 127.7, 128.0, 128.1, 129.5, 129.8, 130.1, 131.3, 131.8, 132.1, 133.2, 138.9, 145.0, 145.5, 168.6, 177.0, 187.0, 189.3. Found (%): C, 71.26; H, 5.44; N, 3.22; S, 7.61. Calc. for $C_{26}H_{23}NO_4S$ (%): C, 70.09; H, 5.20; N, 3.14; S, 7.20.

‡ *Synthesis of 3-acyl-2,6-diphenylpyridines* **6a–c**. Compound **5a–c** (0.5 mmol) was dissolved in EtOH (10 ml) and stirred at 78 °C for 4 h. The solvent was half-evaporated, the concentrate was kept at ~0 °C for one day, the crystals precipitated were filtered off and dried *in vacuo*.

*3-Benzoyl-2,6-diphenylpyridine* **6a**: yield 83%, colourless crystals, mp 102–104 °C. IR (ν/cm$^{-1}$): 1664 (C=O), 1569–1595 (C=C, C=N). $^1$H NMR, δ: 7.86 (d, 1H, $H^5_{pyr}$, $^3J_{HH}$ 7.4 Hz), 7.96 (d, 1H, $H^4_{pyr}$, $^3J_{HH}$ 7.4 Hz), 7.26–7.72, 8.22 (m, 15H, Ar). $^{13}$C NMR, δ: 117.9, 127.3, 128.3, 128.4, 128.9, 129.5, 129.8, 129.9, 132.6, 133.3, 136.9, 138.3, 138.5, 139.6, 157.3, 158.1, 197.6. $^{15}$N NMR, δ: –72.5. Found (%): C, 85.63; H, 5.43; N, 4.02. Calc. for $C_{24}H_{17}NO$ (%): C, 85.94; H, 5.11; N, 4.18.

*3-(2-Furylcarbonyl)-2,6-diphenylpyridine* **6b**: yield 89%, yellow wax-like solid, mp 38–40 °C. IR (ν/cm$^{-1}$): 1648 (C=O), 1549–1582 (C=C, C=N). $^1$H NMR, δ: 6.33 (dd, 1H, $H^4_{fur}$), 6.85 (dd, 1H, $H^3_{fur}$), 7.80 (d, 1H, $H^5_{pyr}$, $^3J_{HH}$ 8.1 Hz), 7.96 (d, 1H, $H^4_{pyr}$, $^3J_{HH}$ 8.1 Hz), 7.26–7.67, 8.16 (m, 11H, Ar, $H^5_{fur}$). $^{13}$C NMR, δ: 112.4, 117.9, 120.5, 127.4, 128.4, 128.9, 129.3, 129.8, 131.7, 138.3, 138.4, 139.8, 147.3, 152.3, 157.3, 158.3, 184.5. $^{15}$N NMR, δ: –71.8. Found (%): C, 81.44; H, 4.62; N, 4.13. Calc. for $C_{22}H_{15}NO_2$ (%): C, 81.21; H, 4.65; N, 4.30.

*3-(2-Thienylcarbonyl)-2,6-diphenylpyridine* **6c**: yield 82%, colourless crystals, mp 128–130 °C. IR (ν/cm$^{-1}$): 1646 (C=O), 1552–1584 (C=C, C=N). $^1$H NMR, δ: 6.98 (dd, 1H, $H^4_{thienyl}$), 7.89 (d, 1H, $H^5_{pyr}$, $^3J_{HH}$ 8.1 Hz), 8.03 (d, 1H, $H^4_{pyr}$, $^3J_{HH}$ 8.1 Hz), 7.34–7.79, 8.26 (m, 12H, Ar, $H^3_{thienyl}$, $H^5_{thienyl}$). $^{13}$C NMR, δ: 117.8, 127.3, 128.2, 128.4, 128.9, 129.0, 129.4, 129.8, 132.6, 135.1, 135.3, 137.9, 138.4, 139.6, 144.2, 156.8, 158.2, 189.5. $^{15}$N NMR, δ: –66.6. Found (%): C, 77.49; H, 4.78; N, 4.38; S, 9.08. Calc. for $C_{22}H_{15}NOS$ (%): C, 77.39; H, 4.43; N, 4.10; S, 9.39.

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*Received: 3rd May 2012; Com. 12/3919*