Synthesis and transformations of some 1,2,4-trisubstituted pyrroles

Jarmila Štetinová*, Viktor Milataa, Naďa Prónayováb, Ognyan Petrovc, and Alexander Bartoviča**

*a Department of Organic Chemistry, b Central Laboratory of Chemical Technics, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovak Republic
c Department of Organic Chemical Technology, Faculty of Chemistry, University of Sofia, BG-1126 Sofia, Bulgaria

E-mail: jarmila.stetinova@stuba.sk

Dedicated to Professor Lubor Fišera on his 60th birthday
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Abstract
Alkyl 1-(2-alkoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylates 3a and 3b (alkyl = Me, Et), prepared from the corresponding alkyl 4-formyl-1H-pyrrole-2-carboxylates 2a and 2b, have been modified to other derivatives of the same structural pattern. A series of β-pyrrolylalkenes 4–8 was obtained from pyrrole 3b and various C–acids. Derivatives 2 and 3 have been also used as synthons for polysubstituted 4-(1H-pyrrol-3-yl)-1,4-dihydropyridines 9–12 under the conditions of the standard and the modified Hantzsch’s dihydropyridine synthesis or by regioselective alkylation of the 1,4-dihydropyridine skeleton.

Keywords: Alkyl 1-(2-alkoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylates, β-pyrrolylalkenes, 4-(1H-pyrrol-3-yl)-1,4-dihydropyridines, regioselective alkylation

Introduction
Just like polysubstituted pyrroles, pyrrolecarboxylic acids and their derivatives also display a broad spectrum of bioactivity. Many of the latter compounds show appreciable antibacterial,1 and antitumor2 activity. Some of them are antibiotics,3 their suitably modified derivatives,4 effective anticonvulsants,5 and anti-inflammatory drugs.6 They can be used in the treatment of osseous diseases.7 The aim of this work is the synthesis of selected 1,2,4-trisubstituted pyrroles –

** present address: Synkola, Mlynská dolina, areál PvF UK, SK-842 15 Bratislava, Slovak Republic
alkyl 1-(2-alkoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylates 3 - and their transformation to a series of \( \beta \)-pyrrolylalkenes 4–8 and polysubstituted 4-(1H-pyrrol-3-yl)-1,4-dihydropyridines 9–12. The specific biological testing of novel derivatives is planned. The alkenes 4–8 are in fact the substituted C-vinylpyrroles – extensively studied building blocks, widely employed in the synthesis of diverse representatives the pyrrole family, especially condensed heterocycles.\(^8\)

### Results and Discussion

The synthesis of compounds of the general formula 3 (Scheme 1) starts from pyrrole and proceeds via 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone and its alcoholysis to the alkyl 1H-pyrrole-2-carboxylates 1,\(^9,10\) followed by the selective Friedel–Crafts formylation to the position 4 of the pyrrole ring.\(^11,12\) The formyl esters 2a and 2b were finally regioselectively alkylated at nitrogen atom with alkyl bromoacetates in the presence of potassium tert-butoxide and tetrabutylammonium bromide in dimethylformamide furnishing the 1,2,4-trisubstituted pyrroles 3a\(^13\) and 3b (yields 86% and 67%, respectively).

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\begin{array}{c}
\text{Scheme 1. Synthesis of alkyl 1-(2-alkoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylates 3 (a)} \\
1. \text{CCl}_3\text{COCl, Et}_2\text{O;} 2. \text{RONa, ROH (R = Me, Et); (b) 1. MeOCHCl}_2, \text{AlCl}_3, \text{MeNO}_2, \text{CH}_2\text{Cl}_2, 1.5 \text{ h} 0 ^\circ \text{C, N}_2; 2. \text{H}_2\text{O, CHCl}_3; (c) 1. \text{BrCH}_2\text{CO}_2\text{R}^1 (\text{R}^1 = \text{Me,Et}), \text{Me}_3\text{COK, Bu}_4\text{N}^+\text{Br}^-, \text{DMF, N}_2, 15-20 (2 \text{ h}) \rightarrow 40 ^\circ \text{C (3 h); 2. 2H}_2\text{O, CHCl}_3.
\end{array}
\]

The structure of 1-alkylformylesters 3 as well as the following newly synthesized derivatives 4–12 was confirmed by elemental and spectral analysis data, mainly \(^1\)H- and \(^{13}\)C NMR data, in some cases supplemented by IR and MS spectra and x-ray analysis.

As in our own compounds 2a and 2b, or those described in literature\(^12\) the \(^1\)H NMR spectra of derivatives 3a and 3b showed higher chemical shift of 5-H protons of the pyrrole ring (\(\delta \) 7.45–7.92) than those of 3-H protons (\(\delta \) 7.26–7.39); the signals are doublets with the interaction constant \(J = 1.6–1.7 \text{ Hz.} \) Alkylation at nitrogen has been confirmed by the presence of the singlet of \(N\text{-CH}_2\) at \(\delta \) 5.09–5.20, as well as by the presence of another alkyl group. The \(^{13}\)C NMR spectral data of 3 correspond to the suggested structure.\(^14\) The x-ray analysis of the methyl ester 3a confirmed that both groups (2-CO\(_2\)CH\(_3\) and 4-CHO) interacted with the \(\pi\)-cloud of the
pyrrole ring. The second methoxycarbonyl group at $N$ is twisted out of the pyrrole plane due to free rotation around the methylene group.\textsuperscript{13}

In connection with the new data about the synthesis of C-vinylpyrroles,\textsuperscript{15} the series of substituted $\beta$-pyrrolylalkenes 4–8 (Scheme 2) was obtained under the conditions of the Knoevenagel reaction of formyl ester 3b and various C-acids, such as ethyl hydrogen malonate,\textsuperscript{16} diethyl malonate, (1,3-benzoxazol-2-yl)acetonitrile,\textsuperscript{17} (1,3-benzothiazol-2-yl)acetonitrile,\textsuperscript{18} (1H-benzimidazol-2-yl)acetonitrile,\textsuperscript{19} $N$-(1,3-benzothiazol-2-yl)cyanoacetamide,\textsuperscript{20a} as well as its 6-methoxyderivative,\textsuperscript{20b} and malonodinitrile. Catalysed by piperidine, glycine, 10% ethanolic sodium ethoxide, and potassium acetate respectively, the reactions gave yields ranging from 50–97%.

Scheme 2. Synthesis of $\beta$-pyrrolylalkenes 4–8 (a) CH$_2$(CO$_2$Et)CO$_2$H, pyridine, piperidine, 90 °C, 24 h; (b) CH$_2$(CO$_2$Et)$_2$, piperidine, EtOH, reflux, 42 h; (c) (1,3-benzoxazol-2-yl)acetonitrile, glycine, EtOH, reflux, 3 h; (d) (1,3-benzothiazol-2-yl)- or (1H-benzimidazol-2-yl)acetonitrile, EtONa, EtOH, reflux, 30 min; (e) $N$-(1,3-benzothiazol-2-yl)- or $N$-(6-methoxy-1,3-benzothiazol-2-yl)cyanoacetamide, AcOK, AcOH, reflux, 3 h; (f) malonodinitrile, EtONa, EtOH, reflux, 1 h.
In compound 4 the interaction constant $^3J(6\text{-H}, 7\text{-H}) = 15.6\ Hz$ confirmed the $E$-arrangement of hydrogens at the newly formed multiple bond and the NOE DIF technique the mutual steric interaction of 3-H and 7-H. Similarly, the coupling constant $^3J(6\text{-H}, 7\text{-H}) = 13.1–14.1\ Hz$ in compounds 6 and 7 (13C NOE technique) indicated the $E$-configuration of their substituents at the C-6–C-7 bond. The x-ray structural analysis of the derivative 6b ($Z = S$) manifested that both the benzothiazole and pyrrole ring were planar within the experimental error, and also approximately coplanar with plane of the ethylene bond (atoms $2'\text{-C}$, $7\text{-C}$, CN, 6-C, 6-H, 4-C).21

Formyled derivatives 2 and 3 were further used for the preparation of polysubstituted 1,4-dihydropyridines 9–12 (Scheme 3). In the area of dihydropyridine derivatives, which belong to notable antihypertensive drugs,22 only the synthesis of 4-(1H-pyrrol-2-yl)-1,4-dihydropyridines has been published,23 and their 3-pyrrolyl analogues remain unknown.

Scheme 3. Synthesis of 4-(1H-pyrrol-3-yl)-1,4-dihydropyridines 9–12 (a) 2 AcCH$_2$CO$_2$Me, NH$_4$OH, MeOH; (b) BrCH$_2$CO$_2$R (R = Me, Et), Me$_3$COK, Bu$_4$NBr, DMF; (c) 2 AcCH$_2$CO$_2$Me, H$_2$NCH$_2$CO$_2$Me.HCl, MeONa, MeOH, reflux, 10 h; (d) BrCH$_2$CO$_2$Me, K$_2$CO$_3$, Aliquat 336, closed tube, 200 °C, 4 days.
Dihydropyridines 9 and 10 were synthesized by the standard Hantzsch’s method,\textsuperscript{24} involving refluxing of one equivalent of derivative 2 or 3 with two equivalents of methyl acetoacetate, and with an excess of ammonium hydroxide in methanol (Scheme 3, route a, yields 34–75%).

1,4-Dihydropyridines 11 and 12, alkylated at nitrogen of the six-membered ring, were obtained by a modified Hantzsch’s reaction,\textsuperscript{25} from formyl derivative 2a and 3a respectively, with methyl acetoacetate and glycin methyl ester, released \textit{in situ} from its hydrochloride by the action of sodium methoxide in methanol (route c, yield 43-45%).

A method of selective alkylation at both nitrogen atoms of the compound with general formula 9 was elaborated. Under the conditions leading to the alkylation of formyl esters 2, by increased concentration of alkylating agent (the ratio substrate : methyl bromoacetate was 1 : 1.2 and 1 : 2.4, respectively), derivatives 9a and 9b underwent alkylation only at pyrrole nitrogen, giving rise to the corresponding compounds 10a and 10b (route b, yield 43-45%). Another alkylation of compound 10 at N atom of 1,4-dihydropyridine could be achieved only under harsh conditions: solid–liquid phase-transfer catalysis without solvent\textsuperscript{26} in a large excess of methyl bromoacetate, K\textsubscript{2}CO\textsubscript{3} and Aliquate 336 (Aldrich), heating at 200 °C in closed tube for 4 days (route d). Under such conditions compound 10a has been transformed to 12, identical with the compound obtained by route c from 3a (R = R\textsuperscript{1} = Me).

The \textsuperscript{1}H NMR spectra of compounds 9–12 showed the chemical shift of proton 4-H of the created 1,4-dihydropyridine ring in the range of δ 4.91–4.96. Both methyl and methoxycarbonyl groups were observed at δ 2.32–2.39 (2,6-Me) and 3.69–3.72 (3,5-CO\textsubscript{2}Me), respectively.\textsuperscript{27} The signals of carbon atoms in the dihydropyridine nucleus of these derivatives were found in the range of δ 141.1–144.9 (2,6-C), 102.9–106.6 (3,5-C), and 30.6–31.3 (4-C).\textsuperscript{27} The chemical shifts of the pyrrole ring carbons were designated with the help of calculations based on the published increments supposing that the effect of the dihydropyridine nucleus attached by its 3 position is similar to that of an isopropyl group. The derivatives 10a–10b showed the best agreement between the calculated and experimental data.

In conclusion, the preparation of β-pyrrolylalkenes 4–8 and 4-(1H-pyrrol-3-yl)-1,4-dihydropyridines 9–12 utilizing alkyl 1-(2-alkoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylates 3 (alkyl = Me, Et), converted from the corresponding alkyl 1H-pyrrole-2-carboxylates 2 was demonstrated. Compounds 4–8 are the prospective synthons for new heterocycles, e. g. derivative 5 for distrontium salt of 3-(1-carboxymethyl-2-carboxypyrrro-4-yl)pentanedioic acid (immobilization of osteoporosis).\textsuperscript{7}

**Experimental Section**

**General procedures.** The temperature data are uncorrected. The melting points were determined on a Kofler hot plate apparatus. The IR spectra of KBr discs were recorded on a FTIR PU 9800 Philips spectrometer. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were taken on a Bruker AC 250 (250 MHz for \textsuperscript{1}H and 75 MHz for \textsuperscript{13}C) in CDCl\textsubscript{3} (TMS as internal reference) and on a Varian VXR-300
spectrometer (299.945 MHz for $^1$H and 75.429 MHz for $^{13}$C) in DMSO-$d_6$ (chemical shift values were related to that of the solvent); APT, HETCOR, NOE and DIF NOE techniques were used for the assignments. The mass spectra (EI) were run with an MS 902 S (A. E. I. Manchester) spectrometer, equipped with direct inlet, electron energy of 70 eV, trap current 100 µA, ion source temperature 100–120 °C (for compounds 3b, 4, 8) or 170–240 °C (for compounds 6 and 7).

**Methyl 1H-pyrrole-2-carboxylate (1a),**

**Ethyl 1H-pyrrole-2-carboxylate (1b),**

**Methyl 4-formyl-1H-pyrrole-2-carboxylate (2a),**

**Ethyl 4-formyl-1H-pyrrole-2-carboxylate (2b),**

were prepared according to literature procedures.

**Methyl 4-formyl-1-(2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (3a).**

Yield 86%. White needles, mp 70–3 °C (toluene / hexane 1:2). IR ν 1709, 1676 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 3.79 (3H, s, 1-CH$_2$CO$_2$Me), 3.83 (3H, s, 2-CO$_2$Me), 5.09 (2H, s, N-CH$_2$), 7.39 (1H, d, $J$ = 1.7, 3-H), 7.45 (d, 1H, $J$ = 1.7, 5–H), 9.78 (1H, s, CHO); $^{13}$C NMR (CDCl$_3$) δ 50.9 (1-CH$_2$CO$_2$Me), 51.6 (N-CH$_2$), 52.5 (2-CO$_2$Me), 117.0 (3-C), 124.3 (4-C), 125.0 (2-C), 134.2 (5-C), 161.0 (2-CO$_2$Me), 186.1 (1-CH$_2$CO$_2$Me), 185.3 (CHO). Anal. Calcd. for C$_{10}$H$_{11}$NO$_5$ (225.2): C, 53.33; H, 4.92; N, 6.22. Found: C, 53.23; H, 4.78; N, 6.08.

**Ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b).** Potassium tert-butoxide (6.15 g, 55 mmol) and tetrabutyl ammonium bromide (1.60 g, 5 mmol) in dimethylformamide (20 mL) were added to a stirred solution of ethyl 4-formyl-1H-pyrrole-2-carboxylate (2b, 8.36 g, 50 mmol) in the same solvent (20 mL) at 10–15 °C, under nitrogen. A solution of ethyl bromoacetate (9.2 g, 55 mmol) in dimethylformamide (20 mL) was added dropwise and the reaction mixture was stirred at 15–20 °C for 2 h and then at 40 °C for 3 h. After evaporation in vacuo, a residue was treated with water (80 mL) and chloroform (60 mL). The combined organic layers were washed with water, 6 N HCl (2 x 30 mL), again with water, dried (anh. MgSO$_4$) and concentrated. After cooling, the oily product was treated with n-pentane (20–30 mL). The separated solid was recrystallized from n-hexane. Yield 8.4 g (67%), white crystals, mp 76–7 °C. IR ν 1752, 1686, 1675 (C=O) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 3.79 (3H, s, 1-CH$_2$CO$_2$Me), 3.83 (3H, s, 2-CO$_2$Me), 5.09 (2H, s, N-CH$_2$), 7.26, 7.92 (1H, d, $J$ = 1.6, 3-H), 7.92 (1H, d, $J$ = 1.6, 5–H), 9.75 (1H, s, CHO); $^{13}$C NMR (DMSO-$d_6$) δ 14.0 (CH$_3$), 50.8 (N-CH$_2$), 60.3, 61.0 (2 x OCH$_2$), 115.9 (3-C), 124.2, 124.4 (2-C, 4-C), 135.9 (5-C), 160.0 (2-CO$_2$Et), 168.1 (1-CH$_2$CO$_2$Et), 185.7 (CHO); MS (EI) M$^+$, m/z 253. Anal. Calcd. for C$_{12}$H$_{15}$NO$_5$ (253.2): C, 56.49; H, 5.88; N, 5.56. Found: C, 56.49; H, 5.88; N, 5.56.

**Ethyl 1-(2-ethoxy-2-oxoethyl)-4-[(1E)-3-ethoxy-3-oxoprop-1-enyl]-1H-pyrrole-2-carboxylate (4).** A mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 2.53 g, 10 mmol), ethyl hydrogen malonate (1.32 g, 10 mmol), pyridine (15 mL) and piperidine (0.5 mL) was stirred at 90 °C for 24 h. After cooling and pouring on ice (100 g) and HCl (37%, 22 mL) mixture, the solid portion was filtered off and recrystallized from n-hexane. Yield 2.3 g (72%), yellowish crystals, mp 73–4 °C. IR ν 1760, 1693 (C=O), 1629 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 1.19, 1.23, 1.25 (3 x 3H, t, OCH$_2$CH$_3$), 4.10–4.20 (6H, m, OCH$_2$CH$_3$), 5.08 (2H, s,
N-\text{CH}_2\), 6.28 (1H, d, \(J = 15.6, 7\)-H), 7.29 (1H, d, \(J = 1.6, 3\)-H), 7.50 (1H, d, \(J = 15.6, 6\)-H), 7.54 (1H, d, \(J = 1.6, 5\)-H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.0, 14.1, 14.2 (3 x CH\(_3\)), 50.5 (N-\text{CH}_2\), 59.6, 60.0, 60.9 (3 x OCH\(_2\)), 114.6 (7-C), 115.7 (3-C), 118.9 (4-C), 123.6 (2-C), 132.5 (5-C), 137.5 (6-C), 160.1 (2-\text{CO}_2\text{Et}), 166.6 (7-\text{CO}_2\text{Et}), 168.4 (1-\text{CH}_2\text{CO}_2\text{Et}); MS (EI) M\(^{+}\), \(m/z\) 323. Anal. Calcd. for C\(_{16}\)H\(_{21}\)N\(_2\)O\(_6\) (323.3): C, 59.43; H, 6.55; N, 4.33. Found: C, 58.56; H, 6.41; N, 4.48.

**Diethyl\{[5-(ethoxycarbonyl)-1-(2-ethoxy-2-oxoethyl)-1H-pyrrol-3yl]methylene\} malonate (5).** Diethyl malonate (3.20 g, 20 mmol) and piperidine (1 mL) were added to a solution of ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 5.06 g, 20 mmol) in anhydrous ethanol (100 mL) and the mixture was stirred at reflux for 42 h. After distillation off of solvent, the residue was treated with water (80 mL) and CHCl\(_3\) (50 mL). The organic layer was separated and aqueous one was extracted with the same solvent (3 x 30 mL). The combined chloroform solutions were washed with water, 6 N HCl (2 x 30 mL), again with water, dried (anh. MgSO\(_4\)) and evaporated to the dryness. Yield 7.55 g (95%), white crystals, mp 42–5 °C (n-hexane). IR \(\nu\) 1733, 1716, 1708 (C=O), 1623 (C=C) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.17–1.30 (12 H, m, OCH\(_2\)CH\(_3\)), 4.10–4.35 (8H, m, OCH\(_2\)CH\(_3\)), 5.14 (2H, s, N-\text{CH}_2\), 7.00 (1H, d, \(J = 1.8, 4\)-H), 7.57 (1H, d, \(J = 1.8, 2\)-H), 7.57 (1H, s, 6-H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 13.7, 14.0, 14.1 (4 x OCH\(_2\)CH\(_3\)), 50.6 (N-\text{CH}_2), 60.2, 60.9, 61.0, 61.3 (4 x OCH\(_2\)CH\(_3\)), 116.0 (3-C), 116.7 (4-C), 121.0 (7-C), 124.0 (5-C), 134.6 (2-C), 134.7 (6-C), 159.8 (5-\text{CO}_2\text{Et}), 163.9, 166.5 (2 x 7-\text{CO}_2\text{Et}), 168.3 (1-\text{CH}_2\text{CO}_2\text{Et}); MS (EI) M\(^{+}\), \(m/z\) 395. Anal. Calcd. for C\(_{19}\)H\(_{25}\)N\(_3\)O\(_8\) (395.4): C, 57.71; H, 6.37; N, 3.54. Found: C, 57.55; H, 6.30; N, 3.66.

**Ethyl 4-[(E)-2-(1,3-benzoxazol-2-yl)-2-cyanovinyl]-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (6a).** A mixture of (1,3-benzoxazol-2-yl)acetonitrile (0.32 g, 2 mmol), 17 ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 0.51 g, 2 mmol), and glycine (0.1 g, 1.35 mmol) was refluxed in ethanol (30 mL) for 3 h. The solid, precipitating after cooling, was filtered off, washed thoroughly with water and dried. Yield 0.65 g (83%), yellow crystals, mp 168–9 °C (ethanol). \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.21, 1.27 (2 x 3H, t, OCH\(_2\)CH\(_3\)), 4.17, 4.24 (2 x 2H, q, OCH\(_2\)CH\(_3\)), 5.24 (2H, s, N-\text{CH}_2\), 7.35–7.55 (2H, m, 5’-H, 6’-H), 7.69 (1H, d, \(J = 1.8, 5\)-H), 8.42 (1H, s, 6-H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.0, 14.1 (2 x CH\(_3\)), 50.9 (N-\text{CH}_2\), 60.5, 61.1 (2 x OCH\(_2\)CH\(_3\)), 93.2 (7-C), 110.7 (7’-C), 115.9 (CN), 116.4 (3-C), 117.2 (4-C), 119.7 (4’-C), 124.8 (2-C), 125.2 (6’-C), 125.8 (5’-C), 136.8 (5-C), 141.2 (3’a-C), 143.3 (6-C), 150.0 (7’a-C), 159.2 (2’-C), 159.7 (2-\text{CO}_2\text{Et}), 168.1 (1-\text{CH}_2\text{CO}_2\text{Et}); \(^3\)J(6-H,CN) = 14.1; MS (EI) M\(^{+}\), \(m/z\) 393. Anal. Calcd. for C\(_{21}\)H\(_{19}\)N\(_3\)O\(_5\) (393.4): C, 64.11; H, 4.87; N, 10.68. Found: C, 63.90; H, 4.83; N, 10.83.

**Ethyl 4-[(E)-2-(1,3-benzothiazol-2-yl)-2-cyanovinyl]-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (6b).** It was prepared from 3b and (1,3-benzothiazol-2-yl)acetonitrile\(^ {18}\) according the lit.\(^ {21}\) Yield 51%. Yellow crystals, mp 146–7 °C (ethanol). \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.21, 1.27 (2 x 3H, t, OCH\(_2\)CH\(_3\)), 4.17, 4.24 (2 x 2H, q, OCH\(_2\)CH\(_3\)), 5.24 (2H, s, N-\text{CH}_2\), 7.35–7.55 (2H, m, 5’-H, 6’-H), 7.69 (1H, d, \(J = 1.8, 3\)-H), 7.70–7.80 (2H, m, 4’-H, 7’-H), 8.03 (1H, d, \(J = 1.8, 5\)-H), 8.42 (1H, s, 6-H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.0, 14.1 (2 x CH\(_3\)), 50.9 (N-\text{CH}_2\), 60.5, 61.1 (2 x OCH\(_2\)CH\(_3\)), 93.2 (7-C), 110.7 (7’-C), 115.9 (CN), 116.4 (3-C), 117.2 (4-C), 119.7 (4’-C), 124.8 (2-C), 125.2 (6’-C), 125.8 (5’-C), 136.8 (5-C), 141.2 (3’a-C), 143.3 (6-C), 150.0 (7’a-C), 159.2 (2’-C), 159.7 (2-\text{CO}_2\text{Et}), 168.1 (1-\text{CH}_2\text{CO}_2\text{Et}); \(^3\)J(6-H,CN) = 14.1; MS (EI) M\(^{+}\), \(m/z\) 393. Anal. Calcd. for C\(_{21}\)H\(_{19}\)N\(_3\)O\(_5\) (393.4): C, 64.11; H, 4.87; N, 10.68. Found: C, 63.90; H, 4.83; N, 10.83.
122.3 (4'-C), 122.7 (7'-C), 124.6 (2'-C), 125.8 (6'-C), 126.9 (7'a-C), 133.9 (7'a-C), 136.4 (5'-C),
141.8 (6-C), 152.9 (2-CO2Et), 163.5 (2'-C), 168.1 (1-CH2CO2Et); \(^3J(6-H, CN) = 14.1\); MS (EI) M\(^+\), m/z 409. Anal. Calcd. for C\(_{21}\)H\(_{19}\)N\(_3\)O\(_4\)S (409.4): C, 61.60; H, 4.68; N, 10.26; S, 7.83. Found: C, 61.63; H, 4.85; N, 10.52; S, 8.15.

**Ethyl-4-[[\((E)\)-2-(1H-benimidazol-2-yl)-2-cyanovinyl]-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (6c)]**. A solution of ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 0.51 g, 2 mmol) in ethanol (10 mL) and 10% ethanolic sodium ethoxide (3–4 drops) were added to a stirred solution of (1H-benimidazol-2-yl)acetonitrile (0.31 g, 2 mmol) in the same solvent (10 mL). After 30 min at reflux, the reaction mixture was gradually cooled to room T with stirring. The precipitate was filtered off and recrystallized from ethanol. Yield 0.4 g (51%), yellow crystals, mp 241–3 °C. IR \(\nu\) 2224 (CN), 1754, 1692 (C=O), 1626 (C=C) cm \(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.20, 1.27 (2 x 3H, t, OCH\(_2\)CH\(_3\)), 4.16, 4.23 (2 x 2H, q, OCH\(_2\)CH\(_3\)), 5.23 (2H, s, N-CH\(_2\)), 7.17–7.25 (2H, m, 5'-H, 6'-H), 7.50–7.64 (m, 4'-H, 7'-H), 7.66 (1H, d, J = 1.8, 3-H), 8.75 (1H, d, J = 1.8, 5-H), 8.18 (1H, s 6-H), 12.9 (1H, bs, NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.0, 14.2 (2 x CH\(_3\)), 50.7 (N-CH\(_2\)), 60.4, 61.8 (2 x OCH\(_2\)), 97.3 (7-C), 115.7 (3-C, 4'-C, 7'-C), 117.1 (CN), 117.4 (4-C), 122.6 (5'-C, 6'-C), 124.5 (2-C), 132.5 (3'-C, 7'-C), 135.3 (5-C), 138.8 (6-C), 147.9 (2'-C), 159.8 (2-CO\(_2\)Et), 168.2 (1-CH\(_2\)CO\(_2\)Et); \(^{3}J(6-H,CN) = 14.1\); MS (EI) M\(^+\), m/z 392. Anal. Calcd. for C\(_{21}\)H\(_{20}\)N\(_4\)O\(_4\) (392.4): C, 64.27; H, 5.14; N, 14.28. Found: C, 63.65; H, 4.96; N, 14.41.

**Ethyl 4-[(1E)-3-(1,3-benzothiazol-2-ylamino)-2-cyano-3-oxoprop-1-enyl]-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (7a)**. A mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 0.51 g, 2 mmol), N-(1,3-benzothiazol-2-yl)cyanoacetamide (0.43 g, 2 mmol), anh. potassium acetate (0.5 g, 5 mmol), and acetic acid (15 mL) was stirred while refluxing for 3 h. After pouring on ice, the raw product was collected by filtration, washed with water, and dried. Yield 0.75 g (83%). Yellow crystals, mp 222–3 °C (acetic acid). \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.22, 1.28 (2 x 3H, t, OCH\(_2\)CH\(_3\)), 4.10–4.30 (2 x 2H, m, OCH\(_2\)CH\(_3\)), 5.22 (1H, s, N-CH\(_2\)), 7.31 (1H, t, J = 7.6, 6'-H), 7.45 (1H, t, J = 7.6, 5'-H), 7.52 (1H, d, J = 8.2, 4'-H), 7.66 (1H, d, J = 1.8, 3-H), 7.90–8.00 (2H, m, 5-H, 7'-H), 8.37 (1H, s, 6-H), 12.3 (1H, bs, NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.2, 14.3 (2 x CH\(_3\)), 50.7 (N-CH\(_2\)), 60.7, 61.3 (2 x OCH\(_2\)), 102.6 (7-C), 116.7 (3-C), 117.0 (4-C), 117.5 (CN), 122.6 (4'-C), 124.0 (7'-C), 125.0 (2-C), 127.0 (5'-C, 6'-C), 129.3 (7'a-C), 137.2 (5-C), 142.0 (3'-a-C), 145.9 (6-C), 159.9 (2'-C, 2-CO\(_2\)Et), 166.0 (C=O); \(^{3}J(6-H,CN) = 13.1\); MS (EI) M\(^+\), m/z 452. Anal. Calcd. for C\(_{22}\)H\(_{20}\)N\(_4\)O\(_5\)S (452.5): C, 58.39; H, 4.46; N, 12.38. Found: C, 57.95; H, 4.75; N, 11.98.

**Ethyl 4-[(1E)-2-cyano-3-(6-methoxy-1,3-benzothiazol-2-ylamino)-3-oxoprop-1-enyl]-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (7b)**. It was prepared from 3b and N-(6-methoxy-1,3-benzothiazol-2-yl)cyanoacetamide\(^{20b}\) according to procedure for 7a. Yield 93%, yellow crystals, mp 229–31 °C (ethanol). \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.21, 1.28 (2 x 3H, t, OCH\(_2\)CH\(_3\)), 3.81 (3H, s OCH\(_3\)), 4.08–4.30 (2 x 2H, m, OCH\(_2\)CH\(_3\)), 5.24 (2H, s, N-CH\(_2\)), 7.06 (1H, dd, J = 8.8, J = 2.5, 5'-H), 7.50–7.61 (2H, m, 4'-H, 7'-H), 7.67 (1H, d, J = 1.6, 3-H), 7.93 (1H, d, J = 1.6, 5-H), 8.37 (1H, s, 6-H), 13.00 (1H, bs, NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 14.0, 14.1 (2 x CH\(_3\)).
50.9 (N-CH₂), 55.6 (OCH₃), 60.5, 61.1 (2 x OCH₂), 102.6 (7-C), 105.4 (7'-C), 115.2 (5'-C), 116.4 (3-C, 4'-C), 116.8 (4-C), 117.2 (CN), 124.8 (2-C), 131.0 (7'a-C), 136.9 (5-C), 140.5 (3'a-C), 145.5 (6-C), 156.3 (6'-C), 159.7 (2'-C, 2-CO₂Et), 165.5 (C=O), 168.1 (1-CH₂C=O₂Et); ¹J(6-H,CN) = 13.6; MS (EI) M⁺, m/z 482. Anal. Calcd. for C₂₃H₂₂N₄O₆S (482.5): C, 57.25; H, 4.60; N, 11.61. Found: C, 57.12; H, 4.86; N, 11.84.

Ethyl 4-(2,2-dicyanovinyl)-1-(2-ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (8). A solution of ethyl 1-(2-ethoxy-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3b, 0.51 g, 2 mmol) in ethanol (20 mL) and 15% ethanolic natrium ethanolate (3–4 drops) were added to a hot solution of malonodinitrile (0.154 g, 2.2 mmol) in the same solvent (10 mL). After stirring at reflux for 1 h, the reaction mixture was treated with charcoal, filtered and cooled. The separated solid was filtered off. Yield 0.3 g (50%), white needles, mp 124–5 °C (ethanol). IR ν 2227 (CN), 1744, 1691 (C=O), cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.17, 1.28 (2 x 3H, t, CH₂CH₃), 4.15, 4.24 (2 x 2H, q, OCH₂CH₃), 5.25 (2H, s, N-CH₂), 7.53 (1H, s, 3-H), 7.93 (1H, s, 5-H), 8.36 (1H, s, 6-H); ¹³C NMR (DMSO-d₆) δ 14.0 (2 x CH₃), 51.0 (N-CH₂), 60.7, 61.2 (2 x OCH₂CH₃), 74.6 (7-C), 114.2, 114.8 (2 x CN), 125.5 (2-C), 137.8 (5-C), 154.6 (6-C), 159.5 (2-CO₂Et), 167.9 (1-CH₂C=O₂Et); MS (EI) M⁺, m/z 301. Anal. Calcd. for C₁₅H₁₅N₃O₄ (301.4): C, 59.79; H, 5.02; N, 13.95. Found: C, 59.45; H, 4.74; N, 14.08.

Dimethyl 4-[5-(alkoxycarbonyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (9). To a solution of alkyl 4-formyl-1H-pyrrole-2-carboxylate 2 (10 mmol) in methanol (50 mL) methyl acetoacetate (2.32 g, 20 mmol) was added followed by NH₄OH (28% NH₃ in water, 2 mL, 15 mmol). The mixture was heated at reflux for 6 h and then poured into ice water and extracted with CHCl₃. The extract was dried (MgSO₄), concentrated to dryness; the product was isolated by column chromatography (silica gel, CHCl₃) and recrystallized from a suitable solvent.

Dimethyl 4-[5-(methoxycarbonyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (9a). Yield 1.18 g (34%), yellowish crystals, mp 214–6 °C (methanol). IR ν 1707, 1684, 1651 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.32 (6H, s, 2,6-Me), 3.69 (6H, s, 3,5-CO₂Me), 3.80 (3H, s, 5'-CO₂Me), 4.96 (1H, s, 4-H), 5.74 (1H, bs, 1-H), 6.70 (1H, m, 4'-H), 6.75 (1H, m, 2'-H), 8.86 (1H, bs, 1'-H); ¹³C NMR (CDCl₃) δ 19.5 (2,6-Me), 31.3 (4-C), 51.1 (3,5-CO₂Me), 51.3 (5'-CO₂Me), 103.5 (3,5-C), 114.0 (4'-C), 120.3 (2'-C), 132.1 (3',5'- C), 144.4 (2,6-C), 161.6 (5'-CO₂Me), 168.0 (3,5-CO₂Me). Anal. calcd. for C₁₇H₂₀N₂O₆ (348.4): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.55; H, 5.70; N, 7.89.

Dimethyl 4-[5-(ethoxycarbonyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (9b). Yield 2.64 g (75%), yellowish crystals, mp 209–11 °C (ethanol). IR ν 1705, 1680, 1655 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (3H, t, 5'-CO₂CH₂CH₃), 2.33 (6H, s, 2,6-Me), 3.70 (6H, s, 3,5-CO₂Me), 4.27 (2H, q, 5'-CO₂CH₂CH₃), 4.96 (1H, s, 4-H), 5.74 (1H, bs, 1-H), 6.71 (2H, m, 2',4'-H), 8.84 (1H, bs, 1'-H); ¹³C NMR (CDCl₃) δ 14.5 (5'-CO₂CH₂CH₃), 19.6 (2,6-Me), 31.3 (4-C), 51.1 (3,5-CO₂Me), 60.1 (5'-CO₂CH₂CH₃), 103.5 (3,5-C), 113.8 (4'-C), 120.1 (2'-C), 132.0 (3',5'- C), 144.3 (2,6-C), 161.3 (5'-CO₂Et), 168.0 (3,5-CO₂Me). Anal. Calcd. for C₁₈H₂₂N₂O₆ (362.4): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.52; H, 6.00; N, 7.54.
Dimethyl 4-[5-(alkoxycarbonyl)-1-(2-alkoxy-2-oxoethyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (10).

**Route a:** by the general procedure for compounds 9, using of formyl derivative 3a and 3b, respectively instead of 2a and 2b.

**Route b:** by the general method for alkylated derivatives 3, using of substituted 1,4-dihydropyridines 9 (10 mmol) as a substrate and the ratio of dihydropyridine: alkylating agent was 1:2 and 1:2.4, respectively. The product was isolated by column chromatography (silica gel, CHCl₃) and recrystallized from a suitable solvent.

**Dimethyl 4-[5-(methoxycarbonyl)-1-(2-methoxy-2-oxoethyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (10a).** Yield 2.2 g (52%, route a), 1.9 g (45%, route b), yellow crystals, mp 192–4 °C (methanol). IR ν 1707, 1694, 1651 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.32 (6H, s, 2,6-Me), 3.70 (6H, s, 3,5-CO₂Me), 3.73 (3H, s, 1'-CH₂CO₂Me), 3.75 (3H, s, 5'-CO₂Me), 4.90 (2H, s, 1'-CH₂CO₂Me), 4.94 (1H, s, 4-H), 5.72 (1H, bs, 1-H), 6.61 (1H, d, J = 2.1, 4'-H), 6.75 (1H, d, J = 2.1, 2'-H); ¹³C NMR (CDCl₃) δ 19.3 (2,6-Me), 31.0 (4-C), 50.4, 50.9 (1'-CH₂CO₂Me, 5'-CO₂Me), 51.0 (3,5-CO₂Me), 52.3 (1'-CH₂CO₂Me), 102.9 (3,5-C), 117.0 (4'-C), 121.4 (5'-C), 127.2 (2'-C), 129.9 (3'-C), 144.9 (2,6-C), 161.6 (5'-CO₂Me), 168.1 (3,5-CO₂Me), 169.4 (1'-CH₃CO₂Me). Anal. Calcd. for C₂₀H₂₄N₂O₈ (420.4): C, 57.15; H, 5.76; N, 6.66. Found: C, 56.99; H, 5.74; N, 6.62.

**Dimethyl 4-[5-(ethoxycarbonyl)-1-(2-ethoxy-2-oxoethyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (10b).** Yield 2.11 g (47%, route a), 1.9 g (42%, route b), yellow crystals, mp 148–50 °C (ethanol). IR ν 1738, 1698, 1651 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 1.30 (6H, m, 1'-CH₂CO₂CH₂CH₃, 5'-CO₂CH₂CH₃), 2.32 (6H, s, 2,6-Me), 3.70 (6H, s, 3,5-CO₂Me), 4.23 (4H, m, 1'-CH₂CO₂CH₂CH₃, 5'-CO₂CH₂CH₃), 4.89 (2H, s, 1'-CH₂CO₂Et), 4.96 (1H, s, 4-H), 5.78 (1H, bs, 1-H), 6.59 (1H, d, J = 2.1, 4'-H), 6.76 (1H, d, J = 2.1, 2'-H); ¹³C NMR (CDCl₃) δ 143.1 (1'-CH₂CO₂CH₂CH₃, 5'-CO₂CH₂CH₃), 19.3 (2,6-Me), 31.0 (4-C), 51.0 (3,5-CO₂Me), 52.3 (1'-CH₂CO₂Et), 59.8 (1'-CH₂CO₂CH₂CH₃, 5'-CO₂CH₂CH₃), 102.9, 103.2 (3,5-C), 116.8 (4'-C), 121.8 (5'-C), 127.1 (2'-C), 129.8 (3'-C), 144.9 (2,6-C), 161.2 (5'-CO₂Et), 168.1 (3,5-CO₂Me), 169.4 (1'-CH₃CO₂Et). Anal. Calcd. for C₂₂H₂₈N₂O₈ (448.5): C, 58.92; H, 6.29; N, 6.25. Found: C, 58.81; H, 6.18; N, 6.17.

**Dimethyl 4-[5-(methoxycarbonyl)-1H-pyrrol-3-yl]-1-(2-methoxy-2-oxoethyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (101).** Sodium methoxide (0.54 g, 10 mmol), methyl acetoacetate (2.32 g, 20 mmol) and methyl 4-formyl-1H-pyrrole-2-carboxylate (2a, 1.53 g, 10 mmol) were added to a solution of glycine methyl ester hydrochloride (1.26 g, 10 mmol) in methanol (50 mL). The reaction mixture was refluxed for 10 h, then evaporated to dryness and purified on a silica gel column using CHCl₃. After distilling off the solvent, the product was obtained as a yellow solid, yield 1.89 g (45%), mp 57–60 °C (methanol). ¹H NMR (CDCl₃) δ 2.39 (6H, s, 2,6-Me), 3.72 (6H, s, 3,5-CO₂Me), 3.74 (3H, s, 1-CH₃CO₂Me), 3.77 (3H, s, 5'-CO₂Me), 4.33 (2H, s, 1-CH₃CO₂Me), 4.94 (1H, s, 4-H), 5.97 (1H, bs, 1'-H), 6.72 (2H, m, 2',4'-H); ¹³C NMR (CDCl₃) δ 16.2 (2,6-Me), 31.2 (4-C), 51.2 (3,5-CO₂Me), 51.4 (1-CH₂CO₂Me, 5'-CO₂Me), 52.2 (1-CH₃CO₂Me), 107.3 (3,5-C), 114.0 (4'-C), 120.7 (2'-C), 131.0 (3',5'-C), 144.0
(2,6-C), 161.5 (5'-CO2Me), 168.2 (3,5-CO2Me), 169.9 (1-CH2CO2Me). Anal. Calcd. for C20H24N2O8 (420.4): C, 57.15; H, 5.76; N, 6.66. Found: C, 57.01; H, 5.67; N, 6.52.

**Dimethyl 4-[5-(methoxycarbonyl)-1-(2-methoxy-2-oxoethyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12).**

**Route c:** By the previous procedure for the compound 11, using the formyl derivative 3a (10 mmol) instead of 2a. Yield 2.12 g (43%), yellow crystals, mp 52–5 °C (methanol).

**Route d:** The mixture of dimethyl 4-[5-(methoxycarbonyl)-1-(2-methoxy-2-oxoethyl)-1H-pyrrol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (10a, 2.10 g, 5 mmol), solid K2CO3 (1.38 g, 10 mmol), Aliquat 336 (4.04 g, 10 mmol), and methyl bromoacetate (6.5 g, 16 mmol) was stirred and heated in closed tube at 200 °C for 4 days. After cooling, the reaction mixture was concentrated and chromatographed on silica gel (eluent CHCl3). Yield 0.86 g (35%), mp 52–5 °C. 1H NMR (CDCl3) δ 2.39 (6H, s, 2,6-Me), 3.72 (6H, s, 3,5-CO2Me), 3.73 (6H, s, 1,1'-CH2CO2Me), 3.76 (3H, s, 5'-CO2Me), 4.34 (2H, s, 1-CH2CO2Me), 4.91 (3H, s, 4-H, 1'-CH2CO2Me), 6.66 (1H, m, 4'-H), 6.74 (1H, m, 2'-H; 13C NMR (CDCl3) δ 15.7 (2,6-Me), 30.6 (4-C), 50.5, 50.9 (1,1'-CH2CO2Me, 5'-CO2Me), 51.8 (3,5-CO2Me), 52.2 (1,1'-CH2CO2Me), 106.6 (3,5-C), 116.4 (4'-C), 121.0 (5'-C), 128.3 (2',3'-C), 141.1 (2,6-C), 161.1 (5'-CO2Me), 167.7 (3,5-CO2Me), 169.5 (1,1'-CH2CO2Me). Anal. Calcd. for C23H28N2O10 (492.5): C, 56.61; H, 5.73; N, 5.69. Found: C, 56.31; H, 5.52; N, 5.40.

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**References and Notes**


28. The compound did not analyze correctly.