ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 4, pp. 564–571. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © E.I. Mikhed'kina, O.S. Bylina, I.I. Mel'nik, D. T. Kozhich, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 4, pp. 578–585.

Reaction of Ethyl 4-[(*E*)-1-Chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate with Hydrazines

E. I. Mikhed'kina[a], O. S. Bylina[a], I. I. Mel'nik[a], and D. T. Kozhich[b]

[a] *"Kharkov Polytechnical Institute" National Technical University, ul. Frunze 21, Kharkov, 61002 Ukraine*
e-mail: bylina@sphere.kharkov.com
[b] *Medical Biology Institute, Minsk, Belarus*

Received July 1, 2008

Abstract—Ethyl 4-[(*E*)-1-chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate reacted with substituted hydrazines in different solvents to give mixtures of regioisomeric 3- and 5-substituted pyrazoles. Conditions were found for selective formation of 1-aryl(alkyl)-5-(5-ethoxycarbonyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-1*H*-pyrazoles.

DOI: 10.1134/S1070428009040162

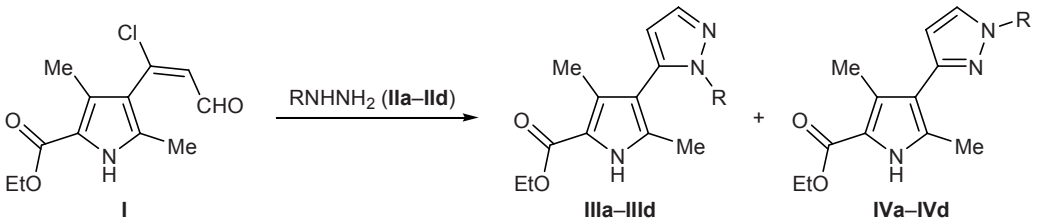
Reactions of β-chloro-substituted α,β-unsaturated aldehydes with difunctional nucleophiles are widely used in the synthesis of various heterocyclic compounds, including pyrazole derivatives [1–3]. Pyrazole ring is a structural fragment of some pharmaceutical agents [4–6]. 1,5- and 1,3-Diarylpyrazoles exhibit antiseptic, analgesic, antiphlogistic [7], anticarcinogenic [8], and herbicidal activity [9, 10]. Molecules of many natural compounds contain a pyrrole ring [11, 12]. Numerous compounds of pharmacological interest have been created on the basis of pyrrole derivatives [13, 14]. It may be anticipated that combination of pyrazole and pyrrole rings in a single molecule would give rise to new interesting properties.

In the present article were report the results of our study on the reaction of ethyl 4-[(*E*)-1-chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**I**) with hydrazines. Accessible ester **I** possessing a chlorovinylcarbaldehyde fragment was prepared from ethyl 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate according to Vilsmeier–Haak [15]. It is a reactive intermediate product in the synthesis of various organic compounds having a pyrazole ring.

It is known that reactions of β-chloro-α,β-unsaturated aldehydes with arylhydrazines are often nonselective, and mixtures of isomeric 1,3- and 1,5-disubstituted pyrazoles at different ratios are formed [16, 17]. The resulting isomer mixtures are often difficult to separate; therefore, development of regioselective procedures for the synthesis of required pyrazole derivatives is an important problem.

We found that compound **I** reacts with phenylhydrazine (**IIa**) in ethanol to give a mixture of two products, presumably 5- and 3-substituted pyrazoles **IIIa** and **IVa**, with an overall yield of 67% (Scheme 1). In the ^{1}H NMR spectrum of the product mixture we observed signals from protons in the pyrazole ring as doublets at δ 6.41 and 7.75 ppm (J = 1.8 Hz) and δ 6.60 and 8.52 ppm (J = 2.6 Hz). According to the signal intensities, the isomer ratio was 82 : 18. We failed to isolate individual isomers by recrystallization or chromatography. Using vacuum sublimation we

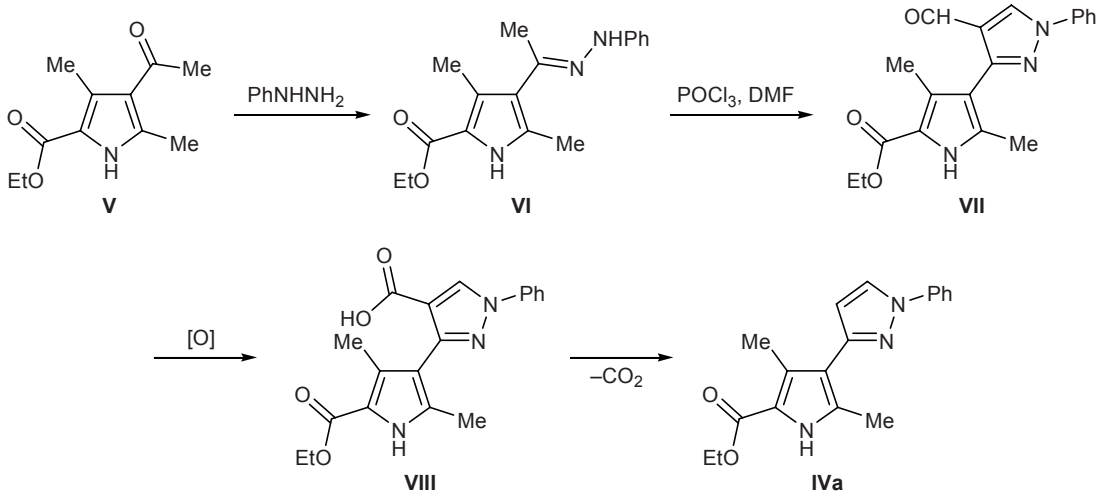
Scheme 1.



I **IIIa–IIId** **IVa–IVd**

R = Ph (**a**), 4-MeC$_6$H$_4$ (**b**), 4-BrC$_6$H$_4$ (**c**), Me (**d**).

Scheme 2.



succeeded in isolating only the minor isomer. When the reaction of aldehyde **I** with phenylhydrazine (**IIa**) was carried out in anhydrous ethanol, we obtained 80% of a mixture of isomeric pyrazoles at a ratio of 97:3 (according to the ^{1}H NMR data). By recrystallization from toluene we isolated the major isomer as individual substance. Its melting point and ^{1}H NMR spectrum (position of signals from pyrazole ring protons and the corresponding coupling constant) differed from those found for the isomer isolated by vacuum sublimation. The mass spectra of both isomers contained the molecular ion peak with *m*/*z* 309 (100%, $[M]^{+\cdot}$). The structure of pyrazole **IVa** was confirmed by independent synthesis from acetylpyrrole **V** through hydrazone **VI** and subsequent treatment of **VI** with phosphoryl chloride in dimethylformamide. 4-Formylpyrazole **VII** thus obtained was oxidized with potassium permanganate to carboxylic acid **VIII** which underwent decarboxylation to pyrazole **IVa** on heating in quinoline in the presence of copper (Scheme 2). The resulting pyrazole **IVa** showed no depression of the melting point on mixing with the product isolated by vacuum sublimation, and their spectral parameters were identical. The structure of pyrazole **IVa** was unambiguously determined by X-ray analysis (the results will be reported elsewhere as a part of other study). Compounds **VI**–**VIII** were identified by IR, ^{1}H NMR, and mass spectra.

Comparison of the ^{1}H NMR spectra of **IIIa** and **IVa**, recorded from solutions in $CDCl_3$ and DMSO-d_6, showed that the position of signals from protons in the pyrazole ring of **IIIa** changed insignificantly. In going from $CDCl_3$ to DMSO-d_6, the downfield shift $\Delta\delta$ was 0.17 and 0.06 ppm for 3-H and 4-H, respectively. The 4-H signal of compound **IVa** also changed its position insignificantly ($\Delta\delta$ = 0.08 ppm), whereas the downfield shift of its 5-H signal was $\Delta\delta$ = 0.54 ppm. A probable reason is that the 5-H proton in **IVa** appears in the vicinity of the phenyl ring on N^1, and change of the solvent may be accompanied by appreciable variation of shielding effect of the phenyl ring (due to its magnetically anisotropic properties) on the neighboring proton. This is consistent with the data of [18], according to which chemical shifts of pyrazole ring protons depend on the solvent polarity. The above data provide an indirect support to the assumed structures of isomeric pyrazoles **IIIa** and **IVa**.

The reaction of aldehyde **I** with phenylhydrazine (**IIa**) was carried out in different solvents with a view to reveal solvent effect on the yield and ratio of isomeric pyrazoles. The results are collected in Table 1. It is seen that the highest yields were obtained in polar solvents (methanol, ethanol, acetonitrile) and that the major product was 1,5-disubstituted pyrazole **IIIa**. We

Table 1. Reaction of aldehyde **I** with phenylhydrazine (**IIa**) in different solvents

Solvent	Overall yield, %	Isomer fractions	
		IIIa	**IVa**
Ethanol	80	97	3
Methanol	87	95	5
Acetic acid	68	92	8
Acetonitrile	81	85	15
Ethyl acetate	46	81	9
Toluene	40	82	18
Methylene chloride	50	80	20

Table 2. Chemical shifts δ and coupling constants ^3J of protons in the pyrazole ring in the ^{1}H NMR spectra (DMSO-d_6) of isomeric pyrazoles **IIIa**–**IIId** and **IVa**–**IVd** and their ratios in the reaction mixtures

Comp. no.	δ, ppm		^3J, Hz	Comp. no.	δ, ppm		^3J, Hz	Ratio **III**:**IV**, %	
	3-H	4-H			5-H	4-H		ethanol	acetonitrile
IIIa	7.75	6.41	1.8	**IVa**	8.52	6.60	2.6	91:9	94:6
IIIb	7.72	6.38	1.8	**IVb**	8.46	6.57	2.6	89:11	96:4
IIIc	7.77	6.43	1.8	**IVc**	8.56	6.63	2.6	98:2	100:0
IIId	7.46	6.13	1.8	**IVd**	7.68	6.23	2.4	79:21	77:23

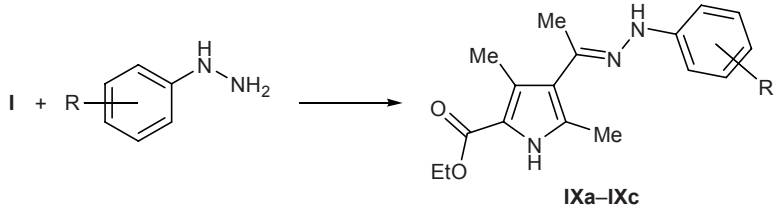
also examined reactions of aldehyde **I** with a series of arylhydrazines having different substituents in the benzene ring. The reaction with 4-methylphenylhydrazine in ethanol was accompanied by fast heterocyclization, so that we failed to detect intermediate hydrazone and isolated pyrazole **IIIb** in 53% yield. Likewise, from methylhydrazine we obtained pyrazole **IIId** (Scheme 1). 4-Nitrophenylhydrazine having an electron-withdrawing nitro group (which reduces the nucleophilicity of the amino nitrogen atom) reacted with aldehyde **I** under analogous conditions to give hydrazone **IXa**, while hydrazone **IXb** was formed in the reaction of **I** with 2,4-dinitrophenylhydrazine only in the presence of excess sulfuric acid (Scheme 3). Hydrazones **IXa** and **IXb** did not undergo heterocyclization on prolonged heating in high-boiling solvents even in the presence of such organic bases as pyridine and triethylamine.

In the ^{1}H NMR spectra of hydrazones **IXa** and **IXb**, signals from the olefinic protons appeared as doublets at δ 6.42 and 8.14 ppm and 6.47 and 8.85 ppm, respectively, with a coupling constant ^3J of 9.1 Hz. The molecular ion peaks in the mass spectra of **IXa** and **IXb** had intensities of 58.5 and 100%, respectively. Hydrazone **IXc** was isolated in 81% yield in the reaction of aldehyde **I** with 4-bromophenylhydrazine in boiling acetonitrile (reaction time 2 h). Prolonged heating of the reactants in boiling ethanol or acetonitrile gave pyrazole **IIIc**. The ratio of isomeric pyrazoles **IIId** and **IVd** formed in the reaction of **I** with methylhydrazine in acetonitrile was 83:17, whereas only pyrazole **IIId** was isolated when the reaction was carried out in ethanol.

The ratios of isomeric pyrazoles **III** and **IV** formed in the reactions of aldehyde **I** with hydrazines **IIa**–**IId** were determined from the ^{1}H NMR spectra of the reaction mixtures. The spectra clearly displayed doublets from protons in the pyrazole rings of **III** and **IV** with characteristic coupling constants [19], and the signal intensities were used to calculate the isomer fractions (Table 2). As follows from the data in Table 2, the reactions of compound **I** with hydrazines **IIa**–**IId** are regioselective, and the major products are the corresponding 1,5-disubstituted pyrazole derivatives **IIIa**–**IIId**. Electron-donating substituents in the hydrazine molecule favor formation of 1,3-disubstituted pyrazoles **IV**. A probable mechanism is illustrated by Scheme 4. The condensation of hydrazine **II** with aldehyde **I** may be followed by cyclization of the hydrazone thus formed via conjugate addition–elimination (path *a*) or initial addition–elimination may be followed by cyclization or condensation of intermediate hydrazino-substituted enones (paths *b* and *c*).

We continued our search for optimal conditions for the selective formation of 1,3-disubstituted pyrazoles by carrying out the reaction of aldehyde **I** with phenylhydrazine in the presence of 1,4-diazabicyclo[2.2.2]-octane (DABCO) which should favor the reaction to follow path *b* [20]. However, in this case the product was a mixture of pyrazoles **IIIa** and **IVa** with in-

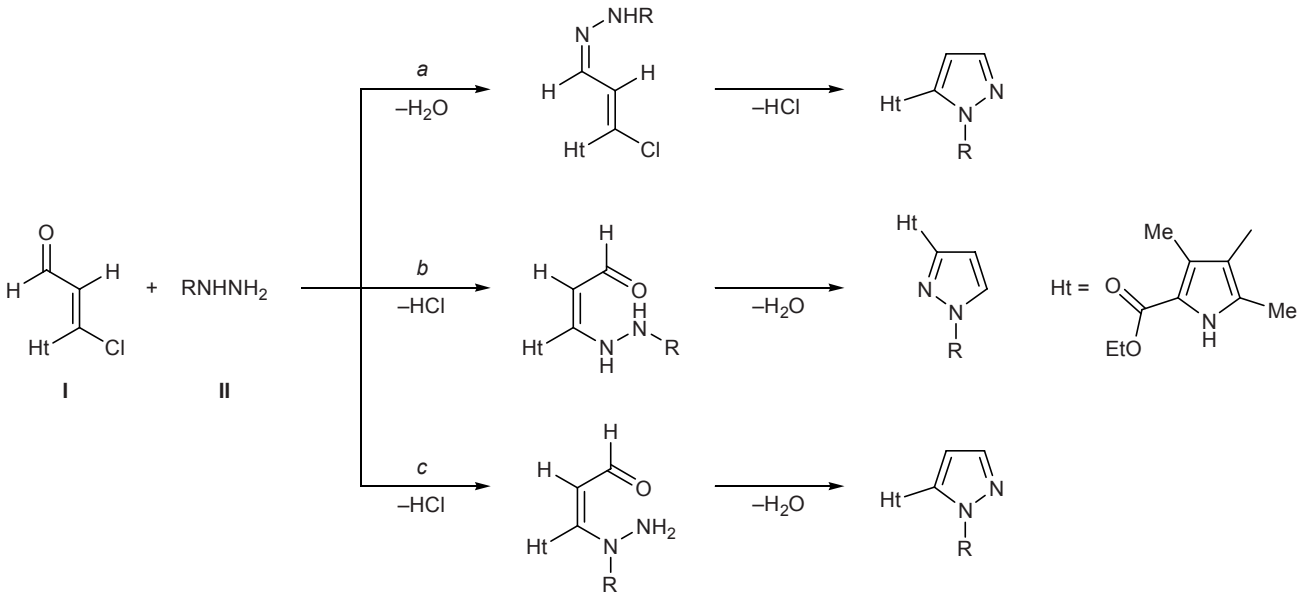
Scheme 3.



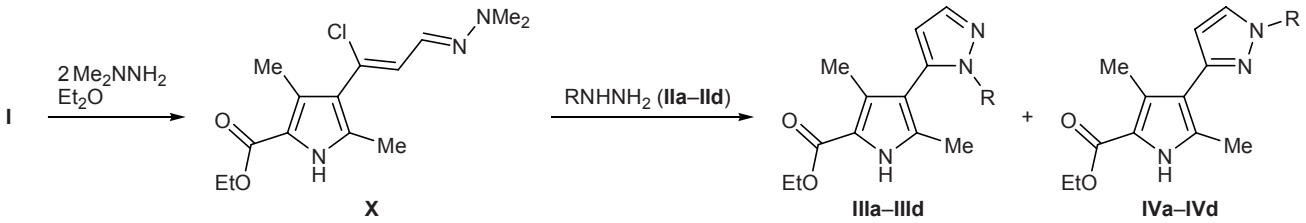
IXa–IXc

R = 4-O_2N (**a**), 2,4-$(O_2N)_2$ (**b**), 4-Br (**c**).

Scheme 4.



Scheme 5.



R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**), Me (**d**).

creased fraction of the latter (22%). Increase in the fraction of 1,3-disubstituted pyrazole was also observed when aldehyde **I** was replaced by its *N*,*N*-dimethylhydrazone **X** in the reaction with hydrazines **IIa**–**IId** (Scheme 5). Taking into account that hydrazide ion is a difficultly departing group as compared to hydroxide ion, the reaction was expected to begin with addition of hydrazine at the double C=C bond with subsequent elimination of hydrogen chloride and cyclization with liberation of dimethylhydrazine. Equimolar amounts of hydrazone **X** and the corresponding hydrazine were heated for 60 h at 75°C in appropriate solvent, the solvent and *N*,*N*-dimethylhydrazine were removed, and the residue was analyzed by ^{1}H NMR. The results are given in Table 3. In fact, the fraction of 1,3-disubstituted pyrazole increased when the reaction was performed in ethanol, especially with methylhydrazine. The reactions in acetonitrile resulted in the formation of only 1,5-disubstituted pyrazoles, their 1,3-disubstituted isomers were not detected, and reaction mixtures contained unreacted hydrazone **X**.

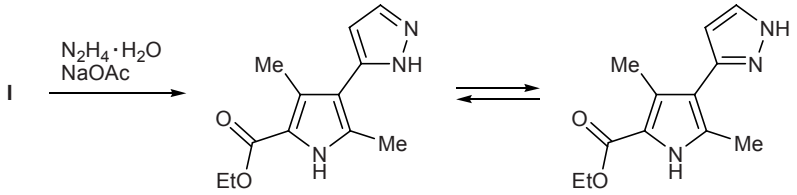
The only product isolated in the reaction of aldehyde **I** with hydrazine hydrate was 3(5)-substituted pyrazole **XI** (Scheme 6). Compound **XI** in DMSO-d_6 displayed in the ^{1}H NMR spectrum (500 MHz, 298 K) two broadened singlets at δ 6.23 and 7.62 ppm instead of characteristic doublets. This pattern may be interpreted in terms of dynamic equilibrium between tautomeric pyrazoles in solution.

Thus, the reactions of ethyl 4-[(*E*)-1-chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbox-

Table 3. Reaction of hydrazone **X** with hydrazines **IIa**–**IId** in ethanol and acetonitrile

Hydrazine	Ratio **III**:**IV**	
	ethanol	acetonitrile
IIa	85:15	41:59
IIb	87:13	42:58
IIc	90:10	45:55
IId	67:33	70:30

Scheme 6.



XI

ylate (**I**) with hydrazines in both acidic and basic media give the corresponding 1,5-disubstituted pyrazoles as the major products. The formation of 1,3-disubstituted isomers is favored by aprotic solvents and the presence of a sterically hindered base capable of forming hydrazide ion in the first step.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Varian Mercury VX-200 (200 MHz) and Bruker Avance DRX-500 (500 MHz) spectrometers using tetramethylsilane as internal standard. The IR spectra were measured in KBr on a Specord M-80 instrument. The mass spectra (electron impact, 70 eV) were obtained on a Varian 1200L mass spectrometer with direct sample admission into the ion source. The progress of reactions was monitored by TLC on Silufol UV-254 plates using chloroform–ethyl acetate (7:3) as eluent.

Reaction of ethyl 4-[(*E*)-1-chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (I) with hydrazines IIa–IId (*general procedure***).** A mixture of 1 mmol (0.26 g) of aldehyde **I** and 1 mmol of hydrazine **IIa**–**IId** in the corresponding solvent was heated under reflux until the initial compound disappeared (TLC). The mixture was evaporated under reduced pressure, and the residue was recrystallized from methylene chloride. The isomer ratio was determined from the ^{1}H NMR spectrum of the residue.

Ethyl 3,5-dimethyl-4-(1-phenyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxylate (IIIa). Solvent ethanol, reaction time 6 h. Yield 0.22 g (70%), mp 152°C. IR spectrum, ν, cm^{-1}: 3304 (NH), 1664 (C=O), 1600, 1504, 1440, 1376, 1272, 1208, 1104, 1024, 784, 760, 688. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.85 s (3H, 3-CH_3), 1.89 s (3H, 5-CH_3), 4.19 q (2H, OCH_2, J = 7.1 Hz), 6.41 d (1H, 4′-H, J = 1.8 Hz), 7.17–7.44 m (5H, C_6H_5), 7.75 d (1H, 3′-H, J = 1.8 Hz), 11.54 s (1H, 1-H). Mass spectrum: m/z 309 $[M]^+$. Found, %: C 70.00; H 6.27; N 13.61. $C_{18}H_{19}N_3O_2$. Calculated, %: C 69.88; H 6.19; N 13.58. M 309.36.

Ethyl 3,5-dimethyl-4-[1-(4-methylphenyl)-1*H*-pyrazol-5-yl]-1*H*-pyrrole-2-carboxylate (IIIb). Solvent ethanol, reaction time 4 h. Yield 0.17 g (53%), mp 172°C. IR spectrum, ν, cm^{-1}: 3312 (NH), 1664 (C=O), 1600, 1512, 1432, 1384, 1280, 1224, 1136, 1104, 1024, 960, 832, 784. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.85 s (3H, 3-CH_3), 1.90 s (3H, 5-CH_3), 2.29 s (3H, CH_3), 4.19 q (2H, OCH_2, J = 7.1 Hz), 6.38 d (1H, 4′-H, J = 1.8 Hz), 7.05–7.22 m (4H, C_6H_4), 7.72 d (1H, 3′-H, J = 1.8 Hz), 11.51 s (1H, 1-H). Mass spectrum: m/z 323 $[M]^+$. Found, %: C 70.68; H 6.64; N 13.04. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.57; H 6.55; N 12.99. M 323.39.

Ethyl 4-[1-(4-bromophenyl)-1*H*-pyrazol-5-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (IIIc). Solvent ethanol, reaction time 6 h. Yield 0.33 g (85%), mp 170–171°C. IR spectrum, ν, cm^{-1}: 3304 (NH), 1664 (C=O), 1488, 1440, 1376, 1280, 1136, 1104, 1024, 1008, 960, 832, 776. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.27 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.87 s (3H, 3-CH_3), 1.90 s (3H, 5-CH_3), 4.20 q (2H, OCH_2, J = 7.1 Hz), 6.43 d (1H, 4′-H, J = 1.8 Hz), 7.14–7.64 m (4H, C_6H_4), 7.77 d (1H, 3′-H, J = 1.8 Hz), 11.59 s (1H, 1-H). Mass spectrum: m/z 389/387 $[M]^+$. Found, %: C 55.76; H 4.76; N 10.87.$C_{18}H_{18}BrN_3O_2$. Calculated, %: C 55.68; H 4.67; N 10.82. M 388.26.

Ethyl 3,5-dimethyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxylate (IIId). Solvent ethanol, reaction time 5 h. Yield 0.12 g (47%), mp 137–138°C. IR spectrum, ν, cm^{-1}: 3296 (NH), 1656 (C=O), 1560, 1496, 1440, 1376, 1272, 1224, 1200, 1104, 1024, 776. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.06 s (6H, 3-CH_3, 5-CH_3), 3.56 s (3H, NCH_3), 4.23 q (2H, OCH_2, J = 7.1 Hz), 6.13 d (1H, 4′-H, J = 1.8 Hz), 7.46 d (1H, 3′-H, J = 1.8 Hz), 11.66 s (1H, 1-H). Mass spectrum: m/z 247 $[M]^+$. Found, %: C 63.24; H 7.01; N 17.04. $C_{13}H_{17}N_3O_2$. Calculated, %: C 63.14; H 6.93; N 16.99. M 247.29.

Ethyl 3,5-dimethyl-4-[1-(2-phenylhydrazono)-ethyl]-1*H*-pyrrole-2-carboxylate (VI). A mixture of 5.31 g (25 mmol) of ethyl 4-acetyl-3,5-dimethyl-1*H*-

pyrrole-2-carboxylate (**V**), 2.80 g (25 mmol) of phenylhydrazine (**IIa**), and 0.61 g (7.6 mmol) of polyphosphoric acid in 74 ml of anhydrous alcohol was heated for 40 h under reflux. The precipitate was filtered off and washed on a filter with water and ethanol. Yield 6.23 g (82%), mp 176°C (from EtOH). IR spectrum, ν, cm^{-1}: 3296 (NH), 1664 (C=O), 1600, 1488, 1504, 1432, 1264, 1208, 1128, 1096, 1064, 1024, 776, 760. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.15 s (3H, CH_3), 2.29 s (3H, 3-CH_3), 2.34 s (3H, 5-CH_3), 4.22 q (2H, OCH_2, J = 7.1 Hz), 6.61–7.21 m (5H, C_6H_5), 8.86 s (1H, NH), 11.32 s (1H, 1-H). Mass spectrum: m/z 299 $[M]^+$. Found, %: C 68.29; H 7.18; N 14.13. $C_{17}H_{21}N_3O_2$. Calculated, %: C 68.20; H 7.07; N 14.04. M 299.37.

Ethyl 4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (VII). Dimethylformamide, 10 ml, was cooled to 0°C, and 6.14 g (40 mmol) of phosphoryl chloride was added under stirring at such a rate that the temperature did not exceed 10°C. The mixture was stirred for 30 min, and a solution of 5.98 g (20 mmol) of phenylhydrazone **VI** in 10 ml of DMF was added under stirring, maintaining the temperature below 10°C. The mixture was stirred for 1 h, heated to 60°C, and kept for 3 h at that temperature. It was then cooled, poured onto 30 g of ice, and neutralized to pH 7 with sodium acetate. The precipitate was filtered off and washed on a filter with water and ethanol. Yield 6.06 g (90%), mp 188°C (from EtOH). IR spectrum, ν, cm^{-1}: 3312 (NH), 1680, 1664 (C=O), 1660, 1544, 1504, 1432, 1280, 1224, 1104, 1024, 752, 688. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_2CH_3, J = 7.1 Hz), 2.19 s (3H, 3-CH_3), 2.21 s (3H, 5-CH_3), 4.25 q (2H, OCH_2, J = 7.1 Hz), 7.35–8.05 m (5H, C_6H_5), 9.27 s (1H, 5′-H), 9.71 s (1H, CHO), 11.66 s (1H, 1-H). Mass spectrum: m/z 337 $[M]^+$. Found, %: C 67.59; H 5.78; N 12.53. $C_{19}H_{19}N_3O_3$. Calculated, %: C 67.64; H 5.68; N 12.46. M 337.37.

3-(5-Ethoxycarbonyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-1-phenyl-1*H*-pyrazole-4-carboxylic acid (VIII). Aldehyde **VII**, 3.37 g (10 mmol), was dispersed in 10 ml of 50% aqueous pyridine, and 1.58 g (10 mmol) of potassium permanganate was added in portions over a period of 1 h under stirring and cooling, maintaining the temperature at 20–22°C. The mixture was stirred for 4 h, the precipitate of manganese dioxide was filtered off, and the filtrate was neutralized to pH 7 with dilute hydrochloric acid. The precipitate was filtered off and washed on a filter with water and ethanol. Yield 2.30 g (65%), mp 223°C (from EtOH). IR spectrum, ν, cm^{-1}: 3296 (NH), 2550–3100 (OH), 1672, 1656 (C=O), 1600, 1520, 1504, 1440, 1280, 1200, 1104, 752, 688. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_2CH_3, J = 7.1 Hz), 2.13 s (3H, 4′-CH_3), 2.15 s (3H, 2′-CH_3), 4.24 q (2H, OCH_2, J = 7.1 Hz), 7.13–8.02 m (5H, C_6H_5), 9.04 s (1H, 5-H), 11.45 s (1H, 1′-H), 12.36 s (1H, COOH). Mass spectrum: m/z 353 $[M]^+$. Found, %: C 64.48; H 5.52; N 11.96. $C_{19}H_{19}N_3O_4$. Calculated, %: C 64.58; H 5.42; N 11.89. M 353.37.

Ethyl 3,5-dimethyl-4-(1-phenyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate (IVa). Copper powder, 1.81 g (29 mmol), was added to a solution of 1.27 g (4 mmol) of carboxylic acid **VIII** in 14 ml of quinoline, and the mixture was heated for 3 h under reflux. It was then cooled, 25 ml of diethyl ether was added, and the copper powder was filtered off and washed with diethyl ether on a filter. The filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized from toluene. Yield 0.88 g (79%), mp 184°C. IR spectrum, ν, cm^{-1}: 3288 (NH), 1656 (C=O), 1600, 1504, 1432, 1344, 1280, 1256, 1208, 1120, 1048, 776, 752, 688. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.38 s (3H, 3-CH_3), 2.44 s (3H, 5-CH_3), 4.23 q (2H, OCH_2, J = 7.1 Hz), 6.60 d (1H, 4′-H, J = 2.6 Hz), 7.20–7.91 m (5H, C_6H_5), 8.52 d (1H, 5′-H, J = 2.6 Hz), 11.46 s (1H, 1-H). Mass spectrum: m/z 309 $[M]^+$. Found, %: C 70.02; H 6.26; N 13.62. $C_{18}H_{19}N_3O_2$. Calculated, %: C 69.88; H 6.19; N 13.58. M 309.36.

Ethyl 4-{1-chloro-3-[2-(4-nitrophenyl)hydrazono]prop-1-en-1-yl}-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (IXa). A mixture of 0.26 g (1 mmol) of aldehyde **I** and 0.15 g (1 mmol) of 4-nitrophenylhydrazine in 10 ml of ethanol was heated for 2 h under reflux. The precipitate was filtered off and washed with ethanol on a filter. Yield 0.33 g (84%), mp 213°C. IR spectrum, ν, cm^{-1}: 3288 (NH), 1680 (C=O), 1600, 1576, 1504, 1480, 1440, 1296, 1272, 1192, 1112, 832, 752. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.26 s (3H, 3-CH_3), 2.29 s (3H, 5-CH_3), 4.24 q (2H, OCH_2, J = 7.1 Hz), 6.42 d (1H, =CH, J = 9.1 Hz), 7.04–7.13 d and 8.08–8.16 d (2H each, C_6H_4), 8.14 d (1H, =CH, J = 9.1 Hz), 11.44 s (1H, NH), 11.70 s (1H, NH). Mass spectrum: m/z 392/390 $[M]^+$. Found, %: C 55.24; H 5.00; N 14.24. $C_{18}H_{19}ClN_4O_4$. Calculated, %: C 55.32; H 4.90; N 14.34. M 390.82.

Ethyl 4-{1-chloro-3-[2-(2,4-dinitrophenyl)hydrazono]prop-1-en-1-yl}-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (IXb). A solution of 0.26 g (1 mmol) of

aldehyde **I** in 5 ml of ethanol was added to a solution of 0.20 g (1 mmol) of 2,4-dinitrophenylhydrazine in a mixture of 5 ml of ethanol, 1.5 ml of water, and 1 ml of sulfuric acid. The mixture was heated for 15 min under reflux, and the precipitate was filtered off and washed on a filter with water and ethanol. Yield 0.42 g (96%), mp 229–230°C. IR spectrum, ν, cm^{-1}: 3288 (NH), 1680 (C=O), 1623, 1608, 1560, 1512, 1424, 1336, 1320, 1280, 1136, 1096, 1024, 832, 744. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.28 s (3H, 3-CH_3), 2.30 s (3H, 5-CH_3), 4.23 q (2H, OCH_2, J = 7.1 Hz), 6.47 d (1H, =CH, J = 9.1 Hz), 7.88 d (1H, 6′-H, J = 9.7 Hz), 8.36 d.d (1H, 5′-H, J = 9.7, 2.7 Hz), 8.84 d (1H, 3′-H, J = 2.7 Hz), 8.85 d (1H, =CH, J = 9.1 Hz), 11.73 s and 11.79 s (1H each, NH). Mass spectrum: m/z 437/435 $[M]^+$. Found, %: C 49.55; H 4.25; N 15.98. $C_{18}H_{18}ClN_5O_6$. Calculated, %: C 49.61; H 4.16; N 16.07. M 435.82.

Ethyl 4-{3-[2-(4-bromophenyl)hydrazono]-1-chloroprop-1-en-1-yl}-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (IXc). A solution of 0.26 g (1 mmol) of aldehyde **I** and 0.19 g (1 mmol) of 4-bromophenylhydrazine (**IIc**) in 10 ml of acetonitrile was heated for 2 h under reflux. The mixture was cooled, and the precipitate was filtered off and washed on a filter with ethanol. Yield 0.34 g (81%), mp 144°C (from EtOH). IR spectrum, ν, cm^{-1}: 3304 (NH), 1672 (C=O), 1616, 1592, 1568, 1512, 1480, 1440, 1288, 1256, 1192, 1168, 1136, 1096, 1024, 856, 808. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.24 s (3H, 3-CH_3), 2.27 s (3H, 5-CH_3), 4.23 q (2H, OCH_2, J = 7.1 Hz), 6.34 d (1H, =CH, J = 9.1 Hz), 6.88–7.40 m (4H, C_6H_4), 7.96 d (1H, =CH, J = 9.1 Hz), 10.68 s and 11.61 s (1H each, NH). Mass spectrum: m/z 425/423 $[M]^+$. Found, %: C 50.81; H 4.60; N 9.81. $C_{18}H_{19}BrClN_3O_2$. Calculated, %: C 50.90; H 4.51; N 9.89. M 424.72.

Reaction of ethyl 4-[(*E*)-1-chloro-3-oxoprop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (I) with phenylhydrazine (IIa) in the presence of 1,4-diazabicyclo[2.2.2]octane. A mixture of 0.27 g (2.5 mmol) of phenylhydrazine and 0.27 g (2.5 mmol) of DABCO in 20 ml of ethanol was heated for 30 min under reflux, a solution of 0.52 g (2 mmol) of aldehyde **I** in 10 ml of ethanol was added, and the mixture was heated for 4 h under reflux. The solvent was removed under reduced pressure, 8 ml of methylene chloride was added to the residue, the precipitate of DABCO salt was filtered off, the filtrate was evaporated, and the residue was analyzed.

Ethyl 4-[1-chloro-3-(2,2-dimethylhydrazono)-prop-1-en-1-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (X). A solution of 1.51 g (6 mmol) of aldehyde **I** and 0.9 ml (12 mmol) of *N*,*N*-dimethylhydrazine in 30 ml of diethyl ether was stirred for 48 h at room temperature. The mixture was evaporated, and the residue was washed with water and recrystallized from ethanol. Yield 1.13 g (64%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 3272 (NH), 1672 (C=O), 1536, 1504, 1440, 1384, 1352, 1288, 1200, 1104, 1048, 1024, 872, 776. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 t (3H, CH_2CH_3, J = 7.1 Hz), 2.20 s (3H, 3-CH_3), 2.24 s (3H, 5-CH_3), 2.91 s (6H, NCH_3), 4.22 q (2H, OCH_2, J = 7.1 Hz), 6.24 d (1H, =CH, J = 8.6 Hz), 7.13 d (1H, =CH, J = 8.6 Hz), 11.55 s (1H, 1-H). Mass spectrum: m/z 299/297 $[M]^+$. Found, %: C 56.42; H 6.86; N 14.02. $C_{14}H_{20}ClN_3O_2$. Calculated, %: C 56.47; H 6.77; N 14.11. M 297.78.

Ethyl 3,5-dimethyl-4-[1*H*-pyrazol-3(5)-yl]-1*H*-pyrrole-2-carboxylate (XI). A mixture of 0.52 g (2 mmol) of aldehyde **I**, 0.33 g (4 mmol) of sodium acetate, and 0.6 ml (12 mmol) of hydrazine hydrate in 10 ml of ethanol was heated for 10 h under reflux. The mixture was evaporated under reduced pressure, and the residue was washed with water and recrystallized from ethanol. Yield 0.44 g (95%), mp 158°C. IR spectrum, ν, cm^{-1}: 3288 (NH), 1656 (C=O), 1600, 1512, 1440, 1280, 1208, 1096, 928, 776. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t (3H, CH_2CH_3, J = 7.1 Hz), 2.25 s (3H, 3-CH_3), 2.30 s (3H, 5-CH_3), 4.22 q (2H, OCH_2, J = 7.1 Hz), 6.22 s and 7.62 s (1H each, 4′-H, 5′-H), 11.43 s (1H, 1-H), 12.64 s (1H, 1′-H). Mass spectrum: m/z 233 $[M]^+$. Found, %: C 61.90; H 6.56; N 18.05. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01. M 233.27.

REFERENCES

1. Pulst, M. and Weiβenfels, M., *Z. Chem*., 1976, vol. 16, p. 337.
2. Marson, Ch.M. and Giles, P.R., *Synthesis Using Vilsmeier Reagents*, Boca Raton: CRC, 1994.
3. Brahma, S. and Ray, J.K., *Tetrahedron*, 2008, vol. 64, p. 2883.
4. *Kompendium 2006: lekarstvennye preparaty* (Compendium 2006: Drugs), Kovalenko, V.N. and Viktorova, A.P., Eds., Morion, 2006; *http://www.compendium.com.us*.
5. Penning, T.D., Talley, J.J., Bertenshaw, S.R., Carter, J.S., Collins, P.W., Docter, S., Graneto, M.J., Lee, L.F., Malecha, J.W., Miyashiro, J.M., Rogers, R.S., Rogier, D.J., Yu, S.S., Anderson, G.D., Burton, E.G., Cogburn, J.N., Gregory, S.A., Koboldt, C.M., Perkins, W.E., Seibert, K.,

Veenhuizen, A.W., Zhang, Y.Y., and Isakson, P.C., *J. Med. Chem*., 1997, vol. 40, p. 1347.

6. Terrett, N.K., Bell, A.S., Brown, D., and Ellis, P., *Bioorg. Med. Chem. Lett*., 1996, vol. 6, p. 1819.
7. Menozzi, G., Merello, L., Fossa, P., Mosti, L., Piana, A., and Mattioli, F., *Farmaco*, 2003, vol. 58, p. 795.
8. Drysdale, M.J., Dymock, B.W., Barril-Alonso, X., Workman, P., Pearl, L.H., Prodromou, Ch., and MacDonald, E., WO Patent no. 2003055860, 2003; *Chem. Abstr*., 2003, vol. 139, no. 101122.
9. Lamberth, C., *Heterocycles*, 2007, vol. 71, p. 1467.
10. Chornous, V.O., Bratenko, M.K., Bukachuk, O.M., Baranova, L.Ya., and Vovk, M.V., *Fiziol. Aktiv. Rechov*., 2002, vol. 34, p. 20.
11. Shrout, D.P. and Lightner, D.A., *Synthesis*, 1990, vol. 11, p. 1062.
12. Preobrazhenskii, N.A. and Evstigneeva, R.P., *Khimiya biologicheski aktivnykh prirodnykh soedinenii* (Chemistry of Biologically Active Natural Compounds), Moscow: Khimiya, 1976, p. 100.
13. Bijev, A.T., Nankov, A.N., and Prodanova, P.P., *Bulg. Chem. Commun*., 2001, vol. 33, p. 173.
14. Bellinaa, F. and Rossi, R., *Tetrahedron*, 2006, vol. 62, p. 7213.
15. Kozhich, D.T., Vasilevskii, V.I., Mironov, A.F., and Evstigneeva, R.P., *Zh. Org. Khim*., 1980, vol. 16, p. 849.
16. Strakova, I., Petrova, M., Belyakov, S., and Strakov, A., *Khim. Geterotsikl. Soedin*., 2003, p. 1827.
17. Zora, M. and Gormen, M., *J. Organomet. Chem*., 2007, p. 5026.
18. Cohen-Fernandes, P., Erkelens, C., Eendenburg, C.G.M., Verhoeven, J.J., and Habraken, C.L., *J. Org. Chem*., 1979, vol. 44, p. 4156.
19. Gupton, J.T., Clough, S.C., Miller, R.B., Norwood, B.K., Hickenboth, C.R., Chertudi, I.B., Cutro, S.R., Petrich, S.A., Hicks, F.A., Wilkinson, D.R., and Sikorski, J.A., *Tetrahedron*, 2002, vol. 58, p. 5467.
20. Peruncheralathan, S., Yadav, A.K., Ila, H., and Junjappa, H., *J. Org. Chem*., 2005, vol. 70, p. 9645.