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4-Functionally-Substituted 3-Heterylpyrazoles: XIX.* 3-Aryl-4-(5-Isoxazolyl)pyrazoles

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Abstract—Oximes of 4-(4-pyrazolyl)-3-buten-2-onees obtained by successive reaction of 3-aryl-4-formylpyrazoles with acetone and hydroxylamine at the treatment with iodine suffered an oxidative cyclization yielding 3-aryl-4-(5-isoxazolyl)pyrazoles.

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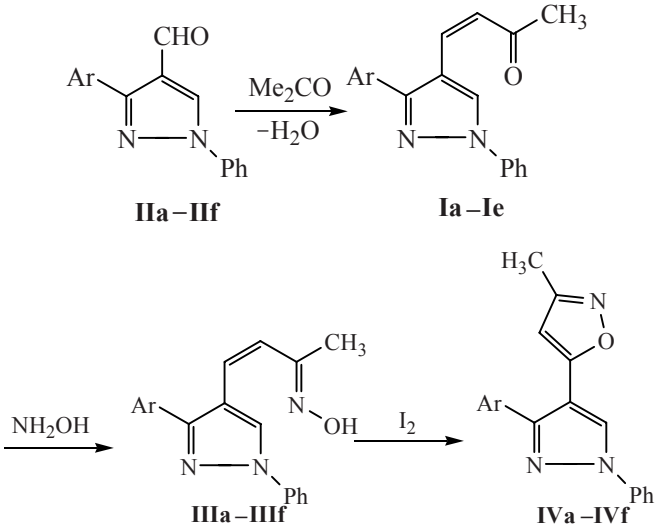
The designing of new types of polyheterocyclic compounds alongside the refining of procedures for preparation of these known substances is an urgent target of the modern heterocyclic chemistry. Many among the heterocyclic ensembles are both convenient models for investigating the interaction of heterofragments and structures with potential high biological activity. The analysis of published data shows the high promise of purposeful synthetic search in the series of heteryl-substituted pyrazoles. In particular, pyrazole derivatives already were formerly obtained containing in the position *4* oxazoline [2], dihydropyridine [3], pyrazoline [4, 5], dihydropyrimidine [6], and benzopyran [7] fragments.

Here we report on investigation results on the synthesis of new pyrazole derivatives functionalized in the position *4* with pharmacologically significant [8] isoxazole ring. The information on similar compounds is limited to [9, 10] where the building up of pyrazole or isoxazole rings respectively occurs based on relatively difficultly available isoxazolyl- or pyrazolyl-β-diketones. The condensation of more accessible β-(1,3-diphenyl-pyrazolyl)-α-ethyl vinyl ketone with hydroxylamine however provided only 4-(4,5-dihydroisoxazolyl)-1,5-diphenylpyrazole [4].

We found that β-(1,3-diphenylpyrazolyl)-α-ethyl vinyl ketones **Ia–If** obtained by condensation of 3-aryl-4-formylpyrazoles **IIa–IIf** with acetone in reaction with hydroxylamine hydrochloride in boiling pyridine did not form a 4,5-dihydroisoxazole ring but give stable oximes **IIIa–IIIf**. Analysis of ^{1}H NMR spectra of α,β-vinyl ketones **Ia–If** indicted that they existed exclusively in the form of *E*-isomers. Yet their oximes formed as *E,Z*- and *E,E*-isomers, the fact previously unknown for 4-aryl-3-buten-2-ones [11–13]. This fact is proved by a double set of signals from protons H^5 of the pyrazole ring and from groups CH_3 and OH. Taking into account the data of [11, 12] it is possible to assume reliably that in the case in question prevailingly form *E,Z*-isomers more stereochemically favorable for further cyclization: The content of these isomers varies in the range 81–85%. The preferable procedure for conversion of oximes **IIIa–IIIf** into target 4-(5-isoxazolyl)pyrazoles **IVa–IVf**



Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 4-EtC_6H_4 (**e**), 4-$MeOC_6H_4$ (**f**).

* For communication XVIII, see [1].

proved to be the oxidative cyclization by means of iodine [13]. The application of a system I_2–KI–$NaHCO_3$ in boiling DMF made it possible to obtain compounds **IVa–IVf** in 58–71% yields.

The structure of 4-isoxazolopyrazoles **IV** was confirmed by ^{1}H NMR spectra where along with typical signals of aromatic and methyl substituents were observed the singlet of proton H^4 from the isoxazole ring (6.19–6.29 ppm) and proton H^5 of the pyrazole ring (8.90–9.11 ppm).

EXPERIMENTAL

IR spectra of compounds were recorded on a spectrophotometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered on a spectrometer Varian-Gemini (300 MHz) in $(CD_3)_2SO$, internal referece TMS.

4-(4-Pyrazolyl)-3-buten-2-ones Ia–If. To a solution of 40 mmol of aldehyde **IIa–IIf** in 50 ml of acetone was added at stirring 5 ml of 10% water solution of NaOH, the mixture was stirred at room temperature for 12 h, then into the reaction mixture 200 ml of ice water was poured. The separated precipitate was filtered off, washed with dilute hydrochloric acid, dried, and recrystallized from ethanol.

4-(1,3-Diphenyl-4-pyrazolyl)-3-buten-2-one (Ia). Yield 73%, mp 124–126°C. IR spectrum, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 6.71 d (1H, H^2, J 16.0 Hz), 7.05–7.64 m (11H, H_{arom}+H^1), 9.17 s (1H, $H^5_{pyrazole}$). Found, %: C 78.89; H 5.67; N 9.60. $C_{19}H_{16}N_2O$. Calculated, %: C 79.16; H 5.56; N 9.72.

4-[1-Phenyl-3-(4-fluorophenyl)-4-pyrazolyl]-3-buten-2-one (Ib). Yield 81%, mp 142–143°C. IR spectrum, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 6.73 d (1H, H^2, J 16.2 Hz), 7.29–7.93 m (10H, 9H_{arom}+H^1), 9.16 s (1H, $H^5_{pyrazole}$). Found, %: C 74.23; H 5.03; N 9.02. $C_{19}H_{15}FN_2O$. Calculated, %: C 74.51; H 4.90; N 9.15.

4-[1-Phenyl-3-(4-chlorophenyl)-4-pyrazolyl]-3-buten-2-one (Ic). Yield 78%, mp 139–141°C. IR spectrum, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 6.73 d (1H, H^2, J 16.2 Hz), 7.32–7.56 m (6H, 5H_{arom}+H^1), 7.68 d (2H, H_{arom}, J 8.4 Hz), 7.91 d (2H_{arom}, J 8.2 Hz), 9.16 s (1H, $H^5_{pyrazole}$). Found, %: C 70.48; H 4.61; N 8.57. $C_{19}H_{15}ClN_2O$. Calculated, %: C 70.70; H 4.65; N 8.68.

4-[3-(4-Tolyl)-1-phenyl-4-pyrazolyl]-3-buten-2-one (Id). Yield 76%, mp 140–142°C. IR spectrum, cm^{-1}: 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 2.27 C (3H, CH_3), 6.74 d (1H, H^2, J 16.2 Hz), 7.32–7.53 m (6H, 5H_{arom}+H^1), 7.63 d (2H_{arom}, J 8.2 Hz), 7.92 d (2H_{arom}, J 7.8 Hz), 9.16 s (1H, $H^5_{pyrazole}$). Found, %: C 79.42; H 6.09; N 9.13. $C_{20}H_{18}N_2O$. Calculated, %: C 79.47; H 5.96; N 9.27.

4-[1-Phenyl-3-(4-ethyl)-4-pyrazolyl]-3-buten-2-one (Ie). Yield 72%, mp 119–120°C. IR spectrum, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3, J 7.5 Hz), 2.27 s (3H, CH_3), 2.70 q (2H, CH_2, J 7.5 Hz), 6.73 d (1H, H^2, J 16.5 Hz), 7.27–7.54 m (8H, 7H_{arom}+H^1), 7.92 d (2H_{arom}), 9.16 s (1H, $H^5_{pyrazole}$). Found, %: C 80.04; H 6.29; N 8.95. $C_{21}H_{20}N_2O$. Calculated, %: C 79.75; H 6.33; N 8.86.

4-[3-(4-Methoxyphenyl)-1-phenyl-4-pyrazolyl]-3-buten-2-one (If). Yield 71%, mp 135–136°C. IR spectrum, cm^{-1}: 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.84 C (3H, CH_3O), 6.72 d (1H, H^2, J 16.2 Hz), 7.05 d (2H_{arom}, J 8.8 Hz), 7.35–7.56 m (6H, 5H_{arom}+H^1), 7.91 d (2H, H_{arom}, J 8.8 Hz), 9.12 s (1H, $H^5_{pyrazole}$). Found, %: C 75.32; H 5.76; N 8.64. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.47; H 5.66; N 8.81.

4-(4-Pyrazolyl)-3-buten-2-ones oximes IIIa–IIIf. To a solution of 10 mmol of vinyl ketone **Ia–If** in 20 ml of pyridine was added 1.39 g (20 mmol) of hydroxylamine hydrochloride, and the mixture was boiled at reflux for 3 h. On cooling to room temperature the reaction mixture was poured into 100 ml of ice water, the separated precipitate was filtered off, washed with 10% hydrochloric acid, dried, and crystallized from ethanol.

4-(1,3-Diphenyl-4-pyrazolyl)-3-buten-2-one oxime (IIIa). Yield 83%, mp 150–152°C. IR spectrum, cm^{-1}: 1630 (C=N), 3280 (OH). ^{1}H NMR spectrum, δ, ppm: 1.95 s, 1.99 s (3H, CH_3), 6.72 d (1H, =CH_A, J 15.5 Hz), 6.79 d (1H, =CH_B, J 15.5 Hz), 7.30–7.51 m (6H_{arom}), 7.65 d (2H_{arom}, J 6.9 Hz), 7.91 d (2H_{arom}, J 7.1 Hz), 8.94 s, 9.01 s (1H, $H^5_{pyrazole}$), 10.08 s, 10.96 s (1H, OH). Found, %: C 75.49; H 5.44; N 14.05. $C_{17}H_{17}N_3O$. Calculated, %: C 75.25; H 5.61; N 13.86.

4-[1-Phenyl-3-(4-fluorophenyl)-4-pyrazolyl]-3-buten-2-one oxime (IIIb). Yield 85%, mp 224–226°C. IR spectrum, cm^{-1}: 1625 (C=N), 3285 (OH). ^{1}H NMR spectrum, δ, ppm: 1.93 s, 1.98 s (3H, CH_3), 6.70 d (1H, =CH_A, J 15.6 Hz), 6.77 d (1H, =CH_B, J 15.6 Hz), 7.25–7.90 m (9H_{arom}), 8.92 s, 8.98 s (1H, $H^5_{pyrazole}$), 10.64 s, 10.78 s (1H, OH). Found, %: C 70.77; H 5.14; N 13.32. $C_{19}H_{16}FN_3O$. Calculated, %: C 71.03; H 4.98; N 13.08.

4-[1-Phenyl-3-(4-chlorophenyl)-4-pyrazolyl]-3-buten-2-one oxime (IIIc). Yield 87%, mp 248–250°C.

IR spectrum, cm^{-1}: 1625 (C=N), 3290 (OH). ^1H NMR spectrum, δ, ppm: 1.95 s, 1.99 s (3H, CH_3), 6.74 d (1H, $=CH_A$, *J* 15.6 Hz), 6.80 d (1H, $=CH_B$, *J* 15.6 Hz), 7.29–7.97 m (9H_{arom}), 8.93 s, 9.01 s (1H, $H^5_{pyrazole}$), 10.68 s, 10.95 s (1H, OH). Found, %: C 67.82; H 4.85; N 12.59. $C_{19}H_{16}ClN_3O$. Calculated, %: C 67.56; H 4.74; N 12.44.

4-[3-(4-Tolylphenyl)-1-phenyl-4-pyrazolyl]-3-buten-2-one oxime (IIId). Yield 78%, mp 223–225°C. IR spectrum, cm^{-1}: 1630 (C=N), 3280 (OH). ^1H NMR spectrum, δ, ppm: 1.94 s, 1.98 s (3H, CH_3), 6.73 d (1H, $=CH_A$, *J* 15.5 Hz), 6.81 d (1H, $=CH_B$, *J* 15.5 Hz), 7.31–7.88 m (9H_{arom}), 8.91 s, 8.99 s (1H, $H^5_{pyrazole}$), 10.72 s, 10.94 s (1H, OH). Found, %: C 75.79; H 6.05; N 13.29. $C_{20}H_{19}N_3O$. Calculated, %: C 75.71; H 5.99; N 13.25.

4-[1-Phenyl-3-(4-ethylphenyl)-4-pyrazolyl]-3-buten-2-one oxime (IIIe). Yield 81%, mp 175–176°C. IR spectrum, cm^{-1}: 1630(C=N), 3280 (OH). ^1H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3, *J* 7.5 Hz), 1.95 s, 1.99 s (3H, CH_3), 2.68 d (2H, CH_2, *J* 7.5 Hz), 6.77 d (1H, $=CH_A$, *J* 15.5 Hz), 6.84 d (1H, $=CH_B$, *J* 15.5 Hz), 7.28–7.94 m (9H_{arom}), 8.93 C, 9.01 s (1H, $H^5_{pyrazole}$), 10.69 s, 10.95 s (1H, OH). Found, %: C 70.77; H 5.14; N 13.32. $C_{19}H_{16}FN_3O$. Calculated, %: C 71.03; H 4.98; N 13.08.

4-[3-(4-Methoxyphenyl)-1-phenyl-4-pyrazolyl]-3-buten-2-one oxime (IIIf). Yield 77%, mp 192–194°C. IR spectrum, cm^{-1}: 1625 (C=N), 3275 (OH). ^1H NMR spectrum, δ, ppm: 1.95 s, 1.99 s (3H, CH_3), 3.83 s (3H, CH_3O) 6.73 d (1H, $=CH_A$, *J* 15.6 Hz), 6.80 d (1H, $=CH_B$, *J* 15.6 Hz), 7.02–7.94 m (9H_{arom}), 8.88 s, 8.96 s (1H, $H^5_{pyrazole}$), 10.64 s, 10.91 s (1H, OH). Found, %: C 71.79; H 5.56; N 12.50. $C_{20}H_{19}N_3O_2$. Calculated, %: C 72.07; H 5.71; N 12.61.

3-Aryl-4-(5-isoxazolyl)pyrazoles IVa–IVf. To a solution of 3.3 mmol of oxime **IIIa–IIIf** in 15 ml of DMF was added a mixture of 0.85 g (3.3mmol) of iodine, 1.8 g (11 mmol) of potassium iodide, and 1 g (12 mmol) of sodium hydrogen carbonate in 5 ml of water, and the reaction mixture was boiled for 3 h. On cooling to room temperature the reaction mixture was poured into 100 ml of 2% solution of sodium thiosulfate, the separated precipitate was filtered off, washed with water, and crystallized from acetic acid.

4-(3-Methyl-5-isoxazolyl)-1,3-diphenylpyrazole (IVa). Yield 68%, mp 116–118°C. ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 6.17 s (1H, $H^4_{isoxazole}$), 7.33–7.61 m (8H_{arom}), 7.92 d (2H_{arom}, *J* 8.1 Hz), 9.06 s (1H, $H^5_{pyrazole}$). Found, %: C 75.69; H 5.05; N 14.00. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

4-(3-Methyl-5-isoxazolyl)-1-phenyl-3-(4-fluorophenyl)pyrazole (IVb). Yield 67%, mp 136–137°C. ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 6.29 s (1H, $H^4_{isoxazole}$), 7.33–7.67 m (7H_{arom}), 7.96 d (2H_{arom}, *J* 7.9 Hz), 9.11 s (1H, $H^5_{pyrazole}$). Found, %: C 71.40; H 4.46; N 13.08. $C_{19}H_{14}FN_3O$. Calculated, %: C 71.46; H 4.42; N 13.16.

4-(3-Methyl-5-isoxazolyl)-1-phenyl-3-(4-chlorophenyl)pyrazole (IVc). Yield 63%, mp 135–136°C. ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 6.24 s (1H, $H^4_{isoxazole}$), 7.36–7.66 m (7H_{arom}), 7.95 d (2H_{arom}, *J* 8.0 Hz), 9.07 s (1H, $H^5_{pyrazole}$). Found, %: C 71.40; H 4.46; N 13.08. $C_{19}H_{14}ClN_3O$. Calculated, %: C 67.96; H 4.20; N 12.51.

4-(3-Methyl-5-isoxazolyl)-3-(4-tolylphenyl)-1-phenylpyrazole (IVd). Yield 71%, mp 142–143°C. ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.40 s (3H, CH_3), 6.20 s (1H, $H^4_{isoxazole}$), 7.26–7.54 m (7H_{arom}), 7.41 d (2H_{arom}, *J* 7.2 Hz), 9.03 s (1H, $H^5_{pyrazole}$). Found, %: C 76.23; H 5.35; N 13.38. $C_{20}H_{17}N_3O$. Calculated, %: C 76.17; H 5.43; N 13.32.

4-(3-Methyl-5-isoxazolyl)-1-phenyl-3-(4-ethylphenyl)pyrazole (IVe). Yield 58%, mp 139–140°C. ^1H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3, *J* 7.5 Hz), 2.24 C (3H, CH_3), 2.71 q (2H, CH_2, *J* 7.5 Hz), 6.17 s (1H, $H^4_{isoxazole}$), 7.31–7.52 m (7H_{arom}), 7.93 d (2H_{arom}, *J* 7.0 Hz), 9.03 s (1H, $H^5_{pyrazole}$). Found, %: C 76.50; H 5.88; N 12.70. $C_{21}H_{19}N_3O$. Calculated, %: C 76.57; H 5.81; N 12.76.

4-(3-Methyl-5-isoxazolyl)-3-(4-methoxyphenyl)-1-phenylpyrazole (IVf). Yield 63%, mp 129–130°C. ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 3.83 C (3H, CH_3O), 6.16 s (1H, $H^4_{isoxazole}$), 7.01 d (2H_{arom}, *J* 6.9 Hz), 7.36–7.53 m (5H_{arom}), 7.92 d (2H_{arom}, *J* 6.9 Hz), 8.99 s (1H, $H^5_{pyrazole}$). Found, %: C 72.40; H 5.27; N 12.63. $C_{20}H_{17}N_3O_2$. Calculated, %: C 72.49; H 5.17; N 12.68.

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