Chemistry of Heterocyclic Compounds, Vol. 41, No. 5, 2005

5-PHENYL-2-(PYRAZOL-4-YL)-1,3,4-THIADIAZOLES

T. V. Shokol, V. V. Semenyuchenko, and V. P. Khilya

By recyclization of 2-R-6-ethyl-7-hydroxy(methoxy)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones when treated with hydrazine hydrate and phenylhydrazine, we synthesized 5-phenyl-2-(3-R-5-R1-1H-pyrazol-4-yl)-1H-1,3,4-thiadiazoles and 2-(3-R-5-R1-1-phenyl-1H-pyrazol-4-yl)-5-phenyl-1H-1,3,4-thiadiazoles. We confirmed the structure of the latter from ^{1}H NMR spectra.

Keywords: pyrazoles, thiadiazoles, chromones.

Pyrazole derivatives have been widely used as dyes [1] and drugs [2]. Derivatives of 1,3,4-thiadiazole also are characterized by a broad spectrum of useful properties: they are carboanhydrase inhibitors and drugs for treatment of gastrointestinal infections, and are used for photometric determination of some metals [3].

Combining the rings of these two heterocycles in the same molecule may lead to products with interesting pharmacological effects. Among pyrazolyl-1,3,4-thiadiazoles, compounds have already been found that are hypoglycemic [4, 5], antiinflammatory [6], bactericidal [7-9], and fungicidal [8, 10]. We note that all the known procedures for synthesis of such compounds are based on adding a thiadiazole ring onto an already constructed pyrazole ring [4-11]. We used an alternative route for synthesis of 5-phenyl-2-(pyrazol-4-yl)-1,3,4-thiadiazoles: formation of a pyrazole ring from compounds containing a thiadiazole moiety by recyclization of 3-hetarylchromones when treated with hydrazine and its derivatives [12, 13]. The starting compounds in this reaction are 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones **1a-f** [14] and their 7-methoxy derivatives **2a-c**, obtained by alkylation of the corresponding products **1a-c** with dimethyl sulfate in dimethyl formamide in the presence of potassium carbonate.

In the ^{1}H NMR spectra of compounds **2a-c**, recorded in DMSO-d_6, there is no downfield signal from the OH-7 group which is typical of the starting products **1a-c**, and instead we see a three-proton singlet for the CH_3-7 group in the 3.84-3.98 ppm region. Signals for the rest of the protons of the corresponding products **1a-c** and **2a-c** are found in the same regions.

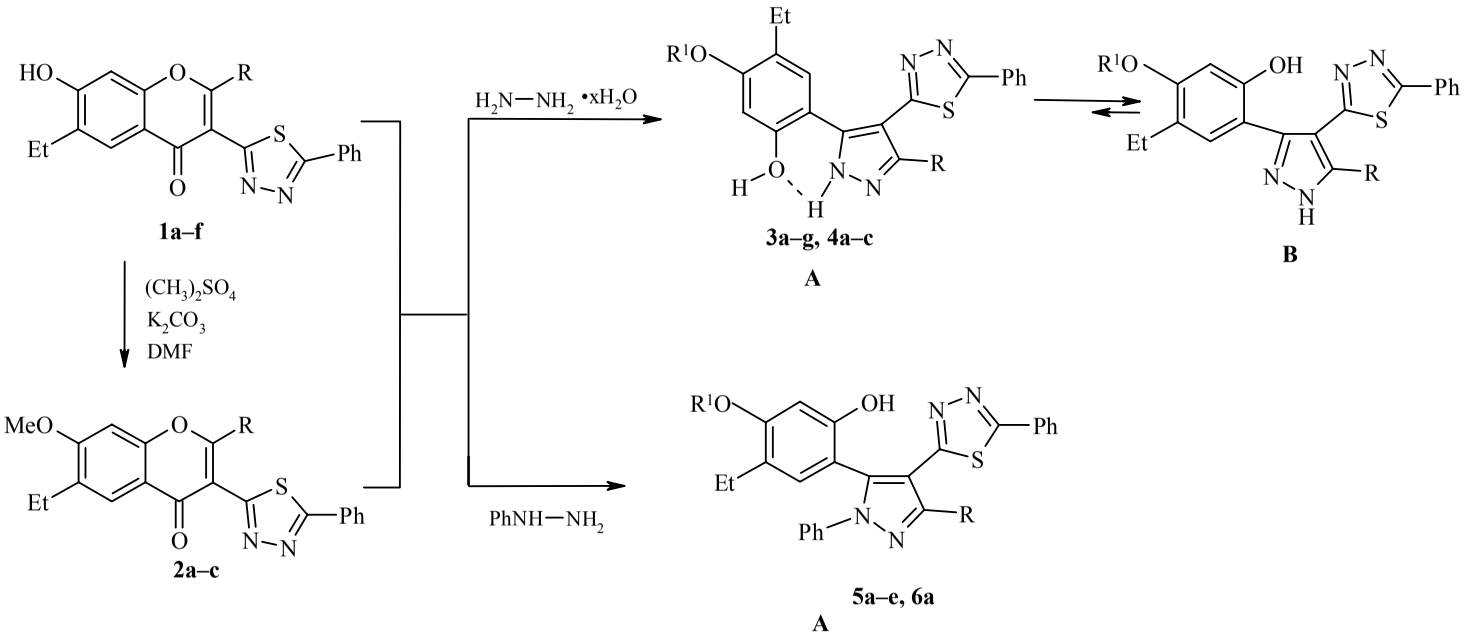
When suspensions of compounds **1a-f** and **2a-c** are boiled in alcohol with excess hydrazine hydrate, practically instantaneously a solution is formed from which chromatographically pure pyrazoles **3a-f** and **4a-c** precipitate or are precipitated by water in quantitative yields. Boiling chromone **1f** for a longer time (10 min) with hydrazine hydrate leads to a mixture of the ester **3f** and the hydrazide **3g**.

The pure hydrazide **3g** was obtained by boiling a mixture of the products **3f** and **3g** with hydrazine hydrate in DMF. Recyclization of chromones **1a-e** and **2a** to form N-phenylpyrazoles **5a-e, 6** when treated with phenylhydrazine in alcohol occurs with a much longer reaction time (1.5-11 h). For compounds **1b,c**, under these conditions the reaction does not go to completion, and boiling in DMF for 2-4.5 h is required for the reaction to finish. Pyrazoles **3-6** readily dissolve in a 2N solution of sodium hydroxide, which indicates the presence of a free phenol hydroxyl in their molecules. The products **3** and **4** form blue-green chelates with an

---

Taras Shevchenko Kiev National University, Kiev 01033, Ukraine; e-mail: vkhilya@univ.kiev.ua.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 781-787, May, 2005. Original article submitted March 11, 2003.

Scheme



1, **3**, **5** R^1 = H; **2, 4, 6** R^1 = Me, **a** R = H, **b** R = Me, **c** R = Et, **d** R = CF_3, **e** R = $(CH_2)_2CO_2H$, **f** R = CO_2Et, **g** R = $CONHNH_2$

alcoholic solution of ferric chloride, due to the presence of a phenol hydroxyl that is favorably located sterically relative to the nitrogen atom in the pyrazole ring. The chelate structure of pyrazoles **3** and **4** allows us to explain the 1.0-1.2 ppm upfield shift of the signal for the H-6 proton (of the phenyl ring) in the ^{1}H NMR spectra (in DMSO-d_6) compared with the position of the H-5 proton peak for the starting chromones **1** and **2**. Evidence for the pyrazole structure of derivatives **3a** and **4a** also comes from the broadened signal for the H-5 proton of the pyrazole ring, which experiences spin–spin coupling with the proton at the nitrogen atom.

In the ^{1}H NMR spectra of compounds **3**, downfield we see a considerably broadened one-proton singlet at 12.6-13.4 ppm and two close broadened singlets in the 9.2-9.5 ppm region. In the spectra of N-phenylpyrazoles **5a-d** and **6**, we also observe two singlets in the 9.3-9.6 ppm region, while the signal in the 13 ppm region is missing. These data allow us to assign the signal furthest downfield in the spectra of pyrazoles **3** to the N–H proton, and we can assign the signals in the 9 ppm region to the hydroxy group protons.

In the spectrum of methoxy derivative **4b**, we also see the broadened singlet for the N–H proton furthest downfield at 12.80 ppm and only one broadened one-proton singlet for the OH-2 group at 9.48 ppm, and a three-proton singlet from the CH_3O-4 group also appears in the 2.57 ppm region. In the spectra of the methoxy derivatives **4a,c** in the region where mobile protons absorb, we observe twice the number of peaks assigned to the protons of the OH-2 groups, the protons of the N–H and C–H (for compound **4a**) of the pyrazole ring, which

TABLE 1. Characteristics of Compounds **2-6**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Solvent for recrystallization	Yield, %
		S	N			
2a	$C_{20}H_{16}N_2O_3S$	8.76 / 8.80	7.86 / 7.69	223	DMF	85
2b	$C_{21}H_{18}N_2O_3S$	8.31 / 8.47	7.65 / 7.40	219	DMF	87
2c	$C_{22}H_{20}N_2O_3S$	8.19 / 8.17	6.90 / 7.14	206	DMF	71
3a	$C_{19}H_{16}N_4O_2S$	8.90 / 8.80	15.62 / 15.38	260	Ethanol	88
3b	$C_{20}H_{18}N_4O_2S$	8.47 / 8.47	14.60 / 14.81	246	Aqueous alcohol	92
3c	$C_{21}H_{20}N_4O_2S$	7.87 / 8.17	14.05 / 14.28	243	Aqueous alcohol	90
3d	$C_{20}H_{15}F_3N_4O_2S$	8.26 / 8.01	14.10 / 13.99	226	Aqueous alcohol	82
3e	$C_{22}H_{20}N_4O_4S$	7.20 / 7.35	13.10 / 12.84	299	Aqueous alcohol	91
3f	$C_{22}H_{20}N_4O_4S$	7.12 / 7.35	12.69 / 12.84	114	Aqueous alcohol	91
3g	$C_{20}H_{18}N_6O_3S$	7.66 / 7.59	20.12 / 19.89	>300	Aqueous alcohol	87
4a	$C_{20}H_{18}N_4O_2S$	8.66 / 8.47	15.06 / 14.81	221	Ethanol	92
4b	$C_{21}H_{20}N_4O_2S$	7.91 / 8.17	14.54 / 14.28	246	Ethanol	77
4c	$C_{22}H_{22}N_4O_2S$	8.13 / 7.89	13.80 / 13.78	196	Aqueous alcohol	98
5a	$C_{25}H_{20}N_4O_2S$	7.46 / 7.29	13.09 / 12.72	234	Ethyl acetate	61
5b	$C_{26}H_{22}N_4O_2S$	6.98 / 7.05	12.58 / 12.33	244	Ethyl acetate	60
5c	$C_{27}H_{24}N_4O_2S$	7.11 / 6.84	12.21 / 11.96	218	Toluene	81
5d	$C_{26}H_{19}F_3N_4O_2S$	6.07 / 6.31	11.24 / 11.02	231	Toluene	79
5e	$C_{28}H_{24}N_4O_4S$	6.48 / 6.26	11.07 / 10.93	273	Methanol	83
6a	$C_{26}H_{22}N_4O_2S$	7.22 / 7.05	12.46 / 12.33	233	Toluene	74

TABLE 2. ^{1}H NMR Spectra of Compounds **2-6**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2a	1.26 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$-6); 2.72 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$-6); 3.99 (3H, s, CH$_3$O-7); 7.23 (1H, s, H-8); 7.53 (3H, s, H$_{Ph}$-3',4',5'); 7.94 (1H, s, H-5); 8.04 (2H, m, H$_{Ph}$-2',6'); 9.38 (1H, s, H-2)
2b	1.23 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 2.69 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$-6); 3.05 (3H, s, CH$_3$-2); 3.96 (3H, s, CH$_3$O-7); 7.12 (1H, s, H-8); 7.53 (3H, m, H$_{Ph}$-3',4',5'); 7.87 (1H, s, H-5); 8.03 (2H, m, H$_{Ph}$-2',6')
2c	1.24 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$-6); 1.47 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$-2); 2.70 (2H, q, CH$_3$C<u>H</u>$_2$-6); 3.45 (2H, q, CH$_3$C<u>H</u>$_2$-2); 3.98 (3H, s, CH$_3$O-7); 7.12 (1H, s, H-8); 7.53 (3H, m, H$_{Ph}$-3',4',5'); 7.87 (1H, s, H-5); 8.02 (2H, m, H$_{Ph}$-2',6')
3a	1.14 (3H, t, *J* = 7.5, CH$_3$); 2.47 (2H, q, *J* = 7.5, CH$_2$); 6.49 (1H, s, H-3); 6.92 (1H, s, H-6); 7.47 (3H, m, H$_{Ph}$-3',4',5'); 7.82 (2H, m, H$_{Ph}$-2',6'); 8.03 (1H, s, H$_{pyrazole}$-5); 9.41 (1H, br. s, OH-4); 9.45 (1H, br. s, OH-2); 13.09 (1H, br. s, N–H)
3b	1.12 (3H, t, *J* = 7.5, CH$_3$); 2.46 (2H, q, *J* = 7.5, CH$_2$); 2.55 (3H, s, CH$_{3\ pyrazole}$); 6.43 (1H, s, H-3); 6.85 (1H, s, H-6); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.81 (2H, m, H$_{Ph}$-2',6'); 9.26 (1H, br. s, OH-4); 9.34 (1H, s, OH-2); 12.70 (1H, br. s, N–H)
3c	1.12 (3H, t, *J* = 7.5, CH$_3$); 1.31 (3H, t, *J* = 7.5, CH$_{3\ pyrazole}$); 2.46 (2H, q, *J* = 7.5, CH$_2$); 2.98 (2H, q, *J* = 7.5, CH$_{2\ pyrazole}$); 6.44 (1H, s, H-3); 6.85 (1H, s, H-6); 7.47 (3H, m, H$_{Ph}$-3',4',5'); 7.80 (2H, m, H$_{Ph}$-2',6'); 9.25 (1H, br. s, OH-4); 9.36 (1H, br. s, OH-2); 12.67 (1H, br. s, N–H)
3d	1.08 (3H, t, *J* = 7.5, CH$_3$); 2.42 (2H, q, *J* = 7.5, CH$_2$); 6.45 (1H, s, H-3); 6.89 (1H, s, H-6); 7.51 (3H, m, H$_{Ph}$-3',4',5'); 7.86 (2H, m, H$_{Ph}$-2',6'); 9.55 (1H, s, OH-4); 9.56 (1H, s, OH-2), 13.82 (1H, s, N–H)
3e	1.11 (3H, t, *J* = 7.5, CH$_3$); 2.48 (2H, q, *J* = 7.5, CH$_2$); 2.63 (2H, t, *J* = 8, C<u>H</u>$_2$CH$_2$COOH); 3.20 (2H, t, *J* = 8, CH$_2$C<u>H</u>$_2$COOH); 6.46 (1H, s, H-3); 6.84 (1H, s, H-6); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.80 (2H, m, H$_{Ph}$-2',6'); remaining protons exchanged with D$_2$O
3f	1.03 (3H, t, *J* = 7.5, CH$_3$); 1.25 (3H, t, *J* = 7.5, CH$_{3\ pyrazole}$); 2.40 (2H, q, *J* = 7.5, CH$_2$); 4.24 (2H, q, *J* = 7.5, CO$_2$CH$_2$); 6.39 (1H, s, H-3); 6.84 (1H, s, H-6); 7.51 (3H, m, H$_{Ph}$-3',4',5'); 7.92 (2H, m, H$_{Ph}$-2',6'); 9.39 (1H, s, OH-4); 9.46 (1H, s, OH-2); 13.58 (1H, s, N–H)
3g	1.09 (3H, t, *J* = 7.5, CH$_3$); 2.46 (2H, q, *J* = 7.5, CH$_2$); 4.49 (2H, br. s, NH$_2$); 6.41 (1H, s, H-3); 6.87 (1H, s, H-6); 7.50 (3H, m, H$_{Ph}$-3',4',5'); 7.87 (2H, m, H$_{Ph}$-2',6'); 9.40 (2H, br. s, OH-2 + OH-4); 10.24 (1H, br. s, N<u>H</u>–NH$_2$); 13.45 (1H, br. s, N–H$_{pyrazole}$)
4a	1.14 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 2.54 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$); 3.84 (3H, s, CH$_3$O); 6.55 (1H, s, H-3); 6.99 (1H, s, H-6); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.83 (2H, m, H$_{Ph}$-2',6'); 8.02 (br. s, H$_{pyrazole}$-5 (**B**)); 8.33 (br. s, H$_{pyrazole}$-3 (**A**)); 9.42 (br. s, O H-2 (**A**)); 9.65 (br. s, OH-2 (**B**)); 13.14 (br. s, N–H (**B**)); 13.33 (br. s, N–H (**A**))
4b	1.11 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 2.53 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$); 2.57 (3H, s, CH$_{3\ pyrazole}$-5); 3.82 (3H, s, CH$_3$O); 6.50 (1H, s, H-3); 6.94 (1H, s, H-6); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.81 (2H, m, H$_{Ph}$-2',6'); 9.48 (1H, br. s, OH-2); 12.80 (1H, br. s, N–H)
4c	1.11 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 1.31 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_{2\ pyrazole}$); 2.50 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$); 3.00 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_{2\ pyrazole}$); 3.82 (3H, s, CH$_3$O); 6.47 (1H, s, H-3); 6.92 (1H, s, H-6); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.81 (2H, m, H$_{Ph}$-2',6'); 9.36 (br. s, OH-2 (**A**)); 9.51 (br. s, OH-2 (**B**)); 12.74 (br. s, N–H (**B**)); 13.07 (br. s, N–H (**A**))
5a	1.03 (3H, t, *J* = 7.5, CH$_3$); 2.43 (2H, q, *J* = 7.5, CH$_2$); 6.46 (1H, s, H-3); 6.71 (1H, s, H-6); 7.36 (5H, s, N–Ph); 7.46 (3H, m, H$_{Ph}$-3',4',5'); 7.78 (2H, m, H$_{Ph}$-2',6'); 8.31 (1H, s, H$_{pyrazole}$-3); 9.39 (1H, s, OH-4); 9.49 (1H, s, OH-2)
5b	1.01 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 2.42 (2H, q, *J* = 7.5, CH$_3$C<u>H</u>$_2$); 2.67 (3H, s, CH$_{3\ pyrazole}$-3); 6.46 (1H, s, H-3); 6.68 (1H, s, H-6); 7.34 (5H, s, N–Ph); 7.47 (3H, m, H$_{Ph}$-3',4',5'); 7.76 (2H, m, H$_{Ph}$-2',6'); 9.41 (1H, s, OH-2); 9.53 (1H, s, OH-4)
5c	1.01 (3H, t, *J* = 7.5, CH$_3$); 1.39 (3H, t, *J* = 7.5, CH$_{3\ pyrazole}$); 2.39 (2H, q, *J* = 7.5, CH$_2$); 3.16 (2H, q, *J* = 7.5, CH$_{2\ pyrazole}$-3); 6.45 (1H, s, H-3); 6.68 (1H, s, H-6); 7.34 (5H, s, N–Ph); 7.47 (3H, m, H$_{Ph}$-3',4',5'); 7.77 (2H, m, H$_{Ph}$-2',6'); 9.39 (1H, s, OH-4); 9.51 (1H, s, OH-2)

TABLE 2 (continued)

1	2
5d	0.98 (3H, t, J = 7.5, CH_3); 2.38 (2H, q, J = 7.5, CH_2); 6.40 (1H, s, H-3); 6.72 (1H, s, H-6); 7.40 (5H, s, N–Ph); 7.51 (3H, m, H_{Ph}-3',4',5'); 7.82 (2H, m, H_{Ph}-2',6'); 9.55 (1H, s, OH-4); 9.60 (1H, s, OH-2)
5e	1.01 (3H, t, J = 7.5, CH_3); 2.42 (2H, q, J = 7.5, $C\underline{H}_2CH_3$); 2.79 (2H, t, J = 8, $C\underline{H}_2CH_2COOH$); 3.35 (2H, t, J = 8, $CH_2C\underline{H}_2COOH$); 6.46 (1H, s, H-3); 6.68 (1H, s, H-6); 7.34 (5H, s, N–Ph); 7.46 (3H, m, H_{Ph}-3',4',5'); 7.77 (2H, m, H_{Ph}-2',6'); 9.41 (1H, br. s, OH-4); 9.52 (1H, br. s, OH-2); 11.92 (1H, br. s, COOH)
6a	1.02 (3H, t, J = 7.5, $C\underline{H}_3CH_2$); 2.46 (2H, q, J = 7.5, $CH_3C\underline{H}_2$); 3.83 (3H, s, CH_3O); 6.51 (1H, s, H-3); 6.80 (1H, s, H-6); 7.35 (5H, s, N–Ph); 7.47 (3H, m, H_{Ph}-3',4',5'); 7.79 (2H, m, H_{Ph}-2',6'); 8.33 (1H, s, $H_{pyrazole}$-3); 9.68 (1H, s, OH-2)

allowed us to hypothesize that in this case, we are observing the prototropism phenomenon due to the existence of two tautomeric forms **A** and **B** in 1:3 ratio. We identified the tautomers **A** and **B** based on data taking into account the chemical shifts of the protons and the integrated intensity of the peaks. We assign the downfield signal in the pair of peaks for the N–H proton to tautomer **A**, since in this case it takes part in formation of the intramolecular hydrogen bond with the oxygen atom of the hydroxy group, which is always accompanied by a paramagnetic shift. In the pair of peaks for the signal from the C–H proton of the pyrazole ring in compound **4a**, the H-3 proton of tautomer **A** absorbs downfield since it is close to the pyridine nitrogen atom, while the H-5 proton of tautomer **B** is close to the pyrrole nitrogen atom. From the integrated intensities of the peaks it follows that the signal from the OH-2 group of tautomer **B** is located downfield while that signal for tautomer **A** is located upfield.

As we go from pyrazoles **3** and **4** (containing hydrogen atoms at the nitrogen atoms) to N-phenylpyrazoles **5** and **6**, formation of two isomers is also possible, but chromatographic analysis showed that only one isomer was present in the reaction mixture. We decided in favor of 2-{3-R-5-[5-ethyl-2-hydroxy-4-(R^1-oxy)phenyl)-1-phenyl]pyrazol-4-yl}-5-phenyl-1,3,4-thiadiazoles (**5a-e** and **6**) based on consideration of the chemical properties and the ^{1}H NMR spectra. Products **5a-e** and **6** do not yield a colored complex with an alcoholic solution of ferric chloride. The phenol hydroxyls appear in the ^{1}H NMR spectra of compounds **5a-e** as two narrow peaks in the 9.3-9.6 pm region, which indicates the absence of intramolecular interaction between the OH-2 group and the nitrogen atom of the pyrazole. The signal from the protons of the N-phenyl group of the pyrazole is a five-proton singlet at 7.34-7.40 ppm, in contrast to the phenyl signals in the thiadiazole ring where we observe three-proton and two-proton multiplets at 7.45-7.50 ppm and 7.77-7.81 ppm. The absence of splitting for the signal from the N-phenyl group indicates that this benzene ring deviates from the plane of the pyrazole ring. Evidence for this also comes from the 0.1-0.2 ppm upfield shift of the H-6 proton signal for the phenol substituent compared with signals from the same protons of pyrazoles **3** and **4**, since this proton is within the region shielded by the ring currents of the N-phenyl ring.

Thus recyclization of 3-(1,3,4-thiadiazolyl)chromones when treated with hydrazine and phenylhydrazine is a simple and convenient method for synthesis of 2-(pyrazol-4-yl)-1,3,4-thiadiazoles with different substituents at the 3 and 5 positions of the pyrazole ring.

EXPERIMENTAL

The homogeneity of the synthesized compounds was monitored using TLC (Silufol UV-254, 9:1 chloroform–methanol). The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Mercury 400 spectrometer (400 MHz). Internal standard: TMS.

The characteristics of compounds **2-6** are given in Table 1; the ^{1}H NMR spectral data are given in Table 2.

2-R-6-Ethyl-7-methoxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones (2a-c). Freshly calcined pulverized potassium carbonate (0.83 g, 6 mmol) was added to a solution of 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromone (**1a-c**) (3 mmol) in DMF (10 ml) and then dimethylsulfate (1.14 g, 9 mmol) was added dropwise. The reaction mixture was stirred with heating for 2 h and then cooled down and added to water (100 ml). The precipitate was filtered out.

5-[R-3-(5-Ethyl-2,4-dihydroxyphenyl)pyrazol-4-yl]-5-phenyl-1,3,4-thiadiazoles (3a-f) and 2-[5-R-3-(5-Ethyl-2-hydroxy-4-methoxyphenyl)pyrazol-4-yl]-5-phenyl-1,3,4-thiadiazoles (4a-c). Hydrazine hydrate (1 g, 30 mmol) was added to a suspension of the corresponding 2-R-6-ethyl-7-hydroxy(methoxy)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromone **1a-f** or **2a-c** (1 mmol) in ethanol (10 ml) and boiled until dissolved (0.5-5 min). The reaction mixture was cooled down and the precipitate was filtered out (in the case of products **2a** and **4b**) or else the mixture was poured into water (100 ml) and then the precipitate was filtered out.

3-(5-Ethyl-2,4-dihydroxyphenyl)-4-(5-phenyl-1,3,4-thiadiazol-2-yl)pyrazol-5-ylcarboxylic Acid Hydrazide (3g). A solution of a mixture of the ethyl ester **3f** and the hydrazide **3g** of 3-(2,4-dihydroxy-5-ethylphenyl)-4-(5-phenyl-1,3,4-thiadiazol-2-yl)pyrazol-5-ylcarboxylic acid (0.35 g) and hydrazine hydrate (1 ml) in DMF (2 ml) was boiled for 5 min and then poured into water (50 ml), and then the precipitate was filtered out.

2-[3-R-5-(5-Ethyl-2,4-dihydroxyphenyl)-1-phenylpyrazol-4-yl]-5-phenyl-1,3,4-thiadiazoles (5a-e). A suspension of the corresponding 2-R-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-6-ethylchromone **1a,d,e** (1 mmol) and phenylhydrazine (0.32 g, 3 mmol) was boiled in ethanol (20 ml) for 1.5-11 h until the precipitate dissolved and then was poured into water (50 ml) and the precipitate was filtered out. The reaction with chromones **2b,c** was carried out with heating in DMF (3 ml) for 2-4.5 h.

2-[5-(5-Ethyl-2-hydroxy-4-methoxyphenyl)-1-phenylpyrazol-4-yl]-5-phenyl-1,3,4-thiadiazole (6) was synthesized by the preceding procedure, with boiling in ethanol for 10 h.

REFERENCES

1. R. C. Elderfield (editor), *Heterocyclic Compounds* [Russian translation], Izdat. Inostr. Lit., Moscow (1961), Vol. 5, p. 42.
2. V. O. Kovtunenko, *Drug Methods Acting on the Central Nervous System* [in Ukrainian], Kiev, Perun, (1997), pp. 246, 373.
3. J. Sandstrom, *Adv. Heterocycl. Chem.*, **9**, 165 (1968).
4. M. A. Hanna, M. M. Girges, D. Rasala, and R. Gawinecki, *Arzneim.-Forsch.*, **45**, 1074 (1995); *Chem. Abstr.,* **124**, 75573 (1996).
5. H. M. Mokhtar and S. M. El-Khawass, *J. Chin. Chem. Soc. (Taipei),* **35**, 57 (1988); *Chem. Abstr.,* **112**, 98456 (1990).
6. El-S. M. El-Khawass and A. E. Bistawroos, *Alexandria J. Pharm. Sci.*, **4**, 77 (1990); *Chem. Abstr.,* **114**, 42668 (1991).
7. R. N. Mahajan, F. H. Havaldar, and P. S. Fernandes, *J. Indian Chem. Soc.*, **68**, 245 (1991); *Chem. Abstr.,* **116**, 20998 (1992).
8. R. P. Kapor, H. Batra, and P. K. Sharma, *Indian Heterocycl. Chem.*, **7**, 1 (1997); *Chem. Abstr.,* **127**, 346344 (1997).
9. R. G. Jones and N. H. Norman, Ger. Offen. Patent 2212080; *Chem. Abstr.,* **78**, 4247 (1973).
10. H. S. Chen, Z. M. Li, Y. F. Han, and Z. W. Wang, *Chin. Chem. Lett.*, **10**, 365 (1999); *Chem. Abstr.,* **131**, 257492 (1999).
11. J. C. Lancelot, D. Maume, and M. Robba, *J. Het. Chem.*, **18**, 1319 (1981).
12. A. L. Kazakov, V. P. Khilya, V. V. Mezheritskii, and Yu. Litkei, *Natural and Modified Isoflavonoids* [in Russian], Izdat. Rostovsk. Univ. (1985).
13. M. S. Frasinyuk and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 3 (1999).
14. T. V. Shokol, V. V. Semenyuchenko, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 1840 (2004).