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SYNTHESIS OF SOME 3-FUNCTIONALLY SUBSTITUTED 2-PYRAZOLINES

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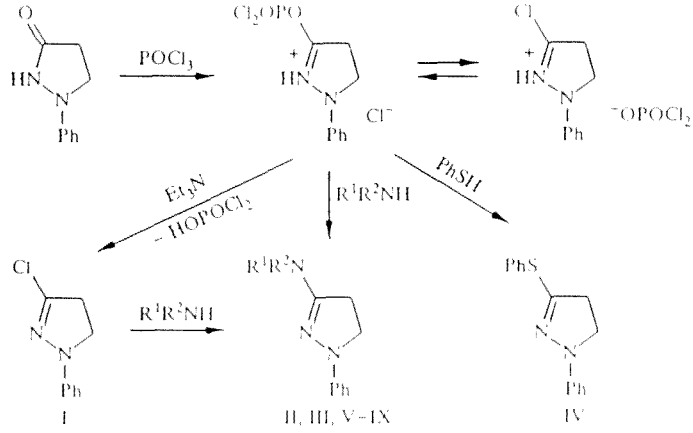
Reaction of the complex of 1-phenyl-3-pyrazolidone and phosphorus oxychloride with nucleophilic agents (amines and thiophenol) leads to the formation of 3-functionally substituted 2-pyrazolines.

Examples of the utilization of Vilsmeier complexes in reactions with various nucleophiles are known [1, 2]. However, the application of analogous complexes of hydrazides of carboxylic acids with inorganic halides is mainly limited to their utilization in different condensations [3, 4]. Moreover, performing substitution reactions on the basis of the complex of the cyclic hydrazide 1-phenyl-3-pyrazolidone (phenidone) and inorganic halides would allow the formation of 3-functionally substituted 2-pyrazolines which are very valuable, but not readily available, substances.

Of all the reagents which we tested (boron trifluoride etherate, oxalyl chloride, sulfuryl chloride, thionyl chloride, tosyl chloride, etc.), we showed that the best one for the complex formation of phenidone is phosphorus oxychloride. The reaction of the complex with the threefold excess of p-bromoaniline in methylene chloride led to the formation of two compounds which we identified as 3-chloro-1-phenyl-2-pyrazoline (I) and 3-(4-bromoanilino)-1-phenyl-2-pyrazoline (II). The yield of each of the reaction products comprised approximately 14%. The secondary formation of the chloropyrazoline (I) is explained readily since the amine utilized is a strong base and breaks down the complex.



II R^1 = *p*-BrC_6H_4, R^2 = H, III R^1 = Ph, R^2 = H, V R^1 = *p*-$CH_3OC_6H_4$, R^2 = H, VI R^1, R^2 = morpholino, VII R^1 = Ph, R^2 = Me, VIII R^1 = $PhCH_2$, R^2 = H, IX R^1 = $HO(CH_2)_3$, R^2 = H

The utilization of aniline as the nucleophilic agent led to the formation of 3-anilino-1-phenyl-2-pyrazoline (III) with the yield of 7% and 3-chloro-1-phenyl-2-pyrazoline (I) with the yield of 36%. The utilization of both more basic (benzylamine) and less basic (p-nitroaniline) amines under these conditions did not lead to favorable results: 3-chloro-1-phenyl-2-pyrazoline (I) was isolated in the first case, and only the initial substances were isolated in the second case.

It should be noted that the 3-aminopyrazolines are highly unstable and, above all, extremely light-sensitive.

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TABLE 1. Properties of the Compounds Obtained

Compound	T_{mp}, °C	Found % / Calculated %				Empirical formula	R_f	IR spectrum, cm^{-1}
		C	H	N	M			
I	105	59,85 59,83	5,04 4,98	15,10 15,51	180 180	$C_9H_{10}ClN_2$	0,98	1610
II*	129	—	—	—	315 315	$C_{15}H_{14}BrN_3$	0,85	1630, 3400, 3440
III*	104	—	—	—	237 237	$C_{15}H_{15}N_3$	—	1645, 3390, 3450
IV	87	69,90 70,86	5,43 5,51	11,25 11,02	254 254	$C_{15}H_{11}SN_2$	0,9	—
V*	123	—	—	—	267 267	$C_{16}H_{17}N_3O$	0,7	1640, 3395, 3440
VI	106	66,74 67,53	7,42 7,36	17,46 18,18	231 231	$C_{13}H_{17}N_3O$	0,85	1620
VII	99	—	—	16,49 16,73	251 251	$C_{16}H_{17}N_3$	0,9	1640
VIII*	oil	—	—	—	251 251	$C_{16}H_{17}N_3$	0,83	1645, 3400, 3435
IX*	97	—	—	—	219 219	$C_{12}H_{17}N_3O$	0,25	1610, 3400

*The elemental analysis was rendered difficult due to the mentioned instability of the compounds obtained.

The reaction of the complex with thiophenol proceeds more successfully, and leads to the isolation of the phenylthio derivative (IV) with the yield of 52%.

The directed synthesis of 3-chloro-1-phenyl-2-pyrazoline with a preparative yield was successfully accomplished by the treatment of the complex of phenidone and phosphorus oxychloride with triethylamine.

In separate references to substitution in 3-chloro-2-pyrazoline [5, 6], the authors noted inertness in nucleophilic substitution reactions which was unexpected for the given class. In fact, the substitution of the chlorine atom in compound (I) only occurs at an adequately high temperature by the heating in an excess of the corresponding amine. The yields of the resulting amino derivatives (I)-(IX) are high (75-93%). Both aromatic and aliphatic amines, including bifunctional amines, can participate in this conversion.

In the course of the IR spectroscopic investigation of some 3-aminopyrazolines, we found that the spectra of solutions of the amino compounds (II), (III), (V), and (VIII) contain two absorption bands of the NH bond, whereby the ratio of their intensities depends not on the concentration, but on the polarity of the solvent; this may indicate the existence of the following two tautomeric forms in the solutions.

Two basic paths are most characteristic for the mass spectral decomposition of the synthesized 3-amino-2-pyrazolines: the sequential cleavage of two hydrogen radicals with the formation of the Φ_1 and Φ_2 ions with the subsequent decomposition of the pyrazole type, and the cleavage of the carbon radical in the 3-amino group with the formation of the Φ_3 ion. The further decomposition occurs with the opening of the pyrazoline ring and is characteristic of the given class of compounds.

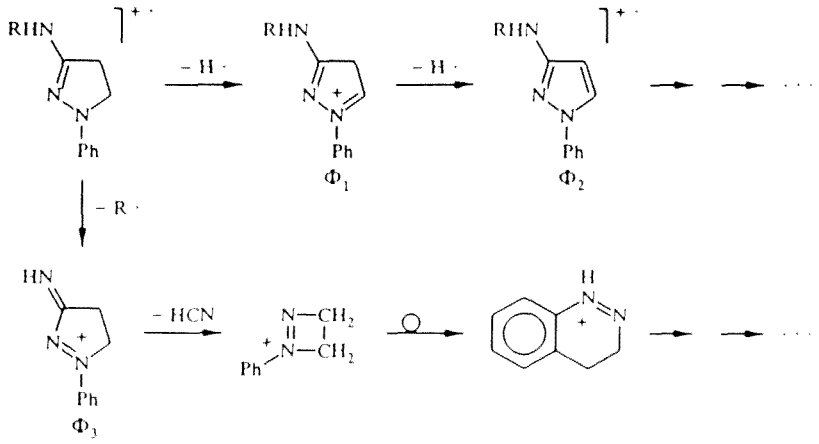
TABLE 2. Spectral Characteristics of the Compounds Obtained

Compound	Chemical shifts, δ, ppm	m/z (I_{rel}, %)
I	PMR: 3,10 (2H, t, 4-H), 3,85 (2H, t, 5-H), 6,90...7,30 (5H, m, Ar-H) NMR ^{13}C: 37,308 ($C_{(4)}$), 50,031 ($C_{(5)}$), 113,033 (*o*-Ph), 119,935 (*p*-Ph), 129,061 (*m*-Ph), 149,091 (*i*-Ph), 142,000 ($C_{(3)}$)	180 (100, M^+), 145 (11), 143 (5), 117 (5), 105 (45), 104 (54), 91 (25), 77 (84)
II	PMR: 3,075 (2H, t, 4-H), 3,780 (2H, t, 5-H), 6,80...7,50 (10H, м, Ar-H) NMR ^{13}C: 30,883 ($C_{(4)}$), 50,676 ($C_{(5)}$), 113,090 (*o*-Ph), 116,085 (*p*-Ph), 119,667 (*o*-BrPh), 120,954 (*p*-BrPh), 128,991 (*m*-Ph), 132,357 (*m*-BrPh), 137,010 (*i*-BrPh), 147,150 (*i*-Ph), 153,706 ($C_{(3)}$)	315 (100, M^+), 314 (10), 313 (10), 236 (8), 208 (17), 170 (2), 158 (7), 145 (10), 131 (20), 105 (5), 104 (8), 91 (21), 77 (22)
III	PMR: 3,40 (2H, t, 4-H), 3,90 (2H, t, 5-H), 6,80...7,50 (10H, m, Ar-H)	237 (100, M^+), 236 (2), 235 (1), 133 (5), 137 (37), 132 (15), 107 (6), 105 (6), 104 (6), 93 (10), 92 (10), 91 (20), 77 (34)
IV	PMR: 3,00 (2H, t, 4-H), 3,90 (2H, t, 5-H), 6,80...7,80 (10H, m, Ar-H)	254 (20, M^+), 253 (100), 252 (7), 149 (10), 145 (5), 117 (2), 116 (4), 109 (28), 105 (30), 104 (42), 91 (17), 77 (32)
V	PMR: 3,10 (2H, t, 4-H), 3,90 (2H, t, 5-H), 3,78 (3H, s, CH_3), 6,08 (1H, d, NH), 7,10...7,80 (9H, m, Ar) NMR ^{13}C: 33,607 ($C_{(4)}$), 55,507 ($C_{(5)}$), 55,584 (OCH_3), 114,542 (*o*-Ph), 115,050 (*p*-Ph), 117,716 (*o*-Ar), 118,442 (*m*-Ar), 129,239 (*m*-Ph), 136,083 (*i*-Ar), 140,000 (*i*-Ph), 154,059 (*p*-Ar), 160,050 ($C_{(3)}$)	267 (100, M^+), 266 (13), 265 (25), 250 (18), 160 (30), 147 (15), 132 (10), 131 (19), 130 (4), 118 (9), 105 (10)
VI	PMR: 2,85 (2H, t, 4-H), 3,30 (4H, t, CH_2OCH_2), 3,65 (2H, t, 5-H), 3,75 (4H, t, CH_2NCH_2), 6,70...7,30 (5H, m, Ar) NMR ^{13}C: 30,674 ($C_{(4)}$), 46,952 (CNC), 49,474 ($C_{(5)}$), 66,327 (COC), 112,818 (*o*-Ph), 117,906 (*p*-Ph), 128,824 (*m*-Ph), 148,959 (*i*-Ph), 156,204 ($C_{(3)}$)	231 (100, M^+), 230 (15), 229 (10), 200 (2), 198 (2), 186 (4), 174 (10), 172 (6), 106 (5), 104 (8), 91 (15), 77 (20)
VII	PMR: 2,84 (3H, s, CH_3), 2,92 (2H, t, 4-H), 3,46 (2H, t, 5-H), 6,50...7,70 (10H, m, Ar-H)	251 (100, M^+), 250 (20), 249 (30), 236 (6), 172 (4), 157 (10), 146 (12), 130 (15), 117 (5), 106 (13), 105 (18), 104 (10), 91 (19), 77 (37)
VIII	—	251 (95, M^+), 160 (100), 106 (28), 105 (25), 91 (62), 77 (42)
IX	PMR: 1,69 (2H, p, 2'-CH_2), 2,70 (2H, t, 4-H), 3,62 (8H, m, 5-H, NH, OH, 1'-CH_2, 3'-CH_2), 6,80...7,40 (5H, m, Ar-H) NMR ^{13}C: 32,408 (2'-C), 32,905 ($C_{(4)}$), 39,771 (1'-C), 49,448 ($C_{(5)}$), 58,729 (3'-C), 113,115 (*o*-Ph), 118,226 (*p*-Ph), 129,056 (*m*-Ph), 149,070 (*i*-Ph), 156,141 ($C_{(3)}$)	219 (100, M^+), 218 (8), 217 (8), 210 (4), 174 (10), 173 (10), 172 (15), 161 (8), 160 (15), 145 (5), 120 (8), 112 (18), 107 (8), 106 (10), 105 (10), 104 (13), 100,5 (5), 92 (8), 91 (15), 77 (30)

EXPERIMENTAL

The IR spectra were measured on the UR-20 instrument or the Specord IR-75 in methylene chloride. The PMR and ^{13}C NMR spectra were measured on the Tesla BS-467 and Varian VXR-400 instruments in CCl_4 and $CDCl_3$. The internal standard was TMS or HMDS. The mass spectra were measured on the MX-1321 A instrument with the introduction of the sample directly at the ion source; the energy of ionization was 70 eV. The UV spectra were measured on the Varian Cary-219 instrument in abs. methanol. The chromatographic separation of mixtures was conducted by the method of flash chromatography on a dry column [7] with the utilization of silica gel type 5/40 μ. Monitoring of the course of reactions and the purity of the compounds obtained was accomplished by TLC on Silufol in the 1:1 system of methyl ethyl ketone – benzene.

3-Anilino-1-phenyl-2-pyrazoline (III). A. To the solution of 1.62 g (0.01 mole) of 1-phenylpyrazolid-3-one in 25 ml of abs. CH_2Cl_2 at 0°C is added, dropwise with stirring, the solution of 0.933 ml (0.01 mole) of $POCl_3$ in 3 ml of abs. CH_2Cl_2. The mixture is maintained at room temperature. After the precipitation of the residue, the mixture is stirred for 1 h



more, and is then cooled to 0°C. All further operations are performed in the dark. The solution of 2.73 ml (0.03 mole) of aniline in 10 ml of abs. CH_2Cl_2 is added carefully. The mixture is stirred for 30 min with cooling, taken to room temperature, and held for 24 h prior to extraction with the 10% aqueous solution of H_2SO_4. The aqueous extracts are neutralized with $NaHCO_3$ to the pH 6.5 and extracted with 4 × 20 ml of benzene; the extract is dried with Na_2SO_4. The benzene is evaporated, and the residue is chromatographed in the diethyl ether–petroleum ether using the 0:1-1:1 gradient. The yields of 650 mg (36%) of 3-chloro-1-phenyl-2-pyrazoline (I) and 160 mg (7%) of 3-anilino-1-phenyl-2-pyrazoline (III) are obtained.

By analogy, 3-(4-bromoanilino)-1-phenyl-2-pyrazoline (II) is obtained with the yield of 14%. The yield of the chloropyrazoline (I) comprises 14%.

B. The solution of 0.4 g (2.2 mmole) of 3-chloro-1-phenyl-2-pyrazoline in 0.93 g (10 mmole) of aniline is protected from light and heated at the boiling temperature of the amine. The reaction mixture is then dissolved in 10 ml of 10% H_2SO_4 solution and carefully made alkaline with $NaHCO_3$ to the pH 6.5; the mixture is extracted with benzene. Extracts are dried over Na_2SO_4. The benzene is evaporated, and the residue is chromatographed in the diethyl ether–petroleum ether–acetone system in the 0:1:0-15:15:1 gradient. The yield is 0.52 g (75%). The substance is identical to that obtained by the method A according to the melting temperature and the IR spectra.

The following compounds were obtained by this method: **3-(4-anisidino)-1-phenyl-2-pyrazoline (V)** with the yield of 93%, **3-morpholino1-1-phenyl-2-pyrazoline (VI)** with the yield of 79%, **3-methylanilino-1-phenyl-2-pyrazoline (VII)** with the yield of 77%, **3-benzylamino-1-phenyl-2-pyrazoline (VIII)** with the yield of 88%, and **3-(3-hydroxypropylamino)-1-phenyl-2-pyrazoline (IX)** with the yield of 85%.

3-Phenylthio-1-phenyl-2-pyrazoline (IV). After the isolation of the complex of phenidone and phosphorus oxychloride (cf. the method A in the preceding method), the solution of 3.3 g (0.03 mole) of thiophenol in 10 ml of abs. CH_2Cl_2 is added with cooling. The mixture is maintained for 48 h at room temperature. The CH_2Cl_2 is distilled off. The residue is dissolved in benzene and washed with an aqueous solution of NaOH at the pH 10 until the disappearance of the yellow coloration of the aqueous phase is achieved. The benzene layer is separated and dried with Na_2SO_4. The benzene is distilled off, and the residue is chromatographed in the diethyl ether–petroleum ether–acetone system using the 0:1:0-30:30:1 gradient. The yield is 52%.

3-Chloro-1-phenyl-2-pyrazoline (I). To the solution of 2 ml of $POCl_3$ (3.29 g, 0.022 mole) in 10 ml of abs. CH_2Cl_2 are added, at 0°C, 1.62 g (0.01 mole) of 1-phenylpyrazolid-3-one. The mixture is maintained at room temperature for 1 h, and is then cooled to 0°C. The solution of 1.4 ml (1.01 g, 0.01 mole) of triethylamine in 5 ml of abs. CH_2Cl_2 is added dropwise. After 1 h, the mixture is boiled until the disappearance of the initial pyrazolidone is achieved using TLC. The solvent and the excess of the initial $POCl_3$ are distilled off *in vacuo*. The dry residue is dissolved in the minimal amount of $CHCl_3$ and applied to a layer of silica gel. Elution is performed with diethyl ether. The yield is 1.37 g (76%).

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