Chemistry of Heterocyclic Compounds, Vol. 39, No. 6, 2003

HALOGEN-CONTAINING PYRIDINES. 8*. SYNTHESIS OF 3,5-DICHLOROPYRIDINES CONTAINING PYRAZOLE AND PYRAZOLINE RESIDUES IN POSITION 2

K. I. Kobrakov[1], I. I. Rybina[1], V. I. Kelarev[2], and V. K. Korolev[1]

The interaction of 3,5-dichloro-2-pyridylhydrazine with α,β-unsaturated carbonyl compounds leads to 1-(3,5-dichloro-2-pyridyl)-3,5-disubstituted Δ²-pyrazolines. It was shown that N-(3,5-dichloro-2-pyridyl)hydrazones of the corresponding aldehydes and ketones are formed as intermediates. Condensation of the hydrazine mentioned above with α,β-diketones gives 1,3,5-trisubstituted pyrazoles, but with acetoacetic ester a 1,3-disubstituted pyrazol-5-one containing a 3,5-dichloropyridyl residue is obtained.

Keywords: halopyridines, N-substituted hydrazones, Δ²-pyrazolines, pyrazolones, pyrazoles, pyridylhydrazines, condensation.

Heteryl-substituted pyrazoles and Δ²-pyrazolines containing, for example, fragments of furan [2], 5-nitrofuran [3], indole [4-7], 1,2-benzisoxazole [8], benzoxazole [9], benzothiazole [10,11], piperazine [12], *sym*-triazine [13,14], etc. display high antibacterial, anti-inflammatory, anticonvulsive, hypoglycemic, and antidiabetic activity, and are CNS depressants and monoamine oxidase inhibitors. They also possess various pesticidal actions. At the same time a significant number of compounds has been described containing a 3,5-dichloropyridyl group which display high and selective biological activity [15], and it was shown that the presence of chlorine atoms in positions 3 and 5 of the pyridine ring causes a significant reduction in the toxicity of a biologically active compound [16].

In continuation of our investigations on the synthesis of azoles with hetaryl substituents [17-19] we report in the present work the preparation of 1,3,5-trisubstituted Δ²-pyrazolines and pyrazoles containing 3,5-dichloropyridyl residues. Bisheterocyclic systems of such type have been studied little and are represented in the literature by single examples [20, 21].

One of the most widespread methods of obtaining 1-substituted Δ²-pyrazolines is the interaction of monosubstituted hydrazines with α,β-unsaturated carbonyl compounds [22]. As starting material for the synthesis of Δ²-pyrazolines of the type mentioned above 3,5-dichloro-2-pyridylhydrazine (**1**) has been used in the present work. By condensing compound **1** with α,β-unsaturated aldehydes **2a,b** or ketones **2c-e** the

* For Part 7 see [1].

[1] Moscow A. N. Kosygin State Textile University, Moscow 117918, Russia; e-mail: office@msta.ac.ru.
[2] I. M. Gubkin Oil and Gas State University, Moscow 117917, Russia; e-mail: himeko@dol.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 877-883, June, 2003. Original article submitted October 19, 2000.

TABLE 1. Characteristics of the Synthesized Compounds **3-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	^{1}H NMR spectrum, δ, ppm (J, HZ)*[2]	Yield, % (method of preparation
		C	H	N				
1	2	3	4	5	6	7	8	9
3a	$C_{14}H_{11}Cl_2N_3$	57.72 / 57.73	3.88 / 3.76	14.07 / 14.38	188-189.5	0.84	2.62 (1H, ddt, $^2J_{AB}$ = 16.8, H_B); 3.15 (1H, ddt, $^3J_{AX}$ = 10.4, H_A); 4.24 (1H, dd, $^3J_{BX}$ = 7.4, H_X); 6.84-6.96 (5H, m, Ph); 7.24 (1H, t, 3-H pyrazoline); 7.59 (1H, d, 4-H pyridine); 8.05 (1H, d, J_{46} = 2.0, 6-H pyridine)	95 (A)
3b	$C_{12}H_8Cl_2N_4O_3$	43.88 / 44.06	2.56 / 2.46	17.10 / 17.13	211-212	0.70	2.38 (1H, ddt, $^2J_{AB}$ = 17.5, H_B); 3.40 (1H, ddt, $^3J_{AX}$ = 8.0, H_A); 3.64 (1H, dd, $^3J_{BX}$ = 5.5, H_X); 6.74 (1H, d, J_{34} = 3.7, 3-H furan); 7.18 (1H, m, 3-H pyrazolone); 7.35 (1H, d, 4-H furan); 7.65 (1H, d, 4-H pyridine); 7.89 (1H, d, J_{46} = 2.2, 6-H pyridine)	94 (A)
3c	$C_{15}H_{13}Cl_2N_3$	59.04 / 58.82	4.10 / 4.25	13.94 / 13.72	172-173.5	0.84	2.54 (3H, s, Me); 2.74 (1H, ddt, $^2J_{AB}$ = 18.0, H_B); 3.38 (1H, ddt, $^3J_{AX}$ = 6.5, H_A); 3.54 (1H, dd, $^3J_{BX}$ = 4.6, H_X); 6.90-7.02 (5H, m, Ph); 7.60 (1H, d, 4-H pyridine); 7.92 (1H, d, J_{46} = 1.8, 6-H pyridine)	89 (A)
3d	$C_{15}H_{13}Cl_2N_3O$	56.07 / 55.90	3.90 / 3.97	13.18 / 12.84	244-245.5	0.74	2.37 (3H, s, Me); 2.80 (1H, ddt, $^2J_{AB}$ = 19.5, H_B); 3.05 (1H, ddt, $^3J_{AX}$ = 7.5, H_A); 3.96 (1H, dd, $^3J_{BX}$ = 7.0, H_X); 5.52 (1H, br. s, OH); 6.92 (2H, dd, J = 8.2, H arom.); 7.25 (2H, dd, H arom.); 7.59 (1H, dd, 4-H pyridine); 7.88 (1H, dd, J_{46} = 2.8, 6-H pyridine)	97 (A)
3e	$C_{20}H_{15}Cl_2N_3$	65.06 / 65.21	3.95 / 4.08	11.28 / 11.41	170-171	0.63	2.48 (1H, ddt, $^2J_{AB}$ = 15.0, H_B); 2.91 (1H, ddt, $^3J_{AX}$ = 10.0, H_A); 4.40 (1H, dd, $^3J_{BX}$ = 3.5, H_X); 6.84-7.05 (10H, m, 2Ph); 7.78 (1H, d, 4-H pyridine); 8.02 (1H, d, J_{46} = 2.5, 6-H pyridine)	83 (A)
4a	$C_{14}H_{11}Cl_2N_3$	57.42 / 57.53	3.68 / 3.76	14.50 / 14.38	195-196.5	0.62	6.60 (1H, d, J = 15.8, CH=CH); 6.84-6.90 (5H, m, Ph); 7.08 (1H, m, N=CH); 7.29 (1H, d, J = 15.8, CH=CH); 7.88 (1H, d, 4-H pyridine); 7.99 (1H, d, J_{46} = 1.7, 6-H pyridine); 8.42 (1H, br. s, NH)	76 (B)

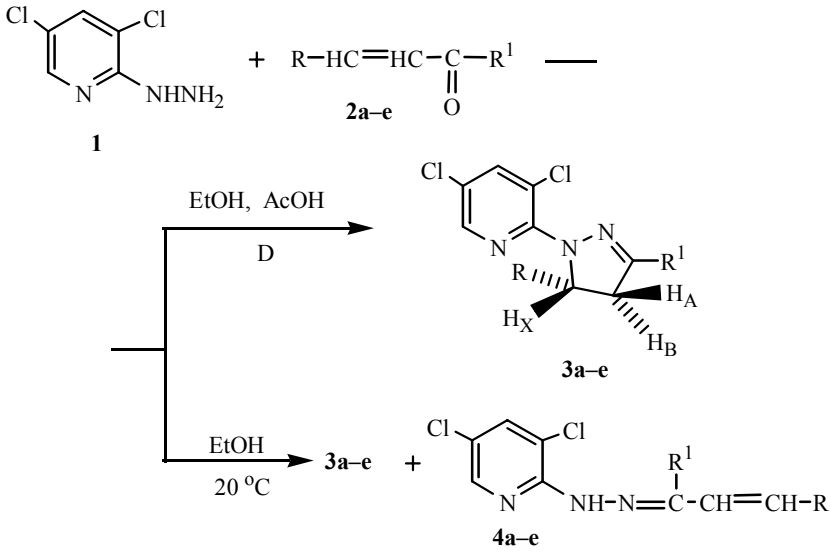
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
4b	$C_{12}H_8Cl_2N_4O_3$	43.80 44.06	2.52 2.46	17.04 17.13	232-234 (dec.)	0.38	6.74 (1H, d, J = 14.2, CH=CH); 6.92 (1H, d, J_{34} = 3.5, 3-H furan); 7.05 (1H, m, N=CH); 7.28 (1H, d, J_{34} = 3.5, 4-H furan); 7.48 (1H, d, J = 14.2, CH=CH); 7.78 (1H, d, 4-H pyridine); 8.24 (1H, d, 6-H pyridine); 8.44 (1H, br. s, NH)	84 (B)
4c	$C_{15}H_{13}Cl_2N_3$	58.70 58.82	4.37 4.25	13.50 13.72	138-139.5 (dec.)	0.32	2.28 (3H, s, Me); 6.80 (1H, d, J = 16.6, CH=CH); 6.92-7.02 (5H, m, Ph); 7.10 (1H, d, J = 16.6, CH=CH); 7.97 (1H, d, 4-H pyridine); 8.14 (1H, d, J_{46} = 2.4, 6-H pyridine); 8.22 (1H, br. s, NH)	10 (B)
4d	$C_{15}H_{13}Cl_2N_3O$	55.74 55.90	4.14 3.97	12.82 12.84	220-222 (dec.)	0.43	2.44 (3H, s, Me); 5.55 (1H, br. s, OH); 6.64 (1H, d, J = 16.0, CH=CH); 6.89 (2H, dd, J = 9.3, H arom.); 7.34 (2H, dd, J = 9.3, H arom.); 7.60 (1H, d, J = 16.0, CH=CH); 7.94 (1H, d, 4-H pyridine); 8.14 (1H, d, J_{46} = 2.2, 6-H pyridine); 8.40 (1H, br. s, NH)	11 (B)
4e	$C_{20}H_{15}Cl_2N_3$	65.10 65.21	3.90 4.08	11.60 11.41	152-153.5 (dec.)	0.50	6.92 (1H, d, J = 17.3, CH=CH); 7.04-7.16 (10H, m, 2Ph); 7.28 (1H, d, J = 17.3, CH=CH); 7.77 (1H, d, 4-H pyridine); 8.04 (1H, d, J_{46} = 2.1, 6-H pyridine); 8.58 (1H, br. s, NH)	68 (B)
5a	$C_{10}H_9Cl_2N_3$	49.37 49.59	3.88 3.72	17.59 17.35	Oil (n_D^{20} 1.5894)	0.45	2.29 (3H, s, 3-Me); 2.37 (3H, s, 5-Me); 6.34 (1H, s, 4-H pyrazole); 7.79 (1H, d, 4-H pyridine); 8.04 (1H, d, J_{46} = 2.7, 6-H pyridine)	70
5b	$C_{20}H_{13}Cl_2N_3$	65.32 65.57	3.64 3.55	11.71 11.47	Oil (n_D^{20} 1.5963)	0.67	6.48 (1H, s, 4-H pyrazole); 6.89-7.05 (10H, m, 2Ph); 7.67 (1H, d, 4-H pyridine); 7.92 (1H, d, J_{46} = 2.2, 6-H pyridine)	75
5c	$C_9H_7Cl_2N_3O$	44.37 44.26	2.91 2.87	17.60 17.21	40-42	0.74	1.97 (3H, s, 3-Me); 2.88 (1H, unsym. d, J_{AB} = 17.4, 4-H pyrazolone); 3.18 (1H, unsym. d, J_{AB} = 17.4, 4-H pyrazolone); 7.74 (1H, d, 4-H pyridine); 7.90 (1H, d, J_{46} = 2.4, 6-H pyridine)	85

* Solvent systems: hexane–acetone, 1:1 (compounds **3a-c,e**, **4a,c**), hexane–acetone, 1:2 (compounds **3d**, **4b,d,e**) and benzene–methanol, 20:1 (compounds **5a-c**).

*[2] The spectra of compounds **3a,c, 4a,c,** and **5a-c** were recorded in $CDCl_3$, and of compounds **3b,d,e** and **4b,d,e** in DMSO-d_6.

1-(3,5-dichloro-2-pyridyl)-3-R-5-aryl(hetaryl)-Δ^2-pyrazolines **3a-e** are formed. The best yields of compounds **3a-d** (90-97%) were achieved on boiling equimolar quantities of reactants in ethanol for 10-30 min in the presence of catalytic amounts of acetic acid. In the case of benzalacetophenone **2e** extended boiling (17 h) is necessary to complete the reaction. Δ^2-Pyrazoline **3e** is formed in 83% yield by this (method A).



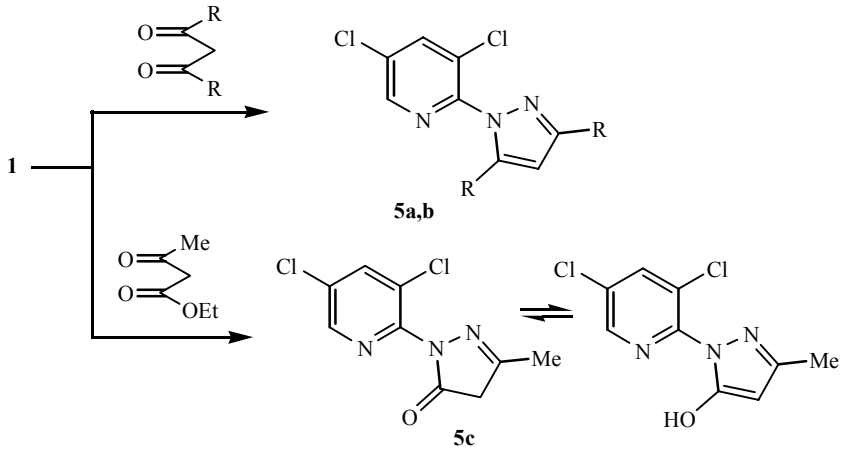
2-4 a R = Ph, R^1 = H; **b** R = 5-nitrofuryl, R^1 = H; **c** R = Ph, R^1 = Me; **d** R = 4-HOC_6H_4, R^1 = Me; **e** R = R^1 = Ph

The observed reduction in reactivity of ketone **2e** in the condensation with hydrazine **1** conflicts with the rule described previously [23]. It was noted in [22] that in individual cases on interacting hydrazines with α,β-unsaturated carbonyl compounds not only were pyrazolines isolated but also the corresponding hydrazones. It was established by us that on maintaining an equimolar mixture of reactants in ethanol at 20°C a mixture was formed in the case of aldehydes **2a,b** and ketones **2c,d** of Δ^2-pyrazoline **3a-d** and the corresponding hydrazone **4a-d** (see Table 2). For aldehydes **2a,b** the main product was the hydrazone **4a,b** but for ketones **2c,d** the main product was the Δ^2-pyrazoline **3c,d** (method B). After maintaining a mixture of hydrazine **1** and ketone **2e** in ethanol for 48 h only N-(3,5-dicloro-2-pyridyl)hydrazone **4e** was isolated in 68% yield from the reaction mixture. The compounds indicated were isolated by HPLC and were characterized by spectral methods. It was established that an increase in reaction temperature causes cyclization of hydrazones **4a-e** into the corresponding Δ^2-pyrazolines. On boiling reaction mixtures containing Δ^2-pyrazoline **3b** and hydrazone **4b** in a ratio of 7:93 for 35-40 min the ratio of compounds changed to 68:32 according to ^{1}H NMR spectral data.

TABLE 2. Interaction of Compound **1** with α,β-Unsaturated Carbonyl Compounds **2a-e** at 20°C (reactant ratio 1:1, ethanol)

Initial compound	Reaction time	Reaction product, yield, %	
		Δ^2-pyrazoline **3**	hydrazone **4**
2a	4 h	12	76
2b	10 min	6	84
2c	48 h	66	10
2d	24 h	65	11
2e	48 h	—	68

Boiling (4-10 h) hydrazine **1** with acetylacetone or dibenzoylmethane (reactant ratio 1:1) in ethanol in the presence of CH_3COOH leads to 1-(3,5-dichloro-2-pyridyl)-3,5-R_2-pyrazole **5a,b**, but for dibenzoylmethane the reaction time requires to be increased 2 to 2.5 times to complete the reaction. Similarly 1-(3,5-dichloro-2-pyridyl)-3-methylpyrazol-5-one (**5c**) was obtained from hydrazine **1** and acetoacetic ester in the presence of conc. HCl. In this case the reaction time required (7-8 h) indicates the relatively low reactivity of hydrazine **1** in the studied condensation.



5 a R = Me, **b** R = Ph

In the IR spectra of compounds **4a-e** intense absorption bands were observed at 1650-1660 and 1620-1630 cm^{-1} characteristic of the stretching vibrations of the C=N group of hydrazones [24, 25] and the C=C bond in conjugated systems [25]. In the high frequency region of the spectra of these hydrazones the broad absorption band at 3220-3270 cm^{-1} corresponds to the stretching vibration of the NH bond. There are strong absorption bands at 1600-1615 cm^{-1} in the spectra of Δ^2-pyrazolones **3a-e** characteristic of the stretching vibrations of C=N in dihydroazoles [26], and at 1320-1330 cm^{-1} belonging to the deformation vibrations of the pyrazole ring C–H.

Absorption bands of various intensity were observed in the spectra of pyrazoles **5a,b** assigned to the pyrazole ring vibrations [26] at 1595-1600, 1555-1560, 1465-1470 (ν ring), 1020-1025 (breathing vibrations of the ring) and 800 cm^{-1} (β ring). The intense absorption maximum at 1705 cm^{-1} in the spectrum of compound **5c** is characteristic of the vibrations of a carbonyl group in pyrazoles [26].

In the ^1H NMR spectra of compounds **3a-e** the pyrazole ring protons form an ABX spin system to a first approximation, assignment of the signal of the position 5 proton (H_X) is beyond doubt, the chemical shift of the H_X proton is observed at 3.54-4.40 ppm as a doublet of doublets. The signals of the position 4 protons are displayed as complex multiplets at 2.38-2.80 and 2.91-3.40 ppm (which on resolving may be considered as ddt). The homonuclear Overhauser effect was used to assign the signals of the H_A and H_B protons [25]. In an experiment with irradiation at the frequency of the H_X proton signal it turned out that for all compounds **3a-e** the intensity of the signal at 2.91-3.40 ppm grew by 7-10%. This indicates that the given proton is spatially close to the H_X proton, i.e. protons H_A and H_X have a cissoid configuration with coupling constant $^3J_{AX}$ = 6.5-10.4 Hz. The coupling constant between the H_X proton and the *trans* proton H_B was $^3J_{BX}$ = 3.5-7.4, J_{AB} = 15.0-19.5 Hz is typical for the geminal disposition of the H_A and H_B protons in an ABX system [25,27].

In the spectra of hydrazones **4a-e** the signals of the vinylic protons are displayed as doublets at 6.60-6.92 and 7.10-7.60 ppm with coupling constant 14.2-17.3 Hz, which confirms the *E*-configuration of the vinylic fragments.

EXPERIMENTAL

The IR spectra of compounds were recorded on a Perkin-Elmer 993 spectrometer in KBr disks or as nujol suspensions. The ^{1}H NMR spectra were recorded on Bruker WP-250 (250 MHz) and Bruker WM-360 (360 Hz) spectrometers for 10-12% solutions, internal standard was TMS. A check on the course of reactions and the purity of the compounds obtained was carried out by TLC on Silpearl UV-254 plates, visualization was with iodine vapor. The preparative separation of reaction products was effected on a Waters-Model 590 liquid chromatograph fitted with a Gilson Model 116 UV detector and a stainless steel column (180 × 1.5 cm) packed with reversed phase Silasorb C_{18} sorbent (10 μm), eluent was heptane–chloroform–methanol, 7:2:1, flow rate 2 ml/min, pressure $95 \cdot 10^5$ Pa.

1-(3,5-Dichloro-2-pyridyl)-3-R-5-aryl(heteryl)-Δ^2-pyrazolines (3a-e). A. A mixture of hydrazine **1** (0.89 g, 5 mmol), carbonyl compound **2a-e** (5 mmol), and CH_3COOH (several drops) in ethanol (5 ml) was boiled for 10-30 min on obtaining compounds **3a-d** or 17 h on obtaining compound **3e** (check by TLC for the disappearance of the initial hydrazine **1**). The reaction mixture was cooled to 20°C, the precipitated solid was filtered off, dried, and chromatographed on a column (25 × 3.5 cm) of Kieselgel 60 Fluka silica gel, eluting with chloroform–acetone, 10:1. After removing the solvent Δ^2-pyrazolines **3a-e** were obtained.

Δ^2-Pyrazolines 3a-e and N-(3,5-Dichloro-2-pyridyl)hydrazones of Carbonyl Compounds (4a-e). B. A mixture of hydrazine **1** (0.89 g, 5 mmol) and carbonyl compound **2a-e** (5 mmol) in ethanol (5 ml) was kept at 20°C until the disappearance from the reaction mixture of the initial hydrazine **1** (check by TLC, see Table 2). The separated solid was filtered off, and the reaction products were separated by preparative HPLC.

1-(3,5-Dichloro-2-pyridyl)-3,5-disubstituted Pyrazoles (5a,b). A mixture of hydrazine **1** (0.89 g, 5 mmol), acetylacetone or dibenzoylmethane (5 mmol), and CH_3COOH (several drops) , in ethanol (5 ml) was boiled for 4-10 h, and evaporated to dryness under reduced pressure. The residue was treated with 5% NaOH solution (15 ml), the organic substances were extracted with ether (2 × 20 ml), and the extract dried over $MgSO_4$. The solvent was removed in vacuum, the residue was chromatographed on a column (25 × 3.5 cm) of Kieselgel 60 Fluka silica gel, eluting with benzene–chloroform, 15:1. After removing the solvent pyrazoles **5a,b** were obtained as dark-yellow viscous uncrystallizable oils.

1-(3,5-Dichloro-2-pyridyl)-3-methylpyrazol-5-one (5c) was obtained analogously from hydrazine **1** and acetoacetic ester in the presence of conc. HCl in ethanol (boiling, 7 h) as a viscous oil, which crystallized on rubbing and extended storage at -15°C.

REFERENCES

1. K. I. Kobrakov, V. K. Korolev, I. I. Rybina, and V. I. Kelarev, *Khim. Geterotsikl. Soedin.*, 1066 (2000).
2. I. G. Mikhailyuchenko, in *Chemistry and Technology of Furan Compounds*, Intercollegiate Collection of Scientific Works, Krasnodar State Technological University, Krasnodar (1988), p. 64.
3. L. K. Kulikova and L. V. Cherkesova, *Khim.-farm. Zh.*, No. 3, 18 (1974).
4. F. Piozzi and C. Fuganti, *Ann. Chim. (Rome)*, **57**, 486 (1967).
5. S. Tripathi, B. R. Pandey, J. P. Barthwal, K. Kishor, and K. P. Bhargawa, *Indian J. Physiol. Pharmacol.*, **24**, 155 (1980).
6. K. Raman, B. R. Pandey, J. P. Barthwal, and S. S. Parmar, *Eur. J. Med. Chem. – Chim. Ther.*, **15**, 567 (1980).
7. V. I. Kelarev and G. A. Shvekhgeimer, *Khim. Geterotsikl. Soedin.*, 147 (1986).
8. K. A. Thakar and A. M. Padhye, *J. Indian Chem. Soc.*, **62**, 465 (1985).
9. M. Z. A. Badr, A. M. Mahmoud, S. A. Mahgoub, and Z. A. Hozien, *Bull. Chem. Soc. Jpn.*, **61**, 1339 (1988).
10. S. P. Singh, I. Prakash, R. K. Tomer, O. Prakash, and S. N. Sawhney, *Indian J. Chem.,* **B22**, 43 (1983).

11. S. P. Singh, D. R. Kodali, I. Prakash, O. Prakash, and S. N. Sawhney, *Indian J. Chem.,* **B23**, 125 (1984).
12. J. Gante, H. Radunz, H. Eckart, D. Orth, K. Minck, A. Wild, and M. Klockow, Ger. Offen. 2906252; *Chem. Abstr.*, **94**, 192323 (1981).
13. S. Yamamoto, T. Kakuta, T. Sato, K. Morimoto, E. Oya, T. Ikai, and T. Nawamaki, Eur. Pat. Appl. 189069; *Chem. Abstr.*, **105**, 191075 (1986).
14. Z. Brzozowski and I. Kozakiewicz, *Acta Pol. Pharm.*, **37**, 601 (1980).
15. N. I. Mel'nikov, *Pesticides* [in Russian], Khimiya, Moscow (1987).
16. V. G. Kartsev, in *Chemistry and Technology of Pyridine-Containing Pesticides*, Proceedings of the All-Union Conference, Chernogolovka (1988), p. 9.
17. K. I. Kobrakov, V. I. Kelarev, I. I. Rybina, and V. K. Korolev, in *Chemical Reactants, Reagents, and Processes of Low-Tonnage Chemistry*, Abstracts XIII International Scientific and Technological Conference, Tula (2000), p. 95.
18. V. I. Kelarev, M. A. Silin, I. G. Kotova, K. I. Kobrakov, I. I. Rybina, and V. K. Korolev, *Khim. Geterotsikl. Soedin.*, 243 (2003).
19. V. I. Kelarev, M. A. Silin, K. I. Kobrakov, I. I. Rybina, and V. K. Korolev, *Khim. Geterotsikl. Soedin.*, 173 (2000).
20. K. Sasse, M. Hammond, F. Seuter, E. Perzborn, B. Pelster, G. Sturton, and T. Abram (A.-G. Bayer), Ger. Offen. DE 3443308; *Chem. Abstr.*, **105**, 153057 (1986).
21. O. Schallner, R. Gehring, and J. Stetter (A.-G. Bayer), Ger. Offen. DE 3520330; *Chem. Abstr.*, **106**, 156458 (1987).
22. A. N. Kost and V. V. Ershov, *Usp. Khim.*, **4**, 431 (1958).
23. S. Beech, J. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).
24. Yu. P. Kitaev and B. I. Buzykin, *Hydrazones* [in Russian], Nauka, Moscow (1974).
25. R. M. Silverstein, G. C. Bassler, and T. I. Morrill, *Spectrometric Identification of Organic Compounds* [Russian translation], Mir, Moscow (1977).
26. A. R. Katritzky (editor), *Physical Methods in Heterocyclic Chemistry,* Academic Press, New York (1963).
27. A. Junker, *Nuclear Magnetic Resonance in Organic Chemistry* [Russian translation], Mir, Moscow (1974), p. 71.