SYNTHESIS OF NEW PYRAZOLE AND ISOXAZOLE DERIVATIVES BASED ON PRODUCTS OF CONDENSATION OF β-DICARBONYL COMPOUNDS WITH 1,2,3-TRIHALOPROPANES

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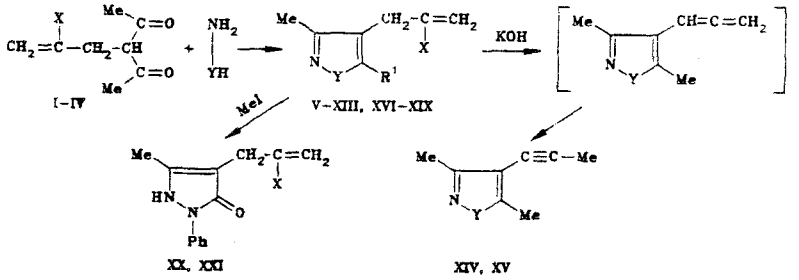
UDC 547.233'234'384.6'772.2'787.1.07

The reaction of 2-(2-halo-3-propenyl)-1,3-dicarbonyl compounds, which are formed in the alkylation of β-dicarbonyl compounds with 1,2,3-trihalopropanes in the presence of potassium carbonate in DMSO, with hydrazine and hydroxylamine derivatives was studied. The synthesis of new pyrazole and isoxazole derivatives on the basis of this reaction is described. Some chemical transformations of the 1,2-azoles obtained were investigated.

The reaction of 1,3-dicarbonyl compounds with hydrazine and hydroxylamine derivatives is a classical method for the synthesis of pyrazole [1] and isoxazole [2] derivatives. However, 1,2-azoles with substituents in the 4 position that are capable of further chemical transformations (for example, compounds similar to those described in [3]) are seldom obtained by this method, evidently as a consequence of the relatively low availability of the starting β-diketones. At the same time, precisely such pyrazole and isoxazole derivatives are being used with increasing frequency in organic synthesis [4, 5].

We recently reported that the alkylation of acetylacetone and ethyl acetoacetate with 1,2,3-trihalopropanes in the K_2CO_3/DMSO system may serve as a method for the synthesis of 2-halo-1-hexen-5-one derivatives I-IV, which have a carbonyl-containing substituent in the 4 position [6]. In the present paper we present the results of our research on the reaction of I-IV with hydrazines and hydroxylamine.

As expected, the condensation of I and II with the hydrochlorides or sulfates of hydrazine, monosubstituted hydrazines, and hydroxylamine in 10% aqueous NAOH solution at 20°C leads to the formation of 3,5-dimethylpyrazoles and 3,5-dimethylisoxazoles with a 2-halo-3-propenyl substituent in the 4 position:



I X=Cl, R=Me; II X=Br, R=Me; III X=Cl, R=OEt; IV X=Br, R=OEt; V X=Br, Y=NH, R¹=Me; VI X=Cl, Y=NH, R¹=Me; VII X=Br, Y=NPh, R¹=Me; VIII X=Cl, Y=NPh, R¹=Me; IX X=Br, Y=NMe, R¹=Me; X X=Cl, Y=NMe, R¹=Me; XI X=Br, Y=NEt, R¹=Me; XII X=Br, Y=O, R¹=Me; XIII X=Cl, Y=O, R¹=Me; XIV Y=NPh; XV, Y=O; XVI X=Cl, Y=NH, R¹=OH; XVII X=Br, Y=NH, R¹=OH; XVIII X=Cl, Y=NPh, R¹=OH; XIX X=Br, Y=NPh, R¹=OH; XX X=Cl; XXI X=Br

The reaction of diketones I and II with semicarbazide is accompanied, under the reaction conditions, by hydrolysis of the carbamoyl group and gives pyrazoles V and VI; this was con-

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0009-3122/87/2306-0651$12.50

TABLE 1. Data from the ^{1}H NMR Spectra of V-XIII and XVI-XVIII

Compound	Chemical shift, ppm: 3-CH_3 (s)	5-CH_3 (s)	CH_2 (narrow m)	=CH_2 (narrow m)	other signals	Solvent
V	2,09	2,09	3,23	4,82, 5,00	11,35 br s NH	CCl_4
VI	2,13	2,13	3,35	5,24	11,85 br s , NH	CCl_4
VII	2,23	2,06	3,48	5,47, 5,37	7,27 m, C_6H_5	CCl_4
VIII	2,28	2,10	3,52	5,32	7,31 m, C_6H_5	CCl_4
IX	2,00	1,93	3,27	5,25, 5,54	3,45 s, N—CH_3	CCl_4
X	2,03	1,95	3,33	5,46	3,47 s, N—CH_3	CCl_4
XI	2,01	1,95	3,33	5,27	1,25 (3H, t, J=7 Hz), 3,85 (2H, q, J=7Hz), NC_2H_5	CCl_4
XII	2,05	2,20	3,38	5,23, 5,50	—	CCl_4
XIII	2,12	2,31	3,36	5,16	—	CCl_4
XVI	2,28	—	3,50	5,33	9,13 br s , 2NH	d_6-DMSO
XVII	2,26	—	3,59	5,57, 5,75	8,45 br s , 2NH	d_6-DMSO
XVII	1,95	—	3,10	5,06, 5,23	—	CF_3COOD
XVIII	2,25	—	3,51	5,06	7,2—8,06 m, C_6H_5	d_6-DMSO
XVIII, CH form	2,05	—	3,58	5,03	7,2—8,06 s, C_6H_5, 2,36 (1H, t, J=5 Hz, CH)	d_6-DMSO

firmed by data from the ^{1}H NMR spectra. Let us also note that pyrazoles IX-XI can also be obtained by alkylation of V and VI with trimethyl or triethyl phosphite. The structures of pyrazoles and isoxazoles V-XIII were confirmed by data from the ^{1}H NMR spectra (Table 1) and the results of elementary analysis (Table 2). The assingment of the signals of the protons of the methyl groups in the 3 and 5 positions was made on the basis of the data in [7, 8].

The substituent in the 4 position is capable of undergoing further chemical transformations. Thus, for example, upon treatment with KOH in triethylene glycol, azoles VIII, IX, XII, and XIII [9] readily split out a hydrogen halide molecule; the intermediately formed allene undergoes isomerization to an acetylene derivative during the reaction. The structures of acetylenic compounds XIV and XV were confirmed by data from the ^{1}H NMR spectra (see the experimental section) and the results of elementary analysis (Table 2). It is interesting to note that in the ^{1}H NMR spectrum of XIV the protons of the two methyl groups become virtually magnetically equivalent as a consequence of the anisotropic effect of the acetylene fragment.

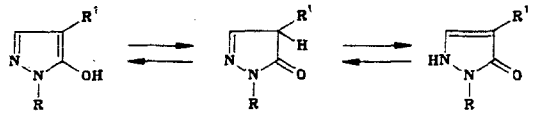
In order to synthesize new bifunctional pyrazole derivatives we also investigated the reaction with hydrazines of the products of alkylation of acetoacetic ester with 1,2,3-trihalopropanes – keto esters III and IV. These reactions require considerably more severe condi-

TABLE 2. Characteristics of the 1,2-Azoles Obtained

Compound	mp or bp (mm), °C	n_D^{20}	d_{20}^4	MR_D found	MR_D calc.	Found, % C	Found, % H	Found, % Hal	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % Hal	Calculated, % N	Yield, %
V	95—96	—	—	—	—	44,7	5,0	37,1	13,1	$C_8H_{11}BrN_2$	44,7	5,1	37,2	13,0	84
VI	86—87	—	—	—	—	56,8	6,5	20,1	15,6	$C_8H_{11}ClN_2$	56,3	6,5	20,8	16,4	90
VII	153—154 (1)	1,5922	1,3331	73,88	73,55	57,6	5,0	26,8	9,7	$C_{14}H_{15}BrN_2$	57,7	5,2	27,5	9,6	69
VIII	68—69	—	—	—	—	68,3	6,1	14,3	11,3	$C_{14}H_{15}ClN_2$	68,2	6,1	14,4	11,4	80
IX	88—89 (1)	1,5300	1,3372	52,90	54,07	47,2	5,5	34,8	12,8	$C_9H_{13}BrN_2$	47,2	5,7	34,9	12,2	87
X	76—77 (1)	1,5100	1,1082	49,79	51,17	58,4	7,1	19,3	15,7	$C_9H_{13}ClN_2$	58,5	7,1	19,2	15,2	90
XI	105 (17)	1,5230	1,2555	59,13	60,23	49,4	5,8	31,1	11,8	$C_{10}H_{15}BrN_2$	49,4	6,2	32,9	11,5	72
XII	80—81 (1)	1,5152	1,4934	45,27	46,69	43,8	5,0	—	6,2	$C_8H_{10}BrNO$	44,4	4,6	37,0	6,5	85
XIII	66—68 (1)	1,4894	1,1208	44,19	44,23	55,8	5,5	20,4	8,0	$C_8H_{10}ClNO$	56,0	5,8	20,7	8,2	71
XIV	132—133 (2)	1,5982	1,0925	65,60	65,93	80,1	6,6	—	13,4	$C_{14}N_{14}N_2$	80,0	6,7	—	13,3	88
XV	45—46 (1)	1,4976	1,0059	39,31	39,53	71,1	6,5	—	10,2	C_8H_9NO	71,1	6,7	—	10,4	84
XVI	243—245	—	—	—	—	48,6	5,2	20,6	16,3	$C_7H_9ClN_2O$	48,7	5,2	20,6	16,2	82
XVII	249—250	—	—	—	—	38,7	4,2	36,8	12,9	$C_7H_9BrN_2O$	38,7	4,2	36,9	12,9	90
XVIII	96—98	—	—	—	—	62,8	5,2	14,2	11,3	$C_{13}H_{13}ClN_2O$	62,8	5,2	14,3	11,3	86
XIX	102—103	—	—	—	—	53,3	4,4	27,4	9,6	$C_{13}H_{13}BrN_2O$	53,2	4,4	27,3	9,6	88
XX	82—83	—	—	—	—	63,9	5,8	13,5	10,7	$C_{14}H_{15}ClN_2O$	64,0	5,7	13,5	10,7	90
XXI	86	—	—	—	—	54,8	5,9	26,1	9,1	$C_{14}H_{15}BrN_2O$	54,7	4,9	26,1	9,1	90

tions that the analogous processes for diketones I and II (T 90°C) and lead to the formation of 5-pyrazolones with a 2-halo-3-propenyl substituent in the 4 position; precisely the use of water as the reaction medium leads to the formation of 5-hydroxy derivatives of pyrazole (for example, 5-ethoxy derivatives are formed when a similar reaction is carried out in absolu ethanol [10]). The structures of pyrazolones XVI-XIX were confirmed by data from ^{1}H NMR spectra (Table 1) and the ^{13}C NMR spectra (see the experimental section), as well as by the result of elementary analysis (Table 2). Let us note that in virtually all of the ^{1}H NMR spectra of the chlorine-containing 1,2-azoles that we obtained (VIII, X, XI, XIII, XVI, XVIII) the sig nals of the protons of the methylene group have the form of a narrow multiplet, while for the analogous bromo derivatives (V, VII, IX, XII, XVII) the difference in the chemical shifts of the methylene protons is 0.11-0.29 ppm.

It is known that 5-pyrazolones can exist in three possible tautomeric forms [7]:



A OH form B CH form C NH form

Preference is given to form B in nonpolar solvents, whereas form C is preferred in polar solvents.

We found that in solution in d_6-DMSO pyrazolones XVI and XVII exist exclusively in form C (according to data from the ^{1}H NMR spectra; Table 1); replacement of the hydrogen atom attached to the nitrogen atom by a phenyl group leads to the existence of substituted pyrazolone XVIII in form B to the extent of 8-10%, as evidenced by the appearance of a triplet methylidyne proton at 2.36 ppm.

In form C of XVIII and XIX the nitrogen atom has clearly expressed nucleophilic properties. Thus pyrazolones XVIII and XIX react with methyl iodide to give 4-substituted antipyrine derivatives XX and XXI.

Thus we have described the synthesis of new pyrazole and isoxazole derivatives based on available dicarbonyl compounds — products of condensation of 1,2,3-trihalopropanes with CH acids under super-base conditions; the newly synthesized 1.2-azoles contain a reactive substituent in the 4 position and can be used in organic synthesis.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The ^{1}H NMR spectra were recorded with a Tesla BS-487 spectrometer (80 MHz), and the ^{13}C NMR spectra were recorded with a Varian FT-80A spectrometer (20 MHz) with complete decoupling of the protons and tetramethylsilane (TMS) as the standard.

2-Chloro-4-acetyl-1-hexen-5-one (I), 2-Bromo-4-acetyl-1-hexen-5-one (II), Ethyl 2-Acetyl-4-chloro-4-penten-1-oate (III), and Ethyl 2-Acetyl-4-bromo-4-penten-1-oate (IV). These compounds were obtained by the method in [6]. The yields and physicochemical properties, as well as the results of elementary analysis of the compounds obtained, are presented in Table 2

General Methods for the Synthesis of 1,2-Azoles. A) a 50-mmole sample of the dicarbonyl compound was stirred with 50 mmole of the hydrazine derivative in 22 ml of 10% NaOH solution at 20°C for 1h, after which the resulting precipitate was removed by filtration, dried, and recrystallized from hexane.

B) A 50-mmole sample of the dicarbonyl compound was stirred with 50 mmole of the hydrazine (hydroxylamine) derivative in 40 ml of 10% NaOH solution at 15°C for 1h, after which the solution was extracted with ether. The extract was dried over calcium chloride, the ether was removed by distillation, and the precipitate was fractionated in vacuo.

C) A 50-mmole sample of the keto ester was stirred with 50 mmole of the hydrazine derivative in 10% sodium acetate solution at 90°C for 6 h, and the resulting precipitate was removed by filtration, dried, and recyrstallized from ethanol.

3,5-Dimethyl-4-(2-bromo-3-propenyl)pyrazole (V). This compound was obtained from 3.43 g of $NH_2NH_2 \cdot HCl$ and 10.95 g of diketone II by method A. The yield was 9.03 g.

3,5-Dimethyl-4(2-chloro-3-propenyl)pyrazole (VI). This compound was obtained from 3.43 g of $NH_2NH_2 \cdot HCl$ and 8.73 g of diketone I by method A. The yield was 7.67 g.

1-Phenyl-3,5-dimethyl-4-(2-bromo-3-propenyl)pyrazole (VII). This compound was obtained from 7.23 g of phenylhydrazine hydrochloride and 10.95 g of diketone II. The yield was 10 g by method A with workup of the reaction mixture by method B.

1-Phenyl-3,5-dimethyl-4-(2-chloro-3-propenyl)pyrazole (VIII). This compound was obtained from 8.73 g of diketone I and 7.23 g of $PhNHNH_2 \cdot HCl$ by method A. The yield was 9.86 g.

1,3,5-Trimethyl-4-(2-bromo-3-propenyl)pyrazole (IX). 1) The reaction of 10.95 g of diketone II and 7.2 g of methylhydrazine hydrosulfate by method B gave 9.96 g of pyrazole IX.

2) A mixture of 1.7 g (7.9 mmole) of pyrazole V and 1.5 g (12 mmole) of trimethyl phosphite was refluxed with stirring in 20 ml of benzene for 1h, after which the solvent was removed by distillation, and the residue was fractionated in vacuo to give 1.23 g (68%) of pyrazole IX.

1-Ethyl-3,5-dimethyl-4-(2-bromo-3-propenyl)pyrazole (XI). This compound was obtained from 1.8 g (8.4 mmole) of pyrazole V and 1.5 g (9 mmole) of triethyl phosphite under the conditions described above. The yield was 1.47 g.

1,3,5-Trimethyl-4-(2-chloro-3-propenyl)pyrazole (X). This compound was obtained from 8.73 g of diketone I and 7.2 g of $MeNHNH_2 \cdot H_2SO_4$ by method B. The yield was 11.09 g.

3,5-Dimethyl-4-(2-bromo-3-propenyl)isoxazole (XII). This compound was obtained from 10.95 g of diketone II and 6.55 g of hydroxylamine hydrosulfate by method B. The yield was 9.18 g.

3,5-Dimethyl-4-(2-chloro-3-propenyl)isoxazole (XIII). This compound was obtained from 8.73 g of diketone I and 6.55 g of $NH_2OH \cdot H_2SO_4$ by method B. The yield was 6.09 g.

1-Phenyl-3,5-dimethyl-4-(1-propynyl)pyrazole (XIV). This compound was obtained from 7.27 g (50 mmole) of pyrazole VII by the action of 7 g (125 mmole) of KOH in 30 ml of triethylene glycol (130°C, 0.5 h) by the method in [9]. The yield was 9.35 g. PMR spectrum (CCl_4): 1.90 (3H, s, $\equiv CCH_3$); 2.15 (6H, s, two CH_3); and 7.77 ppm (5H, m, C_6H_5).

3,5-Dimethyl-4-(1-propynyl)isoxazole (XV). This compound was obtained from 10.8 g (50 mmole) of isoxazole XII by the action of 7 g (125 mmole) of KOH in 30 ml of triethylene glycol under the conditions indicated above. The yield was 5.7 g. PMR spectrum (CCl_4): 1.90 (3H, s, $\equiv CCH_3$); 2.12 (3H, s, 3-CH_3); and 2.31 ppm (3H, s, 5-CH_3).

3-Methyl-4-(2-chloro-3-propenyl)-5-pyrazolone (XVI). This compound was obtained from 10.23 g of keto ester III and 3.43 g of $NH_2NH_2 \cdot HCl$ by method C. The yield was 7.07 g. ^{13}C NMR spectrum (d_6-DMSO): 10.75 (CH_3), 32.42 (CH_2), 97.26 (4-C), 112.86 ($=CH_2$), 139.11 (ClC=), 142.17 (3-C), and 160.89 ppm (C=O). IR spectrum: 1625, 1650 cm^{-1}.

3-Methyl-4-(2-bromo-3-propenyl)-5-pyrazolone (XVII). This compound was obtained from 12.45 g of keto ester IV and 3.43 g of $NH_2NH_2 \cdot HCl$ by method C. The yield was 9.77 g. ^{13}C NMR spectrum (d_6-DMSO): 10.82 (CH_3), 34.91 (CH_2), 97.84 (4-C), 117.91 ($=CH_2$), 134.17 (BrC=), 139.06 (3-C), and 160.88 ppm (C=O).

1-Phenyl-3-methyl-4-(2-chloro-3-propenyl)-5-pyrazolone (XVIII). This compound was obtained from 10.23 g of keto ester III and 7.23 g of $PhNHNH_2 \cdot HCl$ by method C. The yield was 10.69 g. IR spectrum: 1500, 1600, 1630, and 1650 cm^{-1}.

1-Phenyl-3-methyl-4-(2-bromo-3-propenyl)-5-pyrazolone (XIX). This compound was obtained from 12.45 g of keto ester IV and 7.23 g of $PhNHNH_2 \cdot HCl$ by method C. The yield was 12.89 g.

4-(2-chloro-3-propenyl)antipyrine (XX). This compound was obtained from 12.4 g (50 mmole) of pyrazolone XVIII and 7.1 g of methyl iodide in 30 ml of methanol by the method in [11]. The yield was 11.81 g. IR spectrum: 1430, 1450, 1497, 1600, 1630, 1650, and 1670 cm^{-1}. PMR spectrum (CCl_4): 2.43 (3H, s, 3-CH_3), 3.25 (3H, s, NCH_3), 3.50 (2H, narrow m, CH_2), 5.43 (1H, narrow m, $=CH_2$), 5.53 (1H, narrow m, $=CH_2$), and 7.58 ppm (5H, m, C_6H_5). ^{13}C NMR spectrum [$(CH_3)_2CO$]: 11.21 (CH_3); 32.48 (CH_2); 36.50 (N–CH_3); 106.9 (3-C); 112.98 ($=CH_2$); 123.45, 126.08, 129.41, 136.9 (C_{arom}); 140.898 (ClC=); 156.54 ppm (C=O).

4-(2-Bromo-3-propenyl)antipyrine (XXI). This compound was obtained from 14.65 g (50 mmole) of pyrazolone XIX and 7.1 g of CH_3I in 30 ml of methanol under the conditions indicated above. The yield was 13.82 g. PMR spectrum (CCl_4): 2.43 (3H, s, CH_3); 3.24 (3H, s, N–CH_3);

3.61 (2H, narrow m, CH_2); 5.66 (1H, narrow m, $=CH_2$); 5.95 (1H, narrow m, $=CH_2$); and 7.79 ppm (5H, m, C_6H_5). ^{13}C NMR spectrum (d_6-DMSO): 11.73 (CH_3); 34.93 (CH_2); 36.65 ($N-CH_3$); 106.5 (3-C); 117.96 ($=CH_2$); 123.99, 126.62, 129.75, 132.40 (C_{arom}); 136.0 (BrC=); 156.0 ppm (C=O).

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VIBRATIONAL SPECTRA, STRUCTURES, AND CONFORMATIONS OF CONJUGATED AZOMETHINES – 3-IMIDAZOLINE DERIVATIVES

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UDC 547.77+548.737+543.424+543.422.2

The possibility of the use of the ratios of the intensities of the $\nu_{C=N}$ bands in the Raman spectra of the compounds to establish the conformations of the conjugated C=N bonds was demonstrated in the case of conjugated azomethines – derivatives of 2,2,5,5-tetramethyl-3-imidazoline and -3-imidazoline 3-oxide.

It was previously shown [1] in the case of imines and nitrones that are derivatives of 3-imidazoline and 3-imidazoline 3-oxide that the ratios of the intensities of the bands of the stretching vibrations of the multiple bonds in the Raman spectra can be used to establish the conformations of molecules with conjugated C=N bonds. However, a quantitative evaluation of the limits of the change in the ratios of the intensities of the $\nu_{C=N}$ bands in the Raman spectra on passing from s-trans to s-cis systems was not made. In addition, the conformations of the 4-acetyl-3-imidazoline derivatives were not established by independent methods, and this did not enable one to draw well-founded conclusions regarding the boundaries of the chang in the ratios of the intensities in the Raman spectra of s-trans and s-cis systems.

In the present research, to obtain a quantitative evaluation of the boundaries of the change in the ratios of the intensities of the $\nu_{C=N}$ bands in the Raman spectra of s-trans- and s-cis-conjugated azomethine systems we studied the Raman spectra in the region of the stretching vibrations of the C=N bonds of a number of derivatives of 4-formyl-2,2,5,5-tetramethyl-3-imidazolines (I-V, Table 1), 4-formyl-3-imidazoline 3-oxides (VI-XI), and 4-acetyl-3-imidazolines (XII-XV) (Table 1), as well as the Raman spectra of model compounds with con-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 792-797, June, 1987. Original article submitted November 26, 1985.

0009-3122/87/2306-0655$12.50