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Synthesis of Sybstituted Isoxazoles and Pyrazoles Based on 1-Aryl-3,4,4-trichloro-3-buten-1-ones

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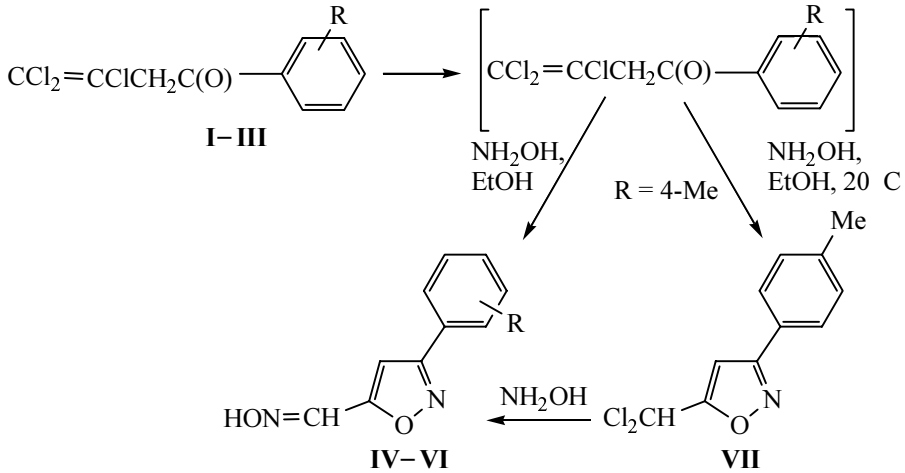
Abstract—3-Aryl-5-methylenehydroxyiminoisoxazoles were synthesized by reaction of 1-aryl-3,4,4-trichloro-3-buten-1-ones with hydroxylamine. Reactions of ketones with hydrazine provided pyrazole structures; therewith two pyrazole molecules underwent "coupling" affording 3-arylpyrazole-5-carbaldehyde azines.

Functional derivatives of isoxazoles and pyrazoles are extensively used as efficient medicines and chemical reagents for plant protection [1–3]. One of classical ways to building up isoxazole and pyrazole rings consists in reacting hydroxylamine and hydrazine with β-chlorovinyl ketones [4]. We recently described a convenient preparation method for 1-aryl-3,4,4-trichloro-3-buten-1-ones from available 3,4,4- trichloro-3-butenoic acid [5]. It was also shown that in reactions with primary and secondary amines these ketones suffered a prototropic allyl rearrangement into 1-aryl-3,4,4-trichloro-2-buten-1-ones where a reactive chlorine atom was located in the β-position with respect to a carbonyl group [6].

The goal of the present study was the synthesis of substituted isoxazoles and pyrazoles by reation of 1-aryl-3,4,4-trichloro-3-buten-1-ones with hydroxylamine and hydrazine. We chose as ketones 1-phenyl-3,4,4-trichloro-3-buten-1-one (**I**), 1-(4-methylphenyl)-3,4,4-trichloro-3-buten-1-one (**II**), and 1-(2,5-dimethylphenyl)-3,4,4-trichloro-3-buten-1-one (**III**).

The reactions of ketones **I–III** with hydroxylamine in ethanol solution at reflux occurred with prototropic allyl rearrangement of ketones, involved into the process the carbonyl group, and were finished by replacement of an internal chlorine and by heterocyclization into an isoxazole system. The arising 3-aryl-5-dichloromethylisoxazoles reacted further with the second hydroxylamine molecule at the dichloromethyl group affording 3-aryl-5-hydroxyiminomethylisoxazoles (**IV–VI**) in 40–75% yield. In the case of ketone **II** we succeeded in isolation and identification of the primary heterocyclization product, 5-dichloromethyl-3-(4-methylphenyl)isoxazole



R = H (**I, IV**), 4-Me (**II, V**), 2,5-Me_2 (**III, VI**).

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(**VII**) when the reaction was performed under milder conditions, at 20°C. We failed to isolate in reactions with ketones **I** and **III** the corresponding isoxazoles with the dichloromethyl group: even under mild conditions and at deficit of hydroxylamine we obtained as reaction products only isoxazolyl oximes **IV** and **VI.**

We carried out the reduction of the oxime group with lithium aluminum hydride in anhydrous ether by an example of 3-(2,5-dimethylphenyl)-5-hydroxyiminomethylisoxazole (**VI**). Thus we obtained the corresponding 5-aminomethyl-3-(2,5-dimethylphenyl)isoxazole (**VIII**) that was characterized as hydrochloride **IX** prepared by passing dry hydrogen chloride through an ether solution of amine **VIII**.

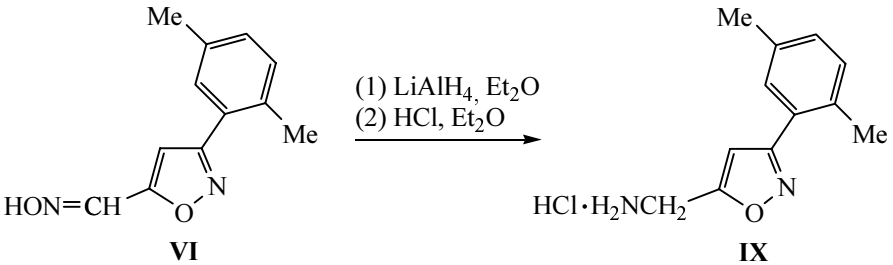
The identification of synthesized compounds **IV–VII**, and **IX** was done proceeding from the data of elemental analysis and IR, ^{1}H NMR, and mass spectra. In the IR spectra of isoxazoles **IV–VII**, and **IX** are present the absorption bands of C=N bonds (1602–1644 cm^{-1}) and of C=C bonds (1503–1603 cm^{-1}).

In the ^{1}H NMR spectra of compounds **IV–VII**, and **IX** are present singlets of protons from the groups =CH of the isoxazole rings, δ 6.80–7.07 ppm, and multiplets from the protons belonging to the benzene fragments of the molecules. The exocylic group $CHCl_2$ of compound **VII** appears in the spectrum as a singlet at 7.28 ppm, CH_2N group of isoxazole **IX** as a singlet at 4.21 ppm, exocyclic CH=N groups in compounds **IV–VI** as singlets with the chemical shifts 8.20–8.23 ppm, OH groups of oximes **IV–VI** as broadened singlets in the region 11.12–11.19 ppm, NH_3^+ of compound **IX** as a broadened singlet at 8.62 ppm.

The mass spectra of the synthesized isoxazoles contain groups of molecular ion peaks, and in the spectrum of hydrochloride **IX** appears a peak of ion [*M*–HCl]$^+$. The fragmentation peaks are also present arising from the compounds under the electron impact. In the mass spectrum of compound **VII** the ratio of maximal isotope components in the group of molecular ion peak (100:65) indicates the presence of two chlorine atoms [7, 8].

Oximes obtained **IV–VI** presumably may exist as four configurational isomers **a–d** with respect to the bond system HON=CH–C=CH. However it was shown that in the course of the reaction they formed as a single isomer whose configuration could not be established using only spectral data. We performed quantum-chemical calculations of the optimum geometry and heat of formation for all possible isomers of compounds **IV–VI** within the framework of the semiempirical method PM3 with complete optimization of all geometrical parameters of the molecules. It turned out that to the minimum heat of formation corresponded the structures **IVc–VIc** with a *s-cis-anti*-configuration of the molecular fragment under consideration, and therefore these structures were thermodynamically preferred.

Reactions of ketones **I–III** with hydrazine involved both C=O group and internal chlorine atom and as with hydroxylamine were accompanied with a prototropic allyl rearrangement of ketones and with coupling of two molecules of arising 3-aryl-5-dichloromethylpyrazoles (**X–XII**). Reaction of hydrazine with the dichloromethyl group with substitution of both chlorine atoms resulted in formation of "coupled" bispyrazole derivatives **XIII–XV** in 42–60% yield. We failed to isolate compounds



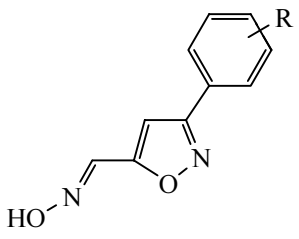
VI **IX**

R = H (**I, X, XIII**), 4-Me (**II, XI, XIV**), 2,5-Me_2 (**III, XII, XV**).

X–XII containing the dichloromethyl group even from reaction with hydrazine deficit, in various solvents, and at cooling the reaction mixture to –20°C.

The composition and structure of compounds **XIII–XV** were established from the data of elemental analysis and IR, ^{1}H NMR, and mass spectra. The formation of bispyrazole derivatives **XIII–XV** was proved by elemental analysis showing absence of chlorine. .

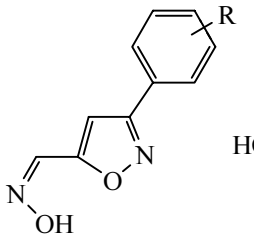
In the IR spectra of compounds **XIII–XV** are observed the absorption bands of C=N bonds (1635–1646 cm^{-1}),



IVa
69.25kcal/mol

Va
59.72 kcal/mol

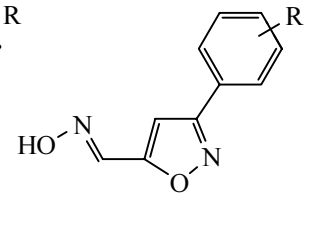
VIa
53.07 kcal/mol



IVb
73.85 kcal/mol

Vb
64.26 kcal/mol

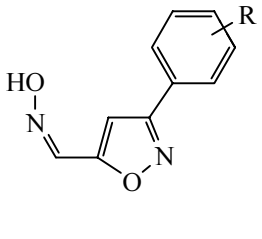
VIb
59.39 kcal/mol



IVc
68.26 kcal/mol

Vc
58.73 kcal/mol

VIc
52.63 kcal/mol



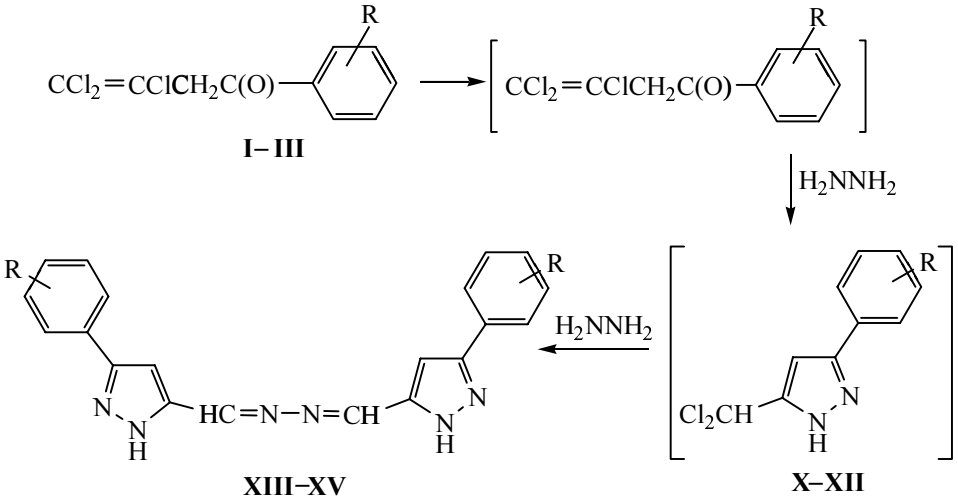
IVd
74.08 kcal/mol

Vd
64.50 kcal/mol

VId
57.86 kcal/mol

of C=C bonds (1508–1585 cm^{-1}), and a broad band belonging to NH group vibrations in the range 3200–3246 cm^{-1}. In the ^1H NMR spectra of compounds **XIII–XV** the protons of =CH groups of the pyrazole rings give rise to singlets at δ 6.93–7.22 ppm, exocyclic =CH groups to singlets in the region 8.62–8.64 ppm, broadened singlets of amino groups appear at 13.50–13.80 ppm. In the spectra are also present the multiplets from the benzene rings and signals from substituents attached thereto. In the mass spectra ions $[M]^+/2$ are observed and peaks from their fragmentation products.

The obtained bispyrazole derivatives are stable high-melting compounds sparingly soluble in the most organic compounds.



I– III

XIII–XV

X–XII

EXPERIMENTAL

IR spectra were recorded on Fourier spectrophotometer Protege-460 from KBr pellets. ^1H NMR spectra were registered on spectrometer Tesla-567A (100 MHz) from solutions in $(CD_3)_2CO$ (**IV–VII**) and $(CD_3)_2SO$ (**IX–XV**), chemical shifts measured relative to TMS. Mass spectra were obtained on mass spectrometer MKh-1320 at ionizing electrons energy 50 eV.

5-(Hydroxyiminomethyl)-3-phenylisoxazole (IV). A mixture of 6.24 g (25 mmol) of 3,4,4-trichloro-1-phenyl-3-buten-1-one (**I**), 4.16 g (126 mmol) of NH_2OH in 50 ml of methanol was heated at reflux for 15 h. Then the reaction mixture was poured into water with ice. The light-yellow precipitate was filtered off, washed with water, and recrystallized from chloroform, We obtained 1.88 g of compound **IV**. Yield 40%, mp 145–147°C. IR spectrum, ν, cm^{-1}: 1613, 1631 (C=N), 1518, 1574, 1592 (C=C), 3244 (O–H). ^1H NMR spectrum, δ, ppm: 7.07 s (1H, =CH heteryl), 7.47–7.54 m (3H arom), 7.85–8.01 m (2H arom), 8.22 s (1H, =CH aliph), 11.19 br.s (1H, OH). Found, %: C 63.38; H 4.44; N 15.14. $[M]^+$ 188.

$C_{10}H_8N_2O_2$. Calculated, %: C 63.83; H 4.29; N 14.89. *M* 188.19.

Likewise were obtained isoxazoles **V** and **VI** from hydroxylamine and an appropriate ketone.

5-(Hydroxyiminomethyl)-3-(4-methylphenyl)-isoxazole (V). Yield 62%, mp 154–156°C. IR spectrum, ν, cm^{-1}: 1614, 1632 (C=N), 1523, 1568 (C=C), 3246 (O–H). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 6.95 s (1H, =CH heteryl.), 7.27–7.41 m (2H arom), 7.60–7.84 m (2H arom), 8.23 s (1H, =CH aliph), 11.19 br.s (1H, OH). Found, %: C 65.57; H 4.93; N 13.70. $[M]^+$ 202. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.33; H 4.98; N 13.86. *M* 202.21.

5-(Hydroxyiminomethyl)-3-(2,5-dimethylphenyl)isoxazole (VI). Yield 75%, mp 156–158°C. IR spectrum, ν, cm^{-1}: 1602, 1644 (C=N), 1503, 1574, 1588 (C=C), 3240 (O–H). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 2.43 s (3H, CH_3), 6.80 s (1H, =CH heteryl.), 7.19–7.27 m (2H arom), 7.51–7.60 m (1H arom), 8.20 s (1H,=CH aliph), 11.12 br.s (1H, OH). Found, %: C 66.30; H 5.63; N 13.04. $[M]^+$ 216. $C_{12}H_{12}N_2O_2$. Calculated, %: C 66.65; H 5.59; N 12.95. *M* 216.24.

5-Dichloromethyl-3-(4-methylphenyl)isoxazole (VII). To a solution of 3.95 g (15 mmol) of 1-(4-methylphenyl)-3,4,4-trichloro-3-buten-1-one (**II**) in 40 ml of ethanol was added a solution of 1.06 g (32 mmol) of hydroxylamine in 20 ml of ethanol, the reaction mixture was stirred at 25°C for 10 h. Excess solvent was removed, the residue was poured into water with ice. The separated colorless precipitate was filtered off, washed with water, dried in a vacuum, and recrystallized from hexane. We obtained 1.38 g of isoxazole **VII**. Yield 38%, mp 66–68°C. IR spectrum, ν, cm^{-1}: 1613 (C=N), 1569, 1603 (C=C), 820 (C–Cl). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 7.19 s (1H, =CH heteryl.), 7.28 s (1H, $CHCl_2$), 7.31–7.51 m (2H arom), 7.69–7.89 m (2H arom). Found, %: C 54.23; H 3.39; Cl 29.26; N 5.83. $[M]^+$ 241 (for ^{35}Cl). $C_{11}H_9Cl_2NO$. Calculated, %: C 54.57; H 3.75; Cl 29.29; N 5.79. *M* 242.10.

3-(2,5-Dimethylphenyl)isoxazol-5-ylmethylammonium hydrochloride (IX). Into a dispersion of 0.6 (15.8 mmol) of lithium aluminum hydride in 40 ml of anhydrous ether was added in one portion 1.08 g (5 mmol) of oxime **VI** The reaction mixture was heated at reflux for 3 h, then treated with a little water. The ether solution was separated, washed with water solution of sodium carbonate, and a flow of dry hydrogen chloride was passed through the ether solution. The precipitated hydrochloride **IX** was filtered off, washed with ether, and dried in a vacuum desiccator over KOH. Yield 0.42 γ (35%), mp 205–207°C. IR spectrum, ν, cm^{-1}: 1620 (C=N), 1503, 1580 (C=C), 2705, 2867, 2910, 2955 (CH_3, CH_2, NH_3^+). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 2.40 s (3H, CH_3), 4.21 s (2H, CH_2), 6.95 s (1H, =CH heteryl), 7.20–7.33 m (2H arom), 7.44–7.58 m (1H arom), 8.62 br.s (3H, NH_3^+). Found, %: C 60.10; H 6.42; Cl 14.44; N 11.90. $[M–HCl]^+$ 202. $C_{12}H_{14}N_2O{\cdot}HCl$. Calculated, %: C 60.38; H 6.33; Cl 14.85; N 11.73. *M* 238.72.

3-Phenylpyrazole-5-carbaldehyde azine (XIII). To a solution of 1.25 g (5 mmol) of 3,4,4-trichloro-1-phenyl-3-buten-1-one (**I**) in 20 ml of methanol at 30°C was added dropwise 1.15 g (23 mmol) of hydrazine hydrate in 15 ml of methanol, and the mixture was stirred for 3 h. Then the reaction mixture was poured into water with ice. The separated light-yellow precipitate was filtered off, washed with CH_2Cl_2, and dried in a vacuum. We obtained 0.36 g of compound **XIII**. Yield 42%, mp 266–269°C (decomp.). IR spectrum, ν, cm^{-1}: 1646 (C=N), 1553, 1585 (C=C), 3246 (N–H). ^1H NMR spectrum, δ, ppm: 7.22 s (2H, 2CH heteryl.), 7.31–7.63 m (6H arom), 7.63–8.03 m (4H arom), 8.64 s (2H, 2CH aliph), 13.80 br.s (2H, 2NH). Found, %: C 72.50; H 5.89; N 21.12. $[M]^+/2$ 170. $C_{20}H_{16}N_6$. Calculated, %: C 72.70; H 6.10; N 21.20. *M* 340.39.

Pyrazole derivatives **XIV** and **XV** were obtained similarly from hydrazine and an appropriate ketone.

3-(4-Methylphenyl)pyrazole-5-carbaldehyde azine (XIV). Yield 48%, mp 263–266°C (decomp.). IR spectrum, ν, cm^{-1}: 1644 (C=N), 1529, 1556 (C=C), 3242 (N–H). ^1H NMR spectrum, δ, ppm: 2.33 s (6H, CH_3), 7.16 s (2H, 2CH heteryl.), 7.20–7.41 m (4H arom), 7.60–7.79 m (4H arom), 8.62 s (2H, 2CH aliph), 13.78 br.s (2H, 2NH). Found, %: C 71.58; H 5.77; N 22.71. $[M]^+/2$ 184. $C_{22}H_{20}N_6$. Calculated, %: C 71.72; H 5.47; N 22.81. *M* 368.44.

3-(2,5-Dimethylphenyl)pyrazole-5-carbaldehyde azine (XV). Yield 60%, mp 219–222°C (decomp.). IR spectrum, ν, cm^{-1}: 1635 (C=N), 1508, 1566 (C=C), 3200 (N–H). ^1H NMR spectrum, δ, ppm: 2.32 s (6H, $2CH_3$), 2.37 s (6H, $2CH_3$), 6.93 s (2H, 2CH heteryl.), 7.05–7.28 m (4H arom), 7.30–7.42 m (2H arom), 8.64 s (2H, 2CH aliph), 13.50 br.s (2H, 2NH). Found, %: C 70.32; H 5.03; N 24.86. $[M]^+/2$ 198. $C_{24}H_{24}N_6$. Calculated, %: C 70.57; H 4.74; N 24.69. *M* 396.50.

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