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New Transformations of 5-Hydrazino-2-phenyl-1,3-oxazole-4-carbonitrile

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Abstract — Treatment of 5-hydrazino-2-phenyl-1,3-oxazole-4-carbonitrile with acetylacetone lead to the formation of a substituted pyrazole residue on C^5, which enhanced the electrophilicity of the cyano group in position 4 so that it became capable of reacting with hydrogen sulfide, sodium azide, and hydroxylamine. As a result, the corresponding azole fragments were introduced into position 4 of the 5-(1*H*-pyrazol-1-yl)-1,3-oxazole system.

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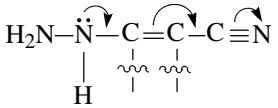
We previously showed [1] that 5-hydrazino-2-phenyl-1,3-oxazole-4-carbonitrile (**I**) can be readily synthesized by cyclocondensation of accessible 2-benzoylamino-3,3-dichloroacrylonitrile with excess hydrazine hydrate. The properties of compound **I** were still poorly studied, though some its specific transformations by the action of acylating agents were reported [1–3].

We have found that the electrophilicity of the triple C≡N in molecule **I** is reduced due to the electron-donor effect of the hydrazino group in the conjugated system shown below.

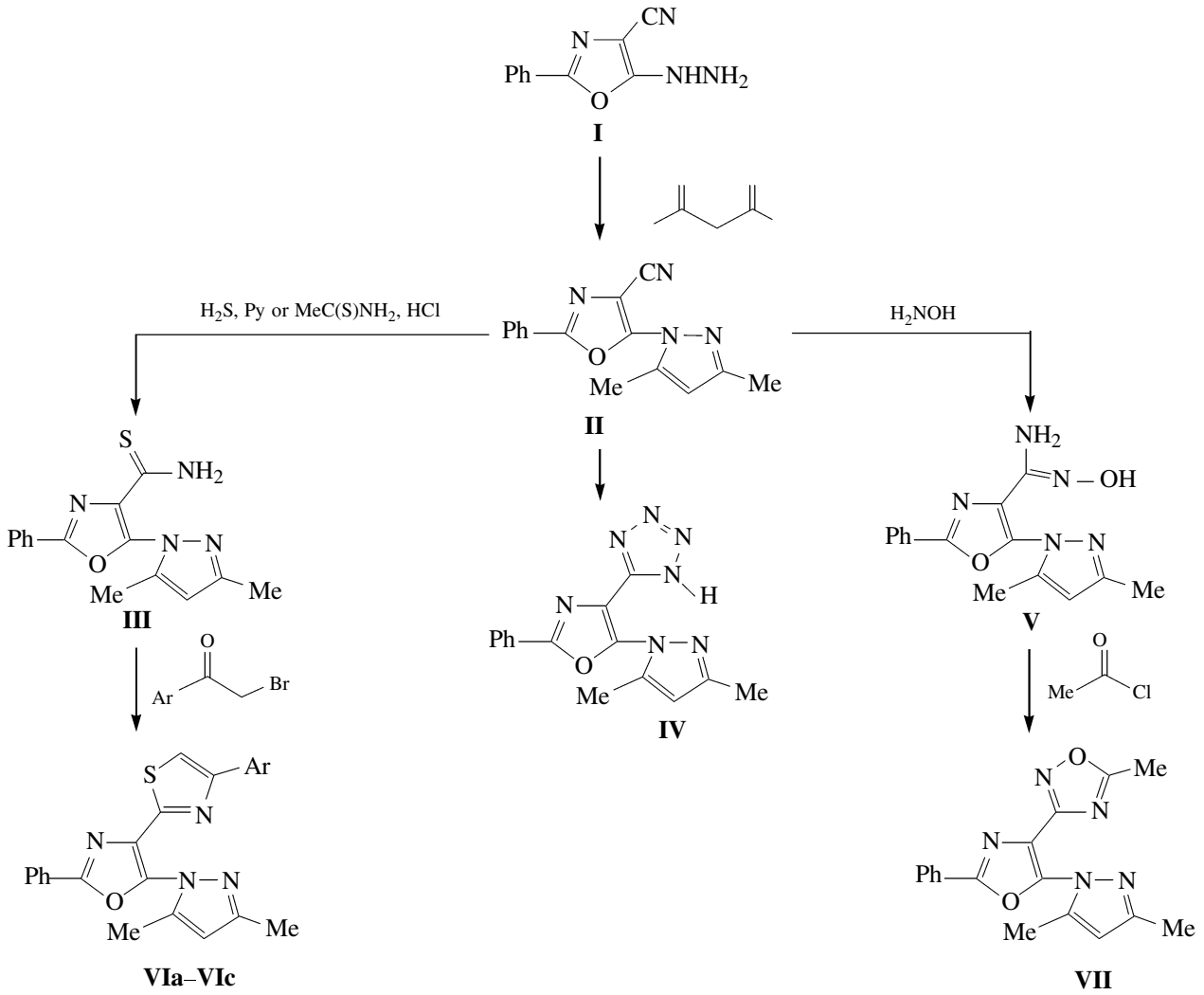


The result is that compound **I** fails to react under mild conditions with those nucleophiles which are usually capable of adding to various substrates of the general formuls HtC≡N (cf. [4–6]). However, treatment of **I** with acetylacetone leads to the transformation of the 5-hydrazino group into 3,5-dimethyl-1*H*-pyrazol-1-yl fragment. The latter is electron-deficient, and it considerably enhances the reactivity of the C≡N group. Compound **II** can react with hydrogen sulfide, thioacetamide, sodium azide, and hydroxylamine to produce the corresponding addition products **III**–**V** (Table 1) whose structure is consistent with the IR and ^{1}H NMR data (Table 2). The IR spectra of **III**–**V** lack absorption assignable to C≡N stretching vibrations (2250 cm^{-1} in the spectrum of **II**). In the ^{1}H NMR spectra of compounds **III**–**V** we observed

Table 1. Yields, melting points, and elemental analyses of compounds **II**–**VII**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
II	85	136–137 (EtOH–H_2O, 20 : 1)	67.92	4.47	21.00	$C_{15}H_{12}N_4O$	68.17	4.58	21.20
III	87 [a]	185–186 (EtOH)	60.15	4.95	18.71	$C_{15}H_{14}N_4OS$ [b]	60.38	4.73	18.78
IV	50	206–207 (EtOH–H_2O, 10 : 1)	58.50	4.19	31.66	$C_{15}H_{13}N_7O$	58.62	4.26	31.90
V	69	171–172 (EtOH–hexane, 1 : 1)	60.46	5.29	23.45	$C_{15}H_{15}N_5O_2$	60.60	5.09	23.56
VIa	75	148–149 (EtOH)	69.66	4.44	13.92	$C_{23}H_{18}N_4OS$ [c]	69.33	4.55	14.06
VIb	70	159–160 (EtOH)	70.10	4.93	13.33	$C_{24}H_{20}N_4OS$ [d]	69.88	4.89	13.58
VIc	83	184–185 (EtOH)	58.11	3.39	11.50	$C_{23}H_{17}BrN_4OS$ [e]	57.88	3.59	11.74
VII	85	161–162 (EtOH)	63.32	4.66	21.61	$C_{17}H_{15}N_5O_2$	63.54	4.71	21.80

[a] Method *a*. [b] Found, %: S 10.89. Calculated, %: S 10.74. [c] Found, %: S 7.92. Calculated, %: S 8.05. [d] Found, %: S 7.58. Calculated, %: S 7.77. [e] Found, %: Br 16.50; S 6.53. Calculated, %: Br 16.74; S 6.72.



Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**).

singlets in the region δ 6.04–6.28 ppm, which may be assigned to proton in position 4 of the pyrazole ring. The presence of a thiocarbamoyl group in compound **III** was proved by the Hantzsch reaction which led to the formation of a 4-aryl-1,3-thiazole residue linked to C^4 of the oxazole ring. Likewise, the *N*-hydroxyamidine moiety in **V** was converted into 1,2,4-oxadiazole fragment by the action of acetyl chloride (**V** → **VII**).

To conclude, the transformation sequences **I** → **II** → **III** → **VI**, **I** → **II** → **IV**, and **I** → **II** → **V** → **VII** shown in the scheme below make it possible to introduce first a 3,5-dimethyl-1*H*-pyrazol-1-yl substituent to C^5 and then build up various azolyl fragments at C^4. Obviously, the conversion of hydrazino group into pyrazole ring is not the only way of eliminating electron-donor effect of the former. Other approaches to activation of the C≡N bond in substrate **I** and its analogs will be the subjects of our further studies.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^1H NMR spectra were measured on a Varian VXR-300 instrument from solutions in DMSO-d6 relative to tetramethylsilane as internal reference. 5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-1,3-oxazole-4-carbonitrile (**II**). Acetic acid, 2 ml, and acetylacetone, 0.045 mol, were added to a suspension of 0.015 mol of 5-hydrazino-2-phenyl-1,3-oxazole-4-carbonitrile [1] in 70 ml of ethanol. The mixture was heated for 2 h under reflux with stirring and cooled to 20- 25°C, and the precipitate was filtered off and purified by recrystallization.

5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-1,3-oxazole-4-carbothioamide (III). *a*. A suspension of 0.01 mol of compound **II** in 10 ml of pyridine and 2 ml of triethylamine was saturated with gaseous

Table 2. ^{1}H NMR and IR spectra of compounds **II**–**VII**

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMCO-d_6)
II[a]	2.27 s (3H, CH_3), 2.59 s (3H, CH_3), 6.24 s (1H, 4-H, pyrazole), 7.58 m (3H, H_{arom}), 7.96 m (2H, H_{arom})
III[b]	2.20 s (3H, CH_3), 2.21 s (3H, CH_3), 6.13 s (1H, 4-H, pyrazole), 7.62 m (3H, H_{arom}), 8.08 m (2H, H_{arom}), 9.56 br.s, 10.02 br.s (2H, NH_2)
IV	2.22 s (3H, CH_3), 2.23 s (3H, CH_3), 3.20 br.s (1H, NH), 6.18 s (1H, 4-H, pyrazole), 7.61 m (3H, H_{arom}), 8.10 m (2H, H_{arom})
V[c]	2.20 s (6H, $2CH_3$), 5.63 br.s (2H, NH_2), 6.05 s (1H, 4-H, pyrazole), 7.55 m (3H, H_{arom}), 8.04 m (2H, H_{arom}), 9.78 br.s (1H, OH)
VIa	2.27 s (6H, CH_3), 6.22 s (1H, 4-H, pyrazole), 7.40 m (3H, H_{arom}), 7.61 m (3H, H_{arom}), 7.81 m (2H, H_{arom}), 8.13 m (2H, H_{arom}), 8.16 s (1H, 5-H, thiazole)
VIb	2.25 s (6H, CH_3), 2.33 s (3H, CH_3), 6.28 s (1H, 4-H, pyrazole), 7.24 m (2H, H_{arom}), 7.63 m (3H, H_{arom}), 7.73 m (2H, H_{arom}), 8.80 m (2H, H_{arom}), 8.20 s (1H, 5-H, thiazole)
VIc	2.27 s (6H, CH_3), 6.20 s (1H, 4-H, pyrazole), 7.57 m (5H, H_{arom}), 7.75 d (2H, H_{arom}), 8.11 m (2H, H_{arom}), 8.22 s (1H, 5-H, thiazole)
VII	2.18 s (3H, CH_3), 2.23 s (3H, CH_3), 2.62 s (3H, CH_3), 6.13 s (1H, 4-H, pyrazole), 7.60 m (3H, H_{arom}), 8.07 m (2H, H_{arom})

[a] IR spectrum, ν, cm^{-1}: 2250 (C≡N). [b] IR spectrum, ν, cm^{-1}: 3280, 3370 (NH_2). [c] IR spectrum, ν, cm^{-1}: 3350, 3450 (NH_2, OH).

hydrogen sulfide at 20–25°C; the mixture was left to stand for 12 h at 20–25°C and diluted with 50 ml of water, and the precipitate was filtered off, washed water, and purified by recrystallization.

b. A suspension of 0.02 mol of compound **II** in 20 ml of DMF was saturated with gaseous hydrogen chloride over a period of 1 h, 0.04 mol of thioacetamide was added, and the mixture was heated for 0.5 h on a water bath. The solvent was removed under reduced pressure, the residue was treated with 100 ml of a 5% aqueous solution of sodium hydrogen carbonate, and the precipitate was filtered off and purified by recrystallization. Yield 95% (after recrystallization from ethanol). Samples of compound **III** prepared according to methods *a* and *b* showed no depression of the melting point on mixing, and their IR and ^{1}H NMR spectra were identical.

5-[5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-1,3-oxazol-4-yl]-1*H*-tetrazole (IV). Sodium azide, 0.0045 mol, and ammonium chloride, 0.0045 mol, were added to a solution of 0.004 mol of compound **II** in 10 ml of DMF, and the mixture was heated for 6 h at 100°C, poured into 70 ml of water, and acidified with hydrochloric acid to pH ~6–7. The precipitate was filtered off, dried in a vacuum desiccator over phosphoric anhydride, and purified by crystallization.

5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-*N*'-hydroxy-2-phenyl-1,3-oxazole-4-carboximidamide (V). Water, 2 ml, was added to a mixture of 0.0075 mol of compound **II**, 0.015 mol of hydroxylamine hydrochloride, and 0.015 mol of sodium hydrogen carbonate. When the evolution of gaseous CO_2 ceased, 20 ml of ethanol was added, the mixture was heated for 2 h under reflux and cooled, the solvent was evaporated to dryness under reduced pressure, and the residue was thoroughly washed with water, dried in a vacuum desiccator over phosphoric anhydride, and purified by recrystallization.

4-(4-Aryl-1,3-thiazol-2-yl)-5-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-1,3-oxazoles VIa–VIc *(general procedure).* Compound **III**, 0.01 mol, was dispersed in 70 ml of methanol, 0.01 mol of the corresponding substituted bromoacetophenone was added, and the mixture was heated for 6 under reflux. After cooling, the precipitate was filtered off, washed with 10 ml of a 5% aqueous solution of sodium hydrogen carbonate and 20 ml of water, and purified by recrystallization from ethanol.

3-[5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-1,3-oxazol-4-yl]-5-methyl-1,2,4-oxadiazole (VII). Amidoxime **V**, 0.03 mol, was dissolved in 10 ml of benzene, 5 ml of pyridine was added, the mixture was cooled to 5–10°C, and a solution of 0.033 mol of acetyl chloride in 5 ml of anhydrous benzene was added over a period of 10 min. The mixture was left to stand for 12 h at 20–25°C, volatile substances were removed under reduced pressure, and the precipitate was thoroughly washed with water, dried in a vacuum desiccator over phosphoric anhydride, and purified by recrystallization from ethanol.

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REFERENCES

1. Pil'o, S.G., Brovarets, V.S., Vinogradova, T.K., Chernega, A.N., and Drach, B.S., *Russ. J. Gen. Chem.,* 2001, vol. 71, no. 2, p. 280.
2. Golovchenko, O.V., Pilyo, S.G., Brovarets, V.S., Chernega, A.N., and Drach, B.S., *Heteroatom Chem.,* 2004, vol. 15, no. 6, p. 454.
3. Golovchenko, A.V., Pil'o, S.G., Brovarets, V.S., Chernega, A.N., and Drach, B.S., *Russ. J. Gen. Chem.,* 2005, vol. 75, no. 3, p. 425.
4. Holland, G.F. and Pereira, J.N., *J. Med. Chem.,* 1967, vol. 10, no. 2, p. 149.
5. Baldwin, J.J., Christy, M.E., Denny, G.H., Habecker, C.N., Freedman, M.B., Lyle, P.A., Ponticello, G.S., Varga, S.L., Gross, D.M., and Sweet, C.S., *J. Med. Chem.,* 1986, vol. 29, no. 6, p. 1065.
6. Chesnyuk, A.A., Mikhailichenko, S.N., Konyushkin, L.D., Firgang, S.I., and Zaplishnyi, V.N., *Izv. Ross. Akad. Nauk, Ser. Khim.,* 2005, no. 8, p. 1845.