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Reaction of 2-Aryl(methyl)-4-cyano-5-hydrazino-1,3-oxazoles with Aryl Isothiocyanates

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Abstract — Accessible 2-aryl(methyl)-4-cyano-5-hydrazino-1,3-oxazoles add to aryl isothiocyanates. The resulting products undergo recyclization to form new 1,3,4-thiadiazole derivatives bearing an acylamino group on C^2 and an (acylamino)(cyano)methyl group on C^5. The structure of the new compounds was proved by their IR and ^{1}H NMR spectra, as well as by conversion in other 1,3,4-thiadiazole derivatives.
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Proceeding with the research on transformations of substituted 5-hydrazino-1,3-oxazoles (**I**) [1–3] we have studied reaction of accessible bases **I** with aryl isothiocyanates. As shown in the scheme, the reaction produces initially expected adducts **II** that are capable of prototropism. Prototropic tautomers **III** lack the aromatic oxazole ring, and, therefore, they can undergo recyclization under fairly mild conditions (heating in dioxane) to form new 1,3,4-thiadiazole derivatives **IV** (Table 1). Analogous recyclization also occurs in the reactions of bases **I** with alkyl and aryl isothiocyanates [3]. However, in spite of this analogy, the structure of compounds **IV**, because of their intricate formation route, had to be reliably confirmed by spectral and chemical methods. The presence of the RCONHCHC≡N fragment in the recyclization products follows no only from the IR and ^{1}H NMR spectra (Table 2), but also was proved by the **IV** → **V** transformation. This transformation readily occurs in trifluoroacetic acid already at 20–25°C, which is characteristic of many simpler α-acylaminonitriles [4]. The involvement of the acylamino fragment and the C≡N bond in the cyclization is consistent the absence from the ^{1}H NMR spectra of compounds **V** of two doublet signals at 6.54–6.81 and 9.52–10.10 ppm, characteristic of the CHNH fragment in compounds **IV**. Furthermore, the presence of the unstable 5-amino-1,3-oxazole fragment in compounds **V** is evidenced by the fact that the latter are cleaved by aqueous acetic acid to give new-type 1,3,4-thiadiazole derivatives **VI**.

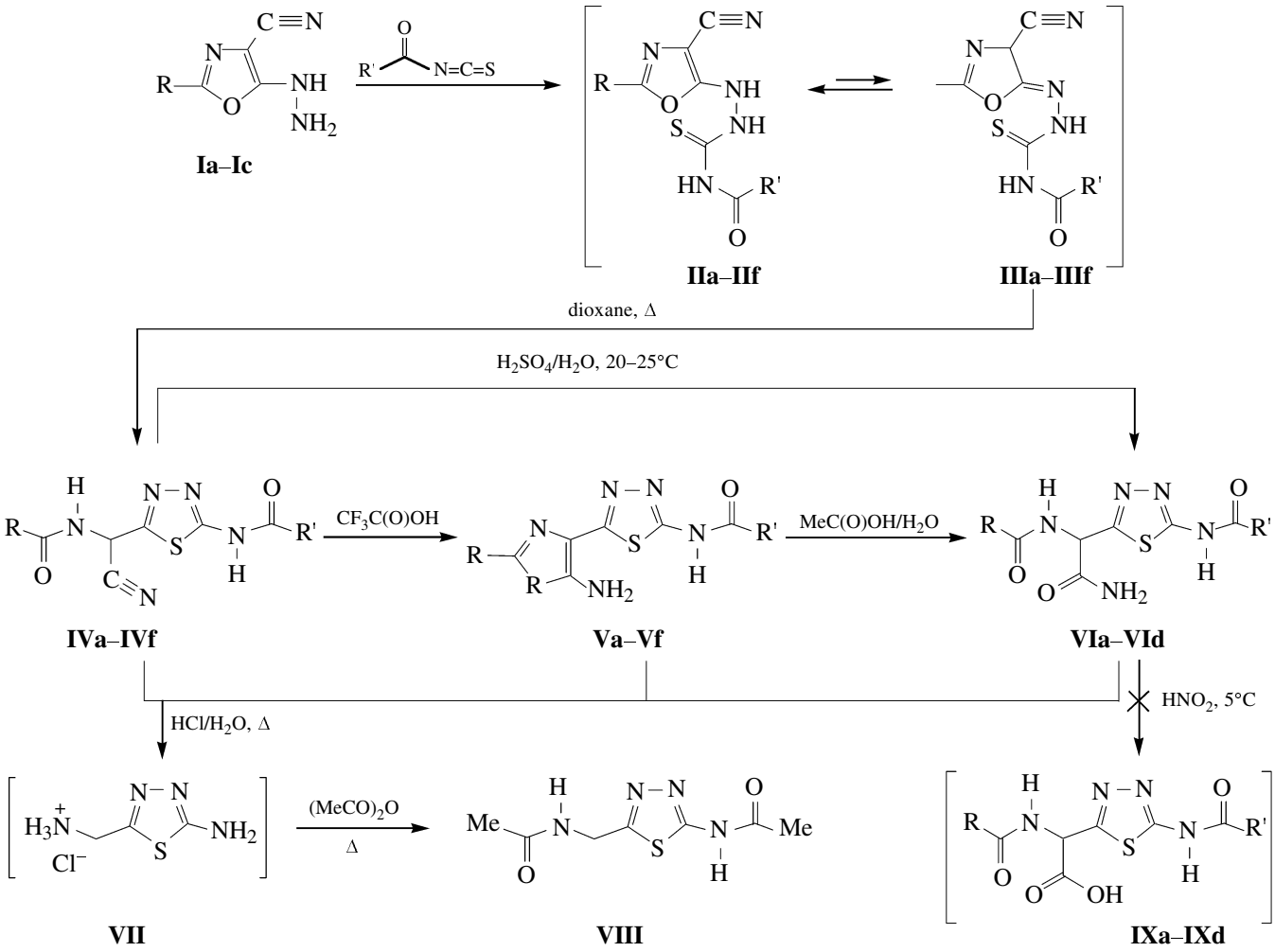
However, from the preparative viewpoint, instead of the **V** → **VI** transformation, one can take better advantage of the acid hydrolysis **IV** → **VI** that occurs already at 20–25°C. The acid hydrolysis of all the three types of relative compounds **IV**–**VI** in rigid conditions is accompanied by deacylation and decarboxylation to form, presumably, one and the same compound, 2-amino-5-(methylamino)-1,3,4-thiadiazole hydrochloride (**VII**). The latter, while not isolated individual, was converted into diacetyl derivative **VIII** which was previously obtained by independent synthesis [5]. Thus, the assignment of compounds **IV**–**VI** to 1,3,4-thiadiazoe derivatives is beyond doubt.

In summary we can conclude that attempted synthesis of one more type of related compounds **IX** containing, along with the thiadiazole ring, an α-amino acid moiety failed. Treatment of amide **VI** with nitrous acid even under very mild conditions gave a complex mixture of compounds, that contained no acid **IX**. At the same time, compounds **IV** and **VI** in the scheme may well be considered as derivatives of not only 1,3,4-thiadiazole, but also of glycine, which is of no low importance for their assessment as potential bioregulators.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer in KBr. The 1H NMR spectra were obtained on a VXR-300 instrument in DMSO-d_6, internal reference TMS.

2-(Acylamino)-2-(2-acylamino-1,3,4-thiadiazol-5-yl)acetonitriles IVa–IVf. Acyl isothiocyanate, 0.01 mol, was added to a stirred solution of 0.01 mol of compound **Ia**–**Ic** [1–3] in 20 ml of anhydrous dioxane. The mixture was refluxed for 15 min, cooled



R = Mf (**Ia, IIa–IIc–Va–Vc**), Ph (**Ib, IId–IIf–Vd–Vf, VIa, VIb; IXa, IXb**), 4-MeC_6H_4 (**Ic, IIg, IIh–Vg, Vh; VIc, Vd; IXc, IXd**); R' = Me (**IIa, IId–Va, Vd**), EtO (**IIb, IIe, IIg–Vb, Ve, Vg; VIb, VIc; IXb, IXc**), Ph (**IIc, IIf, IIh–Vc, Vf, Vh; VId, IXd**).

Table 1. Yields, constants, and elemental analyses of compounds **IV–VI** and **VIII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			N	S		N	S
IVa	66	247–248 (EtOH)	29.11	13.52	$C_8H_9N_5O_2S$	29.27	13.40
IVb	71	246–246 (dioxane)	25.85	12.33	$C_9H_{11}N_5O_3S$	26.01	11.91
IVc	90	290–292 (dioxane)	23.03	10.72	$C_{13}H_{11}N_5O_2S$	23.24	10.64
IVd	82	>300 decomp. (EtOH)	23.01	10.75	$C_{13}H_{11}N_5O_2S$	23.24	10.64
IVe	70	>300 decomp. (dioxane)	21.01	9.53	$C_{14}H_{13}N_5O_3S$	21.14	9.68
IVf	92	260–262 (dioxane)	19.10	8.68	$C_{18}H_{13}N_5O_2S$	19.27	8.82
IVg	75	>300 decomp. (dioxane)	20.08	9.14	$C_{15}H_{15}N_5O_3S$	20.28	9.28
IVh	87	255–257 (dioxane)	18.42	8.30	$C_{19}H_{15}N_5O_2S$	18.56	8.49
Va	85	245–246 decomp. (dioxane)	29.05	13.35	$C_8H_9N_5O_2S$	29.27	13.40
Vb	95	197–198 (CF_3COOH–MeOH, 1 : 10)	25.80	11.73	$C_9H_{11}N_5O_3S$	26.01	11.91
Vc	93	195–196 (CF_3COOH–MeOH, 1 : 10)	23.15	10.75	$C_{13}H_{11}N_5O_2S$	23.24	10.64

Table 1. (Contd.)

Comp. no.	Yield, %	mp, °C (solvent dor crystallization)	Found, %		Formula	Calculated, %	
			N	S		N	S
Vd	91	285–286 decomp. (dioxane)	22.90	10.82	$C_{13}H_{11}N_5O_2S$	23.24	10.64
Ve	96	>300 decomp. (CF_3COOH–MeOH, 1 : 10)	21.03	9.79	$C_{14}H_{13}N_5O_3S$	21.14	9.68
Vf	94	268–269 (CF_3COOH–MeOH ,1 : 10)	19.13	8.70	$C_{18}H_{13}N_5O_2S$	19.27	8.82
Vg	97	>300 decomp. (CF_3COOH–MeOH, 1 : 10)	20.11	9.09	$C_{15}H_{15}N_5O_3S$	20.28	9.28
Vh	92	260–261 (CF_3COOH–MeOH, 1 : 10)	18.44	8.32	$C_{19}H_{15}N_5O_2S$	18.56	8.49
VIa	55[a]	290–291 (DMSO–H_2O, 1 : 10)	21.87	9.98	$C_{13}H_{13}N_5O_3S$	21.93	10.04
VIb	90[a]	233–235 decomp. (CH_3COOH–H_2O, 10 : 1)	19.89	9.34	$C_{14}H_{15}N_5O_4S$	20.01	9.17
VIc	87[a]	203–205 decomp. (CH_3COOH–H_2O, 10 : 1)	19.07	8.95	$C_{15}H_{17}N_5O_4S$	19.27	8.82
VId	85[a]	266–267 decomp. (CH_3COOH–H_2O, 10 : 1)	17.51	8.23	$C_{19}H_{17}N_5O_3S$	17.71	8.11
VIII	51	290–292[b] (EtOH–H_2O, 2 : 1)	26.31	15.01	$C_7H_{10}N_4O_2S$	26.15	14.97

[a] Yield by procedure *a*. [b] Published data [5]: mp 292°C.

Table 2. Spectral data of compounds **IV**–**VI** and **VIII**

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm
IVa	1675 (NC=O), 1705 (NC=O), 3100–3450 (NH as.)	1.95 s (3H, CH_3), 2.20 s (3H, CH_3), 6.61 d (1H, CH, $^3J_{HH}$ 7.8 Hz), 9.55 d (1H, NH, $^3J_{HH}$ 7.8 Hz), 12.70 br.s (1H, NH)
IVb	1660 (NC=O), 1725 (OC=O), 3150–3400 (NH as.)	1.29 t (3H, CH_3), 1.94 s (3H, CH_3), 4.25 q (2H, OCH_2), 6.54 d (1H, CH, $^3J_{HH}$ 8.1 Hz), 9.52 d (1H, NH, $^3J_{HH}$ 8.1 Hz), 12.28 br.s (1H, NH)
IVc	1675[a] (NC=O), 3100–3380 (NH as.)	1.98 s (3H, CH_3), 6.58 d (1H, CH, $^3J_{HH}$ 7.5 Hz), 7.56 m ($3H_{arom}$), 8.14 d ($2H_{arom}$), 9.55 d (1H, NH, $^3J_{HH}$ 7.5 Hz), 13.19 s (1H, NH)
IVd	1670[a] (NC=O), 3000–3300 (NH as.)	2.19 s (3H, CH_3), 6.81 d (1H, CH, $^3J_{HH}$ 7.5 Hz), 7.50 m ($3H_{arom}$), 7.92 d ($2H_{arom}$), 10.07 d (1H, NH, $^3J_{HH}$ 7.5 Hz), 12.69 br.s (1H, NH)
IVf	1650 (NC=O), 1730 (NC=O), 3100–3300 (NH as.)	6.81 d (1H, CH, $^3J_{HH}$ 8.1 Hz), 7.56 m ($6H_{arom}$), 7.95 d ($2H_{arom}$), 8.12 d ($2H_{arom}$), 10.10 d (1H, NH, $^3J_{HH}$ 8.1 Hz), 13.20 br.s (1H, NH)
IVg	1655 (NC=O), 1730 (C=O), 3100–3400 (NH as.)	1.32 t (3H, CH_3), 2.37 s (3H, CH_3), 4.24 † (2H, OCH_2), 6.69 d (1H, CH, $^3J_{HH}$ 7.8 Hz), 7.27 d ($2H_{arom}$), 7.82 d ($2H_{arom}$), 9.93 d (1H, NH, $^3J_{HH}$ 7.8 Hz), 12.25 br.s (1H, NH)
IVh	1650 (NC=O), 1680 (NC=O), 3100–3350 (NH as.)	2.40 s (1H, CH_3), 6.79 d (1H, CH, $^3J_{HH}$ 7.8 Hz), 7.31 d ($2H_{arom}$), 7.60 m ($3H_{arom}$), 7.84 d ($2H_{arom}$), 8.11 d ($2H_{arom}$), 10.01 d (1H, NH, $^3J_{HH}$ 7.8 Hz), 13.19 br.s (1H, NH)
Va	1670[a] (NC=O, δ_{NH_2}), 2800–3200 (NH as.), 3280, 3420 (NH_2)	2.16 s (3H, CH_3), 2.31 s (3H, CH_3), 6.53 br.s (2H, NH_2), 12.14 br.s (1H, NH)
Vb	1670[a] (NC=O, δ_{NH_2}), 1725 (OC=O), 2800–3200 (NH as.), 3350, 3425 (NH_2)	1.30 t (3H, CH_3), 2.32 s (3H, CH_3), 4.22 q (2H, OCH_2), 6.61 br.s (2H, NH_2), 11.79 br.s (1H, NH)
Vc	1650[a] (NC=O, δ_{NH_2}), 3000–3300 (NH as.), 3350, 3420 (NH_2)	2.31 s (3H, CH_3), 6.69 br.s (2H, NH_2), 7.52 m ($3H_{arom}$), 8.11 d ($2H_{arom}$), 12.78 br.s (1H, NH)
Vd	1650 (NC=O, δ_{NH_2}), 2700–3250 (NH as.), 3270, 3380 (NH_2)	2.20 s (3H, CH_3), 7.27 br.s (2H, NH_2), 7.50 m ($3H_{arom}$), 7.83 d ($2H_{arom}$), 12.41 br.s (1H, NH)
Ve	1650[a] (NC=O, δ_{NH_2}), 1740 (OC=O), 2800–3250 (NH as.), 3300, 3430 (NH_2)	1.32 t (3H, CH_3), 4.27 q (2H, OCH_2), 7.07 br.s (2H, NH_2), 7.47 m ($3H_{arom}$), 7.83 d ($2H_{arom}$), 11.88 br.s (1H, NH)
Vf	1650[a] (NC=O, δ_{NH_2}), 2800–3100 (NH as.), 3320, 3450 (NH_2)	7.18 br.s (2H, NH_2), 7.51 m ($6H_{arom}$), 7.87 d ($2H_{arom}$), 8.15 ($2H_{arom}$), 12.60 br.s (1H, NH)
Vg	1655[a] (NC=O, δ_{NH_2}), 1720 (O=OC), 2800–3200 (NH as.), 3325, 3420 (NH_2)	1.31 t (3H, CH_3), 2.37 s (3H, CH_3), 4.24 q (2H, OCH_2), 7.00 br.s (2H, NH_2), 7.35 d ($2H_{arom}$), 7.60 d ($2H_{arom}$), 11.87 br.s (1H, NH)

Table 2. (Contd.)

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm
Vh	1650[a] (NC=O, δ_{NH_2}), 2800–3180 (NH as.), 3340, 3460 (NH_2)	2.38 s (3H, CH_3), 7.12 br.s (2H, NH_2), 7.27 d ($2H_{arom}$), 7.61 m ($3H_{arom}$), 7.75 d ($2H_{arom}$), 8.14 d ($2H_{arom}$), 12.87 br.s (1H, NH)
VIa	1635 (NC=O), 1700[a] (NC=O), 2800–3400 (NH as.)	2.18 s (3H, CH_3), 5.95 d (1H, CH, $^3J_{HH}$ 7.7 Hz), 7.51 m ($3H_{arom}$), 7.55 br.s, 7.83 br.s (2H, NH_2), 7.93 d ($2H_{arom}$), 9.23 d (1H, NH, $^3J_{HH}$ 7.7 Hz), 12.48 br.s (1H, NH)
VIb	1645[a] (NC=O), 1730[a] (OC=O), 2800–3400 (NH as.)	1.28 t (3H, CH_3), 4.22 q (2H, OCH_2), 5.80 d (1H, CH, $^3J_{HH}$ 8.1 Hz), 7.51 m (5H, $3H_{arom}$, NH_2), 7.93 d ($2H_{arom}$), 9.08 d (1H, NH, $^3J_{HH}$ 8.1 Hz), 12.02 br.s (1H, NH)
VIc	1645[a] (NC=O), 1705, 1740 (NC=O, OC=O), 2800–3500 (NH as.)	1.28 t (3H, CH_3), 2.38 s (3H, CH_3), 5.91 d (1H, CH, $^3J_{HH}$ 7.8 Hz), 7.27 d ($2H_{arom}$), 7.47 br.s, 7.74 br.s (2H, NH_2), 7.81 d ($2H_{arom}$), 8.97 d (1H, NH, $^3J_{HH}$ 7.8 Hz), 12.00 br.s (1H, NH)
VId	1645[a] (NC=O), 1665, 1680 (NC=O), 2800–3400 (NH as.)	2.39 s (3H, CH_3), 5.97 d (1H, CH, $^3J_{HH}$ 7.5 Hz), 7.27 d ($2H_{arom}$), 7.52 ($3H_{arom}$), 7.60 br.s, 7.79 br.s (2H, NH_2), 7.84 d ($2H_{arom}$), 8.11 d ($2H_{arom}$), 9.02 d (1H, NH, $^3J_{HH}$ 7.5 Hz), 12.97 br.s (1H, NH)
VIII	1655 (NC=O), 1700 (NC=O), 2900–3280 (NH as.)	1.88 s (3H, CH_3), 2.16 s (3H, CH_3), 4.48 d (2H, CH_2, $^3J_{HH}$ 5.7 Hz), 8.63 t (1H, NH), 12.34 br.s (1H, NH)

[a] Band with a shoulder.

to 20–25°C, the precipitate was filtered off, and compounds **IVa**–**IVf** were purified by crystallization from dioxane.

2-(Acylamino)-5-[2-aryl(methyl)-5-amino-1,3-oxazol-4-yl]-1,3,4-thiadiazoles Va–Vf. A solution of 0.01 mol of compound **IVa**–**IVf** in 20 ml of trifluoroacetic acid was left to stand for 10 min at 20–25°C, poured into 200 ml of ice water, the solution was neutralized to pH ~7 with aqueous sodium carbonate, the precipitate was filtered off, and compounds **Va**–**Vf** were purified by crystallization.

2-(Acylamino)-2-(2-acylamino-1,3,4-thiadiazol-5-yl)acetamides VIa–IVd. *a*. A solution of 0.002 mol of compound **Vd**, **Ve**, **Vg**, or **Vh** in 10 ml of 70% acetic acid was refluxed for 2–3 h, the solvent was removed in a vacuum, the residue was treated with a 5% solution of sodium hydrocarbonate, the precipitate was filtered off, washed with water, and compounds **VIa**–**VId** were purified by crystallization.

b. A solution of 0.004 mol of compound **Vd**, **Ve**, **Vg**, or **Vh** in 2 ml of conc. H_2SO_4 was left to stand for 6 h at 20–25°C, poured into 100 ml of ice water, neutralized with 10% sodium carbonate, the precipitate was filtered off, and compounds **VIa**–**VId** were purified by reprecipitation from acetic acid with water (10 : 1). The yields of compounds **VIa**–**VId** were 60–70%. Mixed samples of samples of compounds VIa–VId prepared by procedures *a* and *b* gave no melting point depression.

2-(Acetylamino)-5-(acetylaminomethyl)-1,3,4-thiadiazole (VIII). A suspension of 0.01 mol of compound **IV**–**VI** in 20 ml of 30% HCl was refluxed for 6 h, the precipitate was filtered off, the mother liquor was evaporated in a vacuum to dryness, the residue was treated with acetone, filtered off, dried, and dissolved in 20 ml of pyridine. Acetic anhydride, 0.06 mol, was then added, the mixture was stirred for 4 h at 50°C, the solvent was removed in a vacuum, the residue was treated with water, filtered, and compound **VIII** was purified by crystallization. A mixture of this sample of compound **VIII** and a sample of the same compound obtained by the known procedure [5] gave no melting point depression.

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