Russian Journal of Organic Chemistry, Vol. 38, No. 4, 2002, pp. 599–601. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 4, 2002, pp. 627–629.

Functionally Substituted 3-Heterylpyrazoles: X.* Reaction of 3-Aryl-1-phenyl-4-pyrazolecarbonyl Isothiocyanates with 3-Amino-5-methylisoxazole

M. V. Vovk, N. V. Mel'nichenko, V. A. Chornous, and M. K. Bratenko

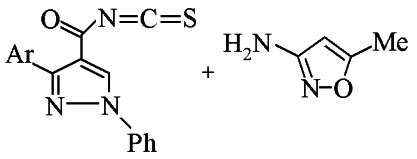
Bukovina State Medical Academy, Chernovtsy, 58000 Ukraine
Institute of Organic Chemistry, Ukrainian Academy of Science, Kiev, Ukraine

Received May 15, 2000

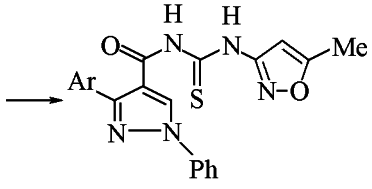
Abstract—3-Aryl-1-phenyl-4-pyrazolecarbonyl isothiocyanates react with 3-amino-5-methylisoxazole to afford 3-aryl-*N*-(3-acetonyl-1,2,4-thiadizol-5-yl)-1-phenylpyrazole-4-carboxamides.

We formerly [2] synthesized 3-aryl-1-phenyl-4-pyrazolecarbonyl isothiocyanates and showed that they react with alkyl-, aryl-, and some heterylamnes giving stable *N*-pyrazolcarbonylthioureas. In the present study a reaction of 4-pyrazolecarbonyl isothiocyanates with a heterylamine containing a labile heterocyclic system, 3-amino-5- methylisoxazole was investigated. The capability of 3-aminoisoxazoles to undergo recyclization was utilized in syntheses of pyrazoles [3], triazoles, tetrazoles, and oxadiazoles [4]. The published data on reaction between isothiocyanates and 3-amino-5-methylisoxazole resulting in derivatives of 5-amino-1,2,4-thiadiazole are limited to application of phenyl isothiocyanate [5] and adamantanecarbonyl isothiocyanates [6]. Therefore we presumed that this kind of reaction would be promising for synthesis of new amides of pyrazole-4-carboxylic acid as potential biologically active substances [7–9].

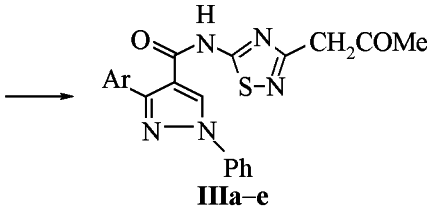
The study of reaction between 4-pyrasolecarbonyl isothiocyanates **Ia–f** with 3-amino-5-methylisoxazole (**II**) revealed that the structure of the final products and their yield depended on the nature of the aromatic substituent in the *3* position of pyrazole **I**, and the solvent applied governed the reaction conditions. For instance, stirring of the reagents in acetonitrile at room temperature for 10 h or heating in boiling toluene for 7 h gave rise to 1,2,4-thiadiazoles **IIIa–e** and thiourea **IVf**. Apparently thioureas **IVa–e** are intermediates in formation of thiadiazoles **IIIa–e** and already in statu nascendi spontaneously transform into **IIIa–e** by attack of nucleophilic thiocarbonyl group on the N–O bond of the isoxazole ring. Relatively low yield of compound **IIIe** is due to steric hindrance from 2-naphthyl substituent hampering formation of thiourea **IVe**. This is also proved by the presence in the reaction mixture of unreacted initial isothiocyanate **Ie**. The inability of thiourea **IVf** to transform into the corresponding thiadiazole even at higher temperature (140°C) is apparently caused by concurrent formation of a charge-transfer complex between C=S group and *m*-bromophenyl susbstituent.



Ia–f **II**



IVa–f



IIIa–e

I, III, IV, Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 2-naphthyl (**e**), 3-BrC_6H_4 (**f**).

The compounds **IIIa–e** obtained (see the table) are colorless crystalline compounds. Their composition

* For communication IX see [1].

1070-4280/01/3804-599$27.00 © 2002 MAIK "Nauka/Interperiodica"

Yields, melting points, elemental analyses, IR and ^{1}H NMR spectra of 3-aryl-*N*-(3-acetyl-1,2,4-thiadiazol-5-yl)-1-phenylpyrazole-4-carboxamides **IIIa–e**

Compd. no.	Yield, %[a]	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	54 (50)	190–192 (acetonitrile)	62.80	4.00	17.49	$C_{21}H_{17}N_5O_2S$	62.51	4.25	17.36
IIIb	65 (61)	205–207 (ethanol–water–dioxane, 3 : 1 : 0.5)	58.03	3.50	15.71	$C_{21}H_{16}ClN_5O_2S$	57.60	3.68	15.99
IIIc	53 (56)	224–226 (ethanol–water–dioxane, 3 : 1 : 0.5)	52.47	3.28	14.22	$C_{21}H_{16}BrN_5O_2S$	52.29	3.34	14.52
IIId	49 (54)	205–207 (ethanol–water, 3:1)	61.39	4.37	16.06	$C_{22}H_{19}N_5O_3S$	60.95	4.42	16.16
IIIe	34 (27)	192–193 (ethanol)	66.29	4.40	15.33	$C_{25}H_{19}N_5O_2S$	66.21	4.22	15.44

Compd. no.	IR spectrum (KBr), ν, cm^{-1}		^{1}H NMR spectrum (DMSO-d_6), δ, ppm
	C=O	N–H	
IIIa	1685, 1715	3300	2.20 s (3H, CH_3), 3.98 s (2H, CH_2), 7.35–7.84 m (10H, H arom), 9.40 s (1H, CH=), 13.09 s (1H, NH)
IIIb	1680, 1715	3285	2.21 s (3H, CH_3), 4.03 s (2H, CH_2), 7.45–7.91 m (9H, H arom), 9.42 s (1H, CH=), 13.21 s (1H, NH)
IIIc	1685, 1720	3250	2.20 s (3H, CH_3), 4.03 s (2H, CH_2), 7.44–7.89 m (9H, H arom), 9.41 s (1H, CH=), 13.17 s (1H, NH)
IIId	1685, 1720	3300	2.20 s (3H, CH_3), 3.82 s (3H, CH_3O), 4.03 s (2H, CH_2), 7.01–7.86 m (9H, H arom), 9.38 © (1H, CH=), 13.17 s (1H, NH)
IIIe	1680, 1710	3280	2.21 s (3H, CH_3), 4.04 s (2H, CH_2), 7.68–8.38 m (12H, H arom), 9.46 s (1H, CH=), 13.28 s (1H, NH)

[a] Yield given is for method *a*, that for method *b* is in parentheses (see EXPERIMENTAL).

was proved by elemental analysis, and structure was confirmed by ^{1}H NMR and IR spectra. In particular, the IR spectra contain absorption bands of ketone (1710–1720 cm^{-1}) and amide (1680–1685 cm^{-1}) carbonyl groups. In the ^{1}H NMR spectra are present singlet from methyl (2.20–2.21 ppm) and methylene (4.02–4.04 ppm) protons of acetyl group in *3* position of thiadiazole ring, also singlets of CH= protons of the pyrazole ring (9.38–9.46 ppm) and of amide NH protons (13.16–13.38 ppm).

EXPERIMENTAL

IR spectra were recorded on spectrometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered on spectrometer Varian-Gemini (300 MHz) in DMSO-d_6, internal reference TMS.

3-aryl-*N*-(3-acetonyl-1,2,4-thiadizol-5-yl)-1-phenylpyrazole-4-carboxamides (IIIa–e). (a) To a solution of 0.01 mol of isothiocyanate **I** in 20 ml of acetonitrile was added 0.98 g (0.01 mol) of 3-amino-isoxazole **II**, and the mixture was stirred at room temperature for 10 h. The precipitate formed was filtered off and recrystallized. (b) The reaction was carried out in boiling toluene for 7 h.

***N*-[3-(3-Bromophenyl)-1-phenyl]-4-pyrazole-4-carbonyl-*N*'-(3-methylisoxazol-5-yl)thiourea (IVe)** was prepared by the same procedure as compounds **III**. Yield 53% (method *a*), 44% (method *b*), mp 185–187°C (ethanol–water, 3 : 1). IR spectrum, ν, cm^{-1}: 1700 (C=O), 3200, 3390 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 6.73 s (1H, CH= of isoxazole), 7.42–8.04 s (9H, H arom), 9.26 s (1H, CH= of pyrazole), 10.58 s (1H, NH), 11.16 c (1H, NH). Found, %: C 52.62; H 3.18; N 14.60. $C_{21}H_{16}$ßrN$_5O_2S$. Calculated, %: C 52.29; H 3.34; N 14.52.

REFERENCES

1. Bratenko, M.K., Chornous, V.A., and Vovk, M.V., *Zh. Org. Khim.*, 2002, vol. 38, no. 4, pp. 620–624.
2. Chornous, V.A., Mel'nichenko, N.V., Bratenko, M.K., and Vovk, M.V., *Zh. Org. Khim.*, 2002, vol. 38, no. 3, pp. 426–431.
3. Ruccia, M., Vivona, N., Cusmano, G., and Macaluso, G., *J. Chem. Soc., Perkin Trans. I*, 1977, no. 6, pp. 589–591.
4. Boulton, A.J., Katritzky, A. R., and Majid Hamid, A., *J. Chem. Soc. (S)*, 1967, no. 20, pp. 2005–2007.
5. Vivona, N., Cusman, G., and Maculuso, G., J. Chem. Soc., Perkin Trans. I, 1977, no. 11, pp. 1616–1619.
6. Semenova, I.G., Klimko, Yu.E., and Yurchenko, O.G., Abstracts of Papers, *Mezhdunarodnaya konferentsiya "Khimiya azotovmisnikh geterotsikliv"* (Int. Conf. on Nitrogen Containing Heterocycles), Kharkov, 2000.
7. Zagorevskii, V.A., Vlasova, N.V., Zykov, D.A., and Kirsanova, Z.D., *Khim.-Farm. Zh.m* 1989, vol. 23, no. 8, pp. 966–971.
8. Morozov, I.S., Klimova, N.V., Bykova, N.V., and Zaitseva, N.M., *Khim.-Farm. Zh.*, 1991, vol. 25, no. 3, pp. 29–31.
9. Wang, A.X., Xie, Q., Lone, B., Mollison, K.W., Hsieh, G.C., Marsh, K., Sheets, M.P., Luly, J.R., and Coghlan, M.I., *Bioorg. Med. Chem. Lett.*, 1998, vol. 19, no. 8, pp. 2787–2792.