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# Functionally Substituted 3-Heterylpyrazoles: IX.* 3-Aryl(heteryl)-4-mercapto(thiocyanato, isothiocyanato)-methylpyrazoles

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**Abstract**—By reaction of 3-aryl(heteryl)-4-chloromethylpyrazoles with thiourea and sodium thiocyanate respectively 3-aryl(heteryl)-4-mercaptomethylpyrazoles and 3-aryl(heteryl)-thiocyanatomethylpyrazoles were obtained. The latter were subjected to thermal isomerization into 3-aryl(heteryl)-isothiocyanatomethylpyrazoles.

In the preceding communication [1] we described a preparation of 3-aryl(heteryl)-4-chloromethylpyrazoles and their application to the synthesis of alkenylpyrazoles. The latter reaction was possible because 4-chloromethylpyrazoles were capable to alkylate triphenylphosphines affording 4-pyrazolylmethylphosphonium salts.

In the present study aiming at the synthesis of new 4-functional sulfur-containing pyrazole derivatives we carried out alkylation of thiourea and sodium thiocyanate with 3-aryl(heteryl)-4-chloromethylpyrasoles **Ia–g**. The reaction of alkyl halides with thiourea affording primarily S-alkylthiuronium salts is extensively applied to preparation of alkanethioles [2]. We demonstrated that 4-chloromethylpyrazoles **Ia, b, d, g** reacted with thiourea at heating in tetrahydrofuran furnishing in high yield S-(4-pyrazolylmethyl)isothiuronium chlorides **IIa, b, d, g** which were isolated and characterized, and then subjected to alkaline hydrolysis with sodium hydroxide. As a result we obtained in 74–84% yield 4-pyrazolylmethanethiols **IIIa, b, d, g** (Table1) as colorless crystalline compounds with no unpleasant odor. Their $^1$H NMR spectra are consistent with the assumed structure: alongside the multiplet signals from the substituents in positions *1* and *3* of the pyrazole ring in the spectra are present a singlet from the proton ¢$^5$H (8.51–8.56 ppm) and broadened singlets from protons of CH$_2$ (3.82–3.87 ppm) and SH groups (2.90–2.94 ppm).

Thiocyanate anion is an ambidental nucleophile, and its kinetically controlled reactions with organic compounds result either from attack by the sulfur atom yielding thiocyanates or by the nitrogen atom affording isocyanates, or both providing mixture of the products [3]. No published data exist on the reaction between azolylmethyl halides and metal thiocyanates, but the kinetics of the reaction of their carbocyclic analogs, benzyl halides, is investigated in detail. In particular, it was shown [4] that in S$_N$2 reaction at the benzyl carbon the relative nucleophilicity of S and N atoms in the thiocyanate anion depends mainly on the temperature and the solvent. Low temperature favors thiocyanate formation, and at high temperature arise isothiocyanates. Therefore we carried out the reaction of 4-chloromethylpyrazoles **Ia–g** and sodium thiocyanate in boiling acetone. It was established that the reaction occurred selectively and within 1 h of heating afforded 4-thiocyanatomethylpyrazoles **IVa–g** (Table 2). Thiocyanates **IVa–d, g** are colorless crystalline substances, compound **IVf** is a viscous light-yellow fluid. Their structure was confirmed by IR spectra (the presence of a weak band belonging to SCN group in the region 2160–2170 cm$^{-1}$) and by $^1$H NMR spectra where appeared characteristic singlets from proton C$^5$H of pyrazole at 8.71–8.84 ppm and from methylene group at 4.56–4.68 ppm.

We found that 4-thiocyanatomethylpyrazoles **IVa–g** same as benzylthiocyanates [6] on heating for 2 h in p-xylene were converted into 4-isothiocyanatomethylpyrazoles **Va–g**. Isothiocyanates **Va–g** are viscous undistillable oily substances with a strong absorption band in the IR spectra at 1970–1990 cm$^{-1}$ belonging to antisymmetrical stretching vibrations of $-N=C=S$ group.

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[*] For communication VIII see [1].

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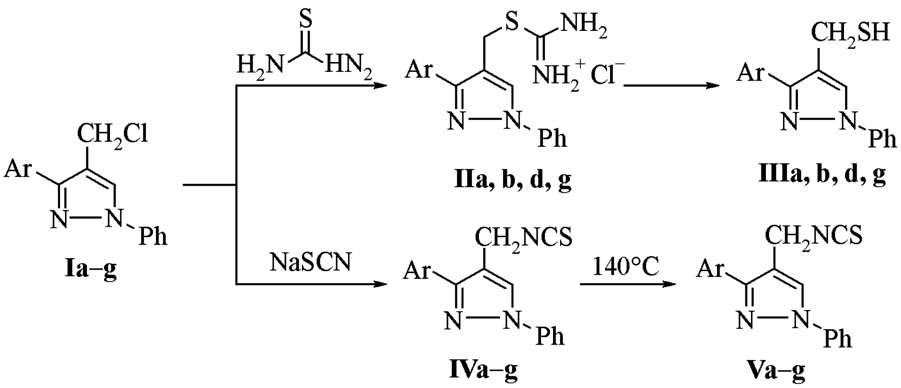
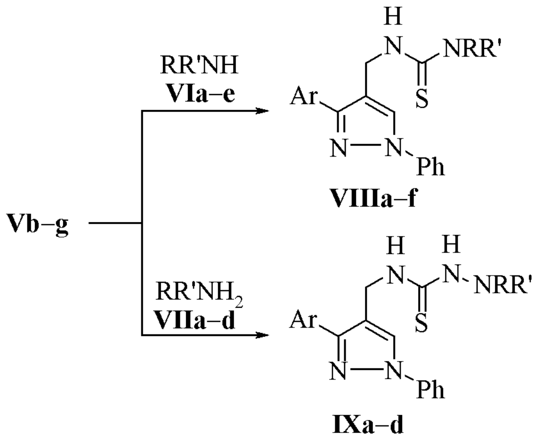


**I**–**V$(24)**, Ar = Ph (**a**), 4-$FC_6H_4$ (**b**), 4-$ClC_6H_4$ (**c**), 4-$BrC_6H_4$ (**d**), 4-$MeC_6H_4$ (**e**), 2-thienyl (**f**), 2-benzo[*b*]furyl (**g**).

Compounds **Va–g** without further purification were reacted with amines **VIa–d**, hydrazines **VIIa–c**, hydrazide **VIId**, and hydrazone **VIIe** to afford thioureas **VIIIa–e** and thiosemicarbazides **IXa–d** (Table 3).



**VI**, R = H, R' = $PhCH_2$ (**a**), 2-pyridylmethyl (**b**), 4-$MeOC_6H_4$ (**c**), 2-pyridyl (**d**), R = R' = $(CH_2)_5$ (**e**); **VII**, R = H, R' = Ph (**a**), 2-benzothiazolyl (**b**), 4-pyridylcarbonyl (**d**); R = R' = $(CH_2)_2N(Me)(CH_2)_2$ (**c**), 3-(3-pyridyl)-1-phenyl-4-pyrazolylmethylene (**e**); **VIII**, Ar = 4-$FC_6H_4$, R = R' = $(CH_2)_5$ (**a**); Ar = 4-$ClC_6H_4$, R = H, R' = 4-$MeOC_6H_4$ (**b**); Ar = 4-$BrC_6H_4$, R = R' = $(CH_2)_5$ (**c**); Ar = 4-$MeC_6H_4$, R = H, R' = 2-pyridyl (**d**); Ar = 2-thienyl, R = H, R' = $PhCH_2$ (**e**); Ar = 2-benzo[*b*]furyl, R = H, R' = 2-pyridylmethyl (**f**); **IE**, Ar = 4-$FC_6H_4$, R = H, R' = Ph (**a**); Ar = 4-$BrC_6H_4$, R = R' = $(CH_2)_2N(Me)(CH_2)_2$ (**b**); Ar = 4-$MeC_6H_4$, R = H, R' = 2-benzothiazolyl (**c**); Ar = 2-thienyl, R = R' = 3-(3-pyridyl)-1-phenyl-4-pyrazolemethylene (**d**); Ar = 2-benzo[*b*]furyl, R = H, R' = 4-pyridylcarbonyl (**e**).

## EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from samples pelleted with KBr. $^1H$ NMR spectra were registered on spectrometer Varian-Gemini (300 MHz) in $(CD_3)_2SO$ solution, internal reference TMS.

3-Aryl(heteryl)-1-phenyl-4-chloromethylpyrazoles **I, e, g** and their initial 3-aryl(heteryl)-4-hydroxymethyl-1-phenylpyrazoles were prepared by procedure [1].

**4-Hydroxymethyl-3-(4-tolyl)-1-phenylpyrazole.** Yield 83%. mp 127–128°C (from ethanol). IR spectrum, ν, $cm^{-1}$: 3340 (OH). $^1H$ NMR spectrum, δ, ppm: 2.28 s (3H, $CH_3$), 4.64 d (2H, $CH_2$), 5.31 t (1H, OH), 7.16–7.72 m (9H, H arom), 8.50 s (1H, CH=). Found, %: C 76.91; H 6.02; N 10.34. $C_{17}H_{16}N_2O$. Calculated, %: C 77.25; H 6.10; N 10.60.

**3-(2-Benzo[*b*]furyl)-4-hydroxymethyl-1-phenylpyrazole.** Yield 80%. mp 128–130°C (from ethanol). IR spectrum, ν, $cm^{-1}$: 3360 (OH). $^1H$ NMR spectrum, δ, ppm: 4.57 d (2H, $CH_2$), 5.28 t (1H, OH), 7.24–7.80 m (10H, H arom), 8.54 s (1H, CH=). Found, %: C 74.69; H 4.90; N 9.31. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.47; H 4.86; N 9.65.

**3-(4-Tolyl)-1-phenyl-4-chloromethylpyrazole (Ie).** Yield 78%. mp 99–101°C (from benzene–hexane, 3 : 1). $^1H$ NMR spectrum, δ, ppm: 2.32 s (3H, $CH_3$), 4.96 s (1H, $CH_2$), 7.34–7.79 m (9H, H arom), 8.82 s (1H, CH=). Found, %: C 72.53; H 5.47; N 10.07. $C_{17}H_{15}ClN_2$. Calculated, %: C 72.21; H 5.35; N 9.91.

**3-(2-Benzo[*b*]furyl)-1-phenyl-4-chloromethylpyrazole (Ig).** Yield 77%. mp 92–93°C (from benz-

**Table 1.** Yields, melting points and elemental analyses of S-[3-aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]thiuronium chlorides (**IIa, b, d, g**) and 3-aryl(heteryl)-1-phenyl-4-pyrazolylmethanethiols (**IIIa, b, d, g**)

| Compd. no. | Yield, % | mp, °C | $^1$H NMR spectra, δ, ppm | Found, % | | | | Formula | Calculated, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S | | C | H | N | S |
| **IIa** | 82 | 176–177 | – | – | – | 16.55 | 9.04 | $C_{17}H_{17}C_1N_4S$ | – | – | 16.25 | 9.30 |
| **IIb** | 90 | 177–178 | – | – | – | 15.11 | 9.03 | $C_{17}H_{16}C_1FN_4S$ | – | – | 15.44 | 8.84 |
| **IId** | 87 | 186–187 | – | – | – | 13.61 | 7.43 | $C_{17}H_{16}BrClN_4S$ | – | – | 13.22 | 7.57 |
| **IIg** | 93 | 184–185 | – | – | – | 14.81 | 8.48 | $C_{19}H_{17}C_1N_4OS$ | – | – | 14.56 | 8.33 |
| **IIIa** | 80 | 43–44 | 2.92 br.s (1H, SH), 3.86 br.s (2H, CH2), 7.32–7.89 m (10H, H arom), 8.55 s (IH, CH=) | 72.45 | 5.08 | 10.68 | – | $C_{16}H_{14}N_2S$ | 72.15 | 5.30 | 10.52 | – |
| **IIIb** | 84 | 56–57 | 2.80 br.s (IH, SH), 3.82 br.s (2H, CH2), 7.43–7.87M(9H, H arom), 8.51 s (IH, CH=) | 67.84 | 4.47 | 10.07 | – | $C_{16}H_{13}FN_2S$ | 67.58 | 4.64 | 9.85 | – |
| **IIId** | 78 | 67–68 | 2.94 br.s (IH, SH), 3.87 br.s (2H, CH2), 7.40–7.79M(9H, H arom), 8.53 s (IH, CH=) | 55.25 | 3.95 | 8.31 | – | $C_{16}H_{13}BrN_2S$ | 55.66 | 3.80 | 8.11 | – |
| **IIIg** | 74 | 99–100 | 2.93 br.s (IH, SH), 3.86 br.s (2H, CH2), 7.29–7.91 m (10H, H arom), 8.56 s (IH, CH=) | 70.56 | 4.61 | 9.14 | – | $C_{18}H_{14}N_2OS$ | 70.56 | 4.81 | 9.11 | – |

**Table 2.** Yields, melting points and elemental analyses of 3-aryl(heteryl)-4-thiocyanatomethyl-1-phenylpyrazoles (**IVa–g**)

| Compd. no. | Yield, % | mp, °C | IR spectrum ν(SCN), cm$^{-1}$ | $^1$H NMR spectra, δ, ppm | Found, % | | | Formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | | C | H | N |
| **IVa** | 81 | 56–57 | 2170 | 4.59 s (2H, $CH_2$), 7.30–7.82 m (10H, H arom), 8.74 s (IH, CH=) | 70.38 | 4.50 | 14.47 | $Cl_7H_{13}N_3S$ | 70.10 | 4.46 | 14.43 |
| **IVb** | 85 | 76 | 2165 | 4.62 s (2H, $CH_2$), 7.41–7.91 m (9H, H arom), 8.80 s (IH, CH=) | 65.83 | 3.64 | 13.41 | $C_{17}H_{12}FN_3S$ | 66.01 | 3.88 | 13.59 |
| **IVc** | 80 | 115–117 | 2165 | 4.64 s (2H, $CH_2$), 7.34–7.97 m (9H, H arom), 8.81 s (IH, CH=) | 62.34 | 3.40 | 12.57 | $C_{17}H_{12}C_1N_3S$ | 62.67 | 3.68 | 12.90 |
| **IVd** | 77 | 124–125 | 2160 | 4.60 s (2H, $CH_2$), 7.40–7.86 m (9H, H arom), 8.83 s (IH, CH=) | 54.92 | 3.02 | 11.07 | $C_{17}H_{12}BrN_3S$ | 55.13 | 3.24 | 11.35 |
| **IVe** | 73 | 64–65 | 2170 | 2.30 s (3H, $CH_3$), 4.59 s (2H, $CH_2$), 7.18–7.69 m (9H, H arom), 8.77 s (IH, CH=) | 70.34 | 4.63 | 13.49 | $C_{18}H_{15}N_3S$ | 70.81 | 4.81 | 13.77 |
| **IVf** | 83[a] | – | 2165 | 4.56 s (2H, $CH_2$), 7.19–7.72 m (8H, H arom), 8.71 s (IH, CH=) | 60.21 | 3.32 | 13.83 | $C_{15}HnN_3S_2$ | 60.60 | 3.70 | 14.14 |
| **IVg** | 86 | 127–128 | 2160 | 4.68 s (2H, $CH_2$), 7.30–7.92 m (10H, H arom), 8.81 s (IH, CH=) | 68.48 | 3.60 | 12.37 | $C_{19}H_{13}N_3OS$ | 68.88 | 3.82 | 12.68 |

[a] Viscous light-yellow liquid purified by chromatography on $A_{12}O_3$, eluent chloroform–ethyl ether, 3 : 1.

**Table 3.** Yields, melting points and elemental analyses of *N*-[3-aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]thioureas **VIIIa**–**f** and 1-[3-aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]thiosemicarbazides **IXa**–**e**

| Compd. no. | Yield, % | mp, °C | Found, % | | | Formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| **VIIIa** | 58 | 169–170 | 66.78 | 5.01 | 19.03 | $C_{22}H_{23}FN_4S$ | 67.00 | 5.83 | 14.24 |
| **VIIIb** | 54 | 190–191 | 69.31 | 5.13 | 13.26 | $C_{24}H_{22}N_4OS$ | 69.56 | 5.31 | 13.52 |
| **VIIIc** | 63 | 170–171 | 57.81 | 4.90 | 12.04 | $C_{22}H_{23}BrN_4S$ | 58.02 | 5.05 | 12.30 |
| **VIIId** | 67 | 184–185 | 68.80 | 5.02 | 17.34 | $C_{23}H_{21}N_5S$ | 69.17 | 5.26 | 17.54 |
| **VIIIe** | 71 | 129–130 | 65.13 | 4.70 | 13.68 | $C_{22}H_{20}N_4S_2$ | 65.34 | 4.95 | 13.86 |
| **VIIIf** | 31 | 215–216 | 68.11 | 4.51 | 15.67 | $C_{25}H_{21}N_5OS$ | 68.33 | 4.78 | 15.94 |
| **IXa** | 58 | 190–192 | 65.97 | 4.56 | 16.61 | $C_{23}H_{20}FN_5S$ | 66.18 | 4.79 | 16.78 |
| **IXb** | 61 | 204–205 | 55.81 | 5.11 | 14.57 | $C_{22}H_{25}BrN_5S$ | 56.05 | 5.30 | 14.86 |
| **IXc** | 47 | 183–184 | 64.07 | 4.40 | 17.10 | $C_{25}H_{22}N_6S_2$ | 63.82 | 4.68 | 17.87 |
| **IXd** | 56 | 221–222 | 64.04 | 4.07 | 19.81 | $C_{30}H_{24}N_8S_2$ | 64.28 | 4.28 | 20.00 |
| **IXe** | 28 | 189–191 | 63.88 | 4.08 | 17.71 | $C_{25}H_{20}N_6O_2S$ | 64.10 | 4.27 | 17.95 |

ene–hexane, 5 : 1). $^1$H NMR spectrum, δ, ppm: 4.95 s (2H, $CH_2$), 7.29–7.91 m (10H, H arom), 8.87 s (1H, CH=). Found, %: C 69.69; H 4.32; N 9.23. $C_{18}H_{13}ClN_2O$. Calculated, %: C 70.02; H 4.24; N 9.07.

**S-[Aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]-thiuronium chlorides IIa, b, d, g (Table 1).** To a solution of 0.015 mol of 4-chloromethylpyrazole **Ia, b, d, g** in 20 ml of THF was added 1.3 g (0.017 mol of thiourea, the reaction mixture was heated to boiling for 0.5 h, and then was left standing at room temperature for 12 h. The precipitate formed was filtered off and crystallized from ethanol.

**3-Aryl(heteryl)-1-phenyl-4-pyrazolylmethane-thiols IIIa, b, d, g** (Table 1). To a heated to boiling solution of 0.01 g of thiuronium salt **IIa, b, d, g** in 40 ml of ethanol was added 15 ml of 10% water solution of sodium hydroxide, and the mixture was stirred for 3 h at 75–80°C. The reaction mixture was cooled, the undissolved precipitate was filtered off,, the filtrate was neutralized with20% sulfuric acid till pH 7, the reaction product was extracted into chloroform (3 × 50 ml), the extract was dried with magnesium sulfate. On removing the solvent the residue was crystallized from a mixture benzene–hexane, 1 : 1.

**Aryl(heteryl)-4-thiocyanatomethyl-1-phenylpyrazoles IVa–g** (Table 2). To a dispersion of 1 g (0.0123 mol) of anhydrous sodium thiocyanate in 10 ml of anhydrous acetone was added 0.01 mol of 4-chloromethylpyrazole **Ia–g**, and the mixture was heated to boiling for 1 h. Then the reaction mixture was cooled to 10°C, the separated precipitate was filtered off and crystallized from ethanol.

***N*-[Aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]-thioureas VIIIa–f and 1-[aryl(heteryl)-1-phenyl-4-pyrazolylmethyl]thiosemicarbazides IXa–d** (Table 3). A solution of 0.002 mol of thiocyanate **Vb–g** in 10 ml of *p*-xylene was heated to boiling for 2 h. In the IR spectrum of the reaction mixture disappeared the absorption band of thiocyano group at 2160–2170 cm$^{-1}$ and was present the band of isothiocyano group at 1970–1990 cm$^{-1}$. To the reaction mixture was added 0.02 mol of amino compound **VIa–d, VIIa–d**, and the heating was continued for 1 h more at the same temperature. The solvent was evaporated, the residue was crystallized from ethanol.

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