

P. Giori*, A. C. Veronese, C. B. Vicentini and M. Guarneri

Istituto di Chimica Farmaceutica, Università degli Studi de Ferrara,

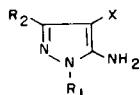
44100 Ferrara, Italy

Received January 4, 1984

Aryl and *t*-butylhydrazines react with 2-cyano-3-ethoxythiocrotonamide affording 2-cyano-3-aryl-*t*-butylhydrazinothiocrotonamides. These intermediates can be easily cyclized to 4-thiocarbamoyl-5-aminopyrazoles by heating a few minutes in a strong base. Alkylhydrazines react with 2-cyano-3-ethoxythiocrotonamide yielding directly a mixture of the cyclized compounds 4-cyano-5-aminopyrazoles and 4-thiocarbamoyl-5-aminopyrazoles.

J. Heterocyclic Chem., **22**, 1093 (1985).

Earlier investigations had demonstrated significant antifungal activity for pyrazoles bearing sulfur-containing functions [1,2]. Recently we have reported that 4-thiocyanato-5-aminopyrazoles **1** and 4-alkylthio-5-aminopyrazoles **2** exhibit a pronounced antifungal activity [3-5].

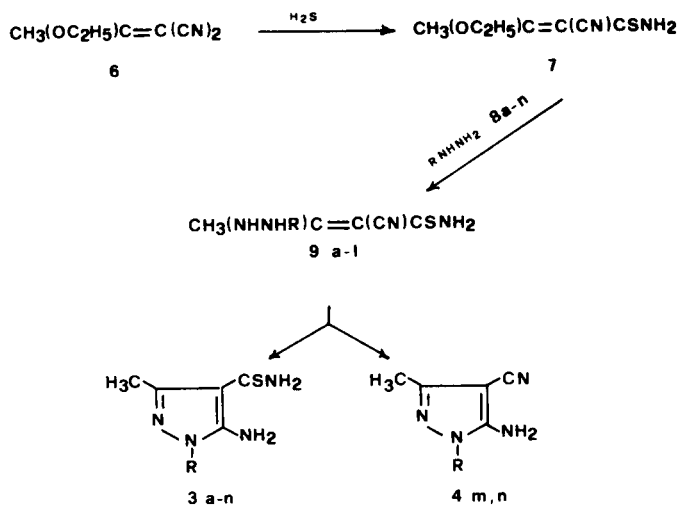


- 1, X = SCN
 2, X = SR
 3, X = CSNH₂
 4, X = CN
 5, X = CONH₂

For all compounds:

R: **a** = phenyl, **b** = 2-chlorophenyl, **c** = 3-chlorophenyl, **d** = 4-chlorophenyl, **e** = 2,4-dichlorophenyl, **f** = 3,4-dichlorophenyl, **g** = 2,5-dichlorophenyl, **h** = 3-nitrophenyl, **i** = 4-nitrophenyl, **l** = *t*-butyl, **m** = methyl, **n** = ethyl.

Scheme 1



In continuation of our research on the biological potential of this class of compounds, we undertook the synthesis of a series of 4-thiocarbamoyl-5-aminopyrazoles **3** that, on the other hand, could be considered as suitable intermediates for the synthesis of 4-mercaptopyrazolo[3,4-*d*]pyrimidines [6], a system of proved biological activity [7].

A survey of the literature showed that prior to this work the only compound possessing structure **3** was 1*H*-3*H*-4-thiocarbamoyl-5-aminopyrazole, obtained by addition of hydrogen sulfide to the pertinent 4-cyano-5-aminopyrazole **4** under drastic conditions [6].

When we tried to prepare analogues of **3** by reacting nitriles **4** with hydrogen sulfide in agreement with reported methods [6,8], very low yields of **3** were recovered. Moreover an attempt to obtain **3** by reacting carboxamides **5** with phosphorus pentasulfide [8] or with the Lawesson's reagent [9] gave the cyano derivatives **4** as the main reaction products. The easy availability from **6** made by the McCall method [10] of 2-cyano-3-ethoxythiocrotonamide **7** whose ethoxy group can be replaced by hydrazines [11], prompted us to undertake a new synthetic route to **3** depicted in Scheme 1.

When **7** was reacted with aryl and *t*-butylhydrazines **8a-1** in chloroform, the intermediates **9a-1** were isolated as stable crystalline compounds (Table 1). To these compounds the isomeric structure of **9Z** (Scheme 2) was assigned, based on the spectral data (¹H-nmr are reported in Table 2, ir data are reported in the Experimental). The ¹H-nmr spectra both in deuteriochloroform and in DMSO-*d*₆ show an absorption at low field strength (about 14 δ) which could be attributed to the NH group intramolecularly bonded to the thiocarbamoyl moiety. In both solvents the spectra are quite similar suggesting that the hydrogen bond is present also in DMSO [12]. The ir spectra show a strong absorption at 2200 cm⁻¹ assigned to the CN group. The intermediates **9Za-1** were cyclized to 4-thiocarbamoyl-5-aminopyrazoles **3a-1** (Scheme 1) by refluxing in xylene for 6-8 hours or by heating a few minutes in sodium hydroxide. No presence of **4** was observed in the reaction mixture (analytical and spectral data of **3** are listed in Tables 3

Table 1

Analytical Data of 2-Cyano-3-aryl (or *t*-Butyl)hydrazinothiuronamides **9**

Compound	Yield %	Mp °C	[a]	Formula	Calcd. %					Found %				
					C	H	N	Cl	S	C	H	N	Cl	S
9a	91	163-165	a	C ₁₁ H ₁₂ N ₄ S	56.87	5.21	24.12		13.80	56.97	5.10	24.19		13.92
9b	79	200-201	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.28	12.01	49.39	4.19	20.82	13.20	12.06
9c	84	173-174	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.28	12.01	49.40	4.15	21.12	13.10	12.23
9d	80	175-176	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.28	12.01	49.71	4.15	20.83	13.06	12.32
9e	86	176-177	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	43.87	3.65	18.53	23.20	10.52
9f	84	186-187	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	44.02	3.19	18.58	23.20	10.73
9g	82	215-216	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	43.87	3.46	18.84	23.42	11.00
9h	80	183-185	a	C ₁₁ H ₁₁ N ₅ O ₂ S	47.64	3.99	25.25		11.56	47.87	3.92	25.31		11.80
9i	68	161-162	a	C ₁₁ H ₁₁ N ₅ O ₂ S	47.64	3.99	25.25		11.56	47.62	3.86	25.12		11.90
9l	87	156-158	c-d	C ₉ H ₁₆ N ₄ S	50.91	7.59	26.39		15.10	51.04	7.59	26.28		15.18

[a] Crystallisation solvent: a = ethanol, b = ethyl acetate, c = chloroform, d = light petroleum.

Table 2

¹H-NMR Data of 2-Cyano-3-aryl (or *t*-Butyl)hydrazinothiuronamides **9** [a]

Compound	Solvent [b]	CH ₃	CSNH ₂ [c]	RNH [d]	RNHNH [d]	R-N	
9a	A	2.40	7.5	8.3	8.2	13.9	6.8-7.4 (m)
9b	A	2.35	8.0	8.8	8.42	13.85	6.8-7.5 (m)
9c	A	2.35	8.1	8.7	8.76	13.8	6.7-7.4 (m)
9d	A	2.31	8.0	8.7	8.63	13.85	7.8 (2H, d), 7.3 (2H, D, J = 9 Hz)
9e	A	2.32	8.0	8.85	8.55	13.8	6.8-7.6 (m)
9f	A	2.35	8.1	8.8	8.88	13.85	7.05 (1H, d, J = 3 Hz), 7.52 (1H, d, J = 9 Hz), 6.85 (1H, dd, J = 9 and 3 Hz)
9g	A	2.4	7.75	8.7	8.5	13.9	7.35 (1H, d, J = 9 Hz), 6.9-7.1 (2H, m)
9h	A	2.41	7.8	8.5	8.85	13.95	7.1-7.8 (m)
9i	A	2.40	7.6	8.5	9.3	14.0	6.9 (2H, d), 8.5 (2H, d, J = 9 Hz)
9l	B	2.40		6.65	3.65	13.45	1.15 (9H)

[a] The signals are singlets, unless stated otherwise. [b] A: DMSO-d₆; B: deuteriochloroform. [c] Very broad signals, exchange with deuterium oxide in a few minutes. For the compounds **9a-i** two different signals are present, due to a slow rotation around the C-N bond of thiocarbamoyl group. [d] Broad signals, exchange with deuterium oxide in a few minutes.

Table 3

Analytical Data of 4-Thiocarbamoyl-5-aminopyrazoles **3**

Compound	Yield %	Mp °C	[a]	Formula	Calcd. %					Found %				
					C	H	N	Cl	S	C	H	N	Cl	S
3a	86	180-181	a	C ₁₁ H ₁₂ N ₄ S	56.87	5.21	24.12		13.80	56.77	5.21	24.21		13.76
3b	70	171-172	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.29	12.01	49.29	4.28	21.18	13.32	11.91
3c	89	181-182	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.29	12.01	49.41	4.26	21.11	13.16	12.33
3d	75	207-209	a	C ₁₁ H ₁₁ ClN ₄ S	49.52	4.15	21.00	13.29	12.01	49.62	4.11	21.02	13.19	12.16
3e	73	241-242	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	43.88	3.24	18.63	24.40	10.78
3f	88	231-232	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	44.00	3.23	18.83	23.50	10.84
3g	80	238-239	a	C ₁₁ H ₁₀ Cl ₂ N ₄ S	43.86	3.34	18.60	23.53	10.64	43.77	3.32	18.52	23.52	10.60
3h	91	194-196	a	C ₁₁ H ₁₁ N ₅ O ₂ S	47.74	3.99	25.25		11.56	47.96	3.91	25.04		11.40
3i	90	226-227	b	C ₁₁ H ₁₁ N ₅ O ₂ S	47.74	3.99	25.25		11.56	47.73	4.06	25.16		11.45
3l	78	198-199	b	C ₉ H ₁₆ N ₄ S	50.91	7.59	26.39		15.10	51.07	7.71	26.17		15.25
3m	42	175-176	b	C ₉ H ₁₆ N ₄ S	42.33	5.92	32.91		18.83	42.56	5.89	33.06		18.71
3n	73	173-174	b	C ₇ H ₁₂ N ₄ S	45.62	6.56	30.40		17.40	45.80	6.69	30.28		17.36

[a] Crystallisation solvent: a = ethanol, b = benzene. Yields are referred to method A (see Experimental).

Table 4

¹H-NMR Data of 4-Thiocarbamoyl-5-aminopyrazoles **3** [a]

Compound	Solvent [b]	CH ₃	NH ₂ [c]	CSNH ₂ [d]		N-R
3a	A	2.48	6.8	7.5		7.4-7.5 (m)
3b	A	2.38	7.2	8.0	8.8	7.4-7.7 (m)
3c	A	2.45	7.3	7.6	8.3	7.3-7.6 (m)
3d	A	2.35	7.3	7.8	8.8	7.6
3e	A	2.35	7.3	7.6	8.8	7.9 (1H, d, J = 3 Hz), 7.5-7.6 (2H, m)
3f	A	2.40	7.4	7.6	8.9	7.6-7.9 (m)
3g	A	2.38	7.35	7.7	8.8	7.6-7.9 (m)
3h	A	2.42	7.52	8.0	9.0	7.7-8.4 (m)
3i	A	2.42	7.57	8.0	9.1	7.8 (2H, d), 8.37 (2H, d, J = 9 Hz)
3l	B	2.42	6.2	6.2		1.6
3m	B	2.4	7.1	7.4		3 . 5 5
3n	B	2.4	6.85	7.2		1.35 (3H, t), 3.9 (2H, q, J = 7.5 Hz)

[a] The signals are singlets, unless stated otherwise. [b] A: DMSO-d₆; B: deuteriochloroform. [c] Broad signals, exchange with deuterium oxide in a few minutes. [d] Very broad signals, exchange with deuterium oxide in a few minutes. For the compounds **3b-i** two different signals are present, due to a slow rotation around the C-N bond of thiocarbamoyl group.

and **4** respectively). The reaction of alkylhydrazines **8m,n** with **7** in chloroform gave directly a mixture of the two cyclized products **3m,n** and **4m,n** without isolation of the intermediate **9** (ratio **3m:4m** = 1:1.5; ratio **3n:4n** = 3:1). Hydrogen sulfide was evolved from the reaction mixture. When the same reaction was carried out in water, the yield of **3** was increased (ratio **3m:4m** = 1:1; ratio **3n:4n** = 5:1).

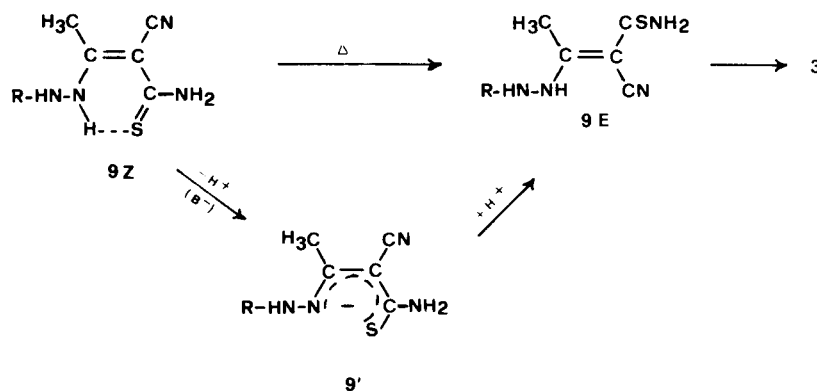
It is of interest to note that any attempt to convert **3** into **4** under the conditions used for synthesis of **4** was unsuccessful. Only under very drastic conditions was this conversion possible (heating of **3** at 300° for 4 hours). Therefore, we supposed that cyanopyrazoles **4** were not formed from the corresponding thiocarbamoyl intermediates **3**, but that the cyclisation process takes place through two different routes: cyano pyrazoles **4** arise by the attack of the hydrazine NH group of **9** on the thiocarbamoyl function with displacement of hydrogen sulfide, whereas thiocarbamoylpyrazoles **3** arise by attack of the same NH group on the cyano function. The results obtained may be explained as follows:

i) When the nucleophilicity of the NH group of the hydrazines **8a-l** is low for steric (R = *t*-butyl) or electronic (R = aryl) factors, the intermediates **9Z** are stable, isolable products. They cyclize by the attack of the hydrazine NH group on the more reactive cyano function to give compounds **3**. This implies a rotation around the C=C double bond leading to the unstable isomer **9E** that cyclizes to **3** (Scheme 2). The rotation occurs slowly thermally and more quickly by the action of a strong base, possibly through the formation of the anion **9'** [13].

ii) When the nucleophilicity of the NH group of hydrazines is enhanced by electron releasing radicals (R = CH₃, C₂H₅), the attack becomes possible also on the less reactive thiocarbamoyl function leading to a mixture of **3** and **4**. The relative ratio depends upon the reaction solvent.

In conclusion, the method described is selective for the preparation of 4-thiocarbamoyl-5-aminopyrazoles **3** where position 1 was substituted with *t*-butyl or aryl radicals, whereas it affords a mixture of **3** and **4** when the substituents at position 1 are alkyl radicals. However, the separation of **3** from **4** can be easily performed by means of co-

Scheme 2



lumn chromatography.

The results of the biological screening for antifungal activity will be reported elsewhere.

EXPERIMENTAL

Melting points were taken on a Buchi capillary apparatus and are uncorrected. The ir spectra were obtained with a Hitachi-Perkin 157G spectrometer using potassium bromide pellets. The ¹H-nmr spectra were recorded on a Perkin-Elmer spectrometer R32 (90 MHz); chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard. The compounds were checked for purity by tlc on precoated silica gel plates (F₂₅₄ Merck) using the following solvent systems: 1-butanol/acetic acid/water (15:5:5 v/v); chloroform/methanol/benzene (85:10:5 v/v). Yields were based on the weight of vacuum dried products. For column chromatography, silica gel (Kieselgel 60 Merck, 70-230 mesh ASTM) was used.

2-Cyano-3-phenylhydrazinethiocrotonamide (9a).

2-Cyano-3-ethoxythiocrotonamide **7** (3.4 g, 20 mmoles) was added to a solution of phenylhydrazine **8a** (2.16 g, 20 mmoles) in chloroform (50 ml). The mixture was refluxed for 20 minutes. After ice-cooling, the precipitate was collected and crystallized from ethanol, yield 4.23 g (91%), mp 163-165°; ir: 3420, 3300, 3200 (NH), 2200 (CN), 1620, 1600, 1580, 1420, 1250, 850 cm⁻¹.

Compounds **9b-1** were prepared by the same procedure (analytical data in Table 1, ¹H-nmr in Table 2).

1-Phenyl-3-methyl-4-thiocarbamoyl-5-aminopyrazole (3a). Method A.

A suspension of 2-cyano-3-phenylhydrazinethiocrotonamide **9a** (2.32 g, 10 mmoles) in 0.1 N sodium hydroxide (50 ml) was heated to 80-85°. Within a few minutes, the solid was dissolved giving an orange solution from which a white precipitate immediately separated. After ice-cooling, the precipitate was collected, washed with water and crystallized from ethanol, 2.00 g (86%), mp 180-181°; ir: 3460, 3390, 3300, 3180 (NH), 1620, 1605, 1535 (pyrazole ring), 1480, 1280, 860 cm⁻¹.

Method B.

A suspension of 2-cyano-3-phenylhydrazinethiocrotonamide **9a** (1.16 g, 5 mmoles) in xylene (150 ml) was refluxed for 6 hours. The solution was then evaporated to an oily residue which was crystallized from ethanol, 0.7 g (60%). The product was identical to that obtained by the above described method.

Compounds **3b-1** were preferably prepared according to method A (analytical data in Table 3, ¹H-nmr in Table 4).

Reaction of Alkylhydrazines **8m,n** with **7**.

Ethylhydrazine **8n** with **7**.

2-Cyano-3-ethoxythiocrotonamide **7** (1.7 g, 10 mmoles) was added to a solution of ethylhydrazine **8n** (0.6 g, 10 mmoles) in water (10 ml). The mixture was stirred at room temperature until evolution of hydrogen sulfide had finished. The reaction mixture was evaporated to a solid residue which was charged onto a silica gel column (1.5 × 90 cm) previously equilibrated with ethyl acetate-light petroleum (3:1 v/v). The column was

eluted with the same solvent system. Two main peaks were detected by means of tlc.

Fractions corresponding to the more polar peak were evaporated and the residue was crystallized from benzene, to give a product characterized as 1-ethyl-3-methyl-4-thiocarbamoyl-5-aminopyrazole **3n**, yield 1.34 g (73%) mp 173-174°; (¹H-nmr in Table 4), ir: 3460, 3390, 3280, 3180 (NH), 1620, 1605, 1550 (pyrazole ring), 1490, 1400, 1300, 870, 850 cm⁻¹.

Fractions corresponding to the less polar peak were treated as above, giving a solid that was crystallized from benzene and characterized as 1-ethyl-3-methyl-4-cyano-5-aminopyrazole, yield 0.22 g (15%), mp 116-118°; ir: 3390, 3160 (NH), 2200 (CN), 1650, 1550 (pyrazole ring) cm⁻¹; ¹H-nmr (deuteriochloroform-DMSO-d₆, 1:1): 1.3 (CH₃, J = 8 Hz), 2.18 (s, CH₃), 3.92 (CH₂, q, J = 8 Hz), 5.88 (NH₂).

Anal. Calcd. for C₇H₁₀N₄: C, 55.97; H, 6.71; N, 37.30. Found: C, 55.55; H, 6.80; N, 37.42.

Following the same procedure, methylhydrazine **8m** was reacted with **7**, affording a mixture of 1,3-dimethyl-4-thiocarbamoyl-5-aminopyrazole **3m** (yield 42%, analytical data in Table 3; ¹H-nmr in Table 4) and 1,3-dimethyl-4-cyano-5-aminopyrazole, yield 42%, mp 193-194° (benzene), lit [14] 194°.

Acknowledgements.

The authors are grateful to Mr. M. Manfrini for technical assistance and to Mr. P. Orlandini for ¹H-nmr spectra.

REFERENCES AND NOTES

- [1] J. Kinugawa and M. Ochiai, *Chem. Pharm. Bull.*, **12**, 23 (1964).
- [2] J. Kinugawa, M. Ochiai, C. Matsumura and M. Yamamoto, *Chem. Pharm. Bull.*, **12**, 182 (1964).
- [3] G. L. Vannini, G. Dall'Olio and P. Giori, *Mycopathologia*, **58**, 39 (1977).
- [4] G. L. Vannini, D. Mares, P. Giori and A. Bonora, *Mycopathologia*, **74**, 7 (1981).
- [5] P. Giori, D. Mazzotta, G. Vertuani, M. Guarneri, D. Pancaldi and A. Brunelli, *Farmaco, Ed. Sci.*, **38**, 274 (1983).
- [6] R. Bovara, R. Largaiolli and G. Meroni, *J. Labelled Comp.*, **7**, 357 (1971).
- [7] H. G. Mautner, *J. Org. Chem.*, **23**, 1450 (1958).
- [8] O. E. Schultz and U. Ranke, *Arch. Pharm.*, **66**, 82 (1961).
- [9] S. Scheibye, B. S. Pedersen and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 229 (1978).
- [10] M. A. McCall, *J. Org. Chem.*, **27**, 2433 (1962).
- [11] A. Kreutzberger and K. Burgwitz, *Arch. Pharm.*, **313**, 906 (1980).
- [12] M. Michalik and J. Kreutzmann, *J. Prakt. Chem.*, **325**, 919 (1983).
- [13a] Y. Shvo and I. Belsky, *Tetrahedron*, **25**, 4649 (1969); [b] V. I. Bakhmutov and V. A. Burmistov, *Org. Magn. Reson.*, **12**, 185 (1979).
- [14] C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).