Research on Chemical Intermediates
https://doi.org/10.1007/s11164-018-3633-4

Reactive intermediates in the reaction of hydrazinecarbothioamides with 2-(bis(methylthio) methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate

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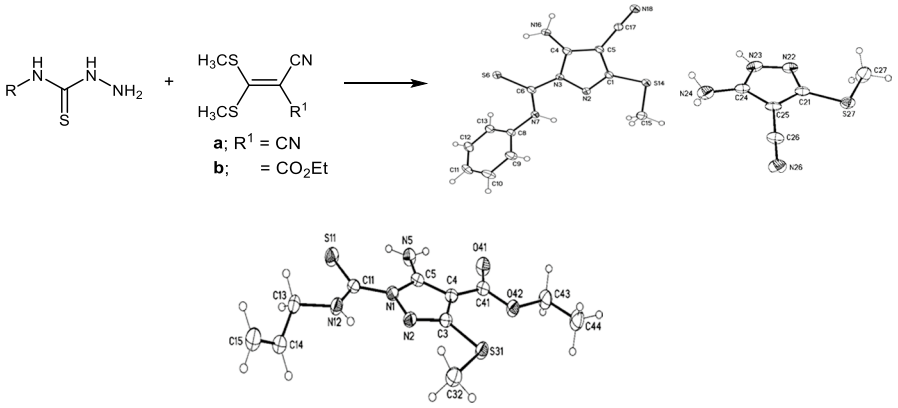
Received: 4 June 2018 / Accepted: 8 October 2018

Abstract

The reaction of *N*-substituted hydrazinecarbothioamides with both 2-(bis(methylthio) methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate afforded various heterocyclic rings such as 5-amino-4-cyano-3-(methylthio)-*N*-phenyl-1*H*-pyrazole-1-carbothioamide, 5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile, 4-substituted-3-(substituted amino)-1*H*-1,2,4-triazole-5(4*H*)-thione, ethyl 5-amino-3-(methylthio)-1-(substituted carbamothioyl)-1*H*-pyrazole-4-carboxylate, and (*Z*)-ethyl 2-cyano-2-(5-(substituted amino)-1,3,4-thiadiazol-2(3*H*)-ylidene)acetate. However, under gentle heating, the reaction of the same starting substances behaved differently. The structure of the obtained products was fully characterized using different spectral techniques including infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS) together with elemental analyses as well as single-crystal X-ray diffraction analysis.

Graphical abstract



Keywords *N*-substituted hydrazinecarbothioamides · 2-(Bis(methylthio)methylene) malononitriles · Reactive intermediates · Various heterocycles · X-ray structure analyses

Published online: 29 October 2018

Introduction

Hydrazinecarbothioamides are usually used as building blocks with several π-deficient compounds for synthesis of different heterocycles such as 1,3,4-thiadiazoles and 1,3,4-thiadiazepines [1], pyridazinethiones and triazolopyridazine-thiones [2], oxathiadiazoles and benzothiadiazines [3], and thiadiazepine, thiadiazole, dithiadiazole, and oxathiadiazole derivatives [4]. Recently, spiro(indolone-3,2′-[1,3,4-thiadiazol])-2-ones [5] and 1,2,4-triazepinethiones [6] were synthesized via refluxing substituted hydrazinecarbothioamides with 3-(dicyanomethylene)-2-indolone and dimethyl acetylenedicarboxylate or dibenzoylacetylene, respectively. Aly et al. reported that the reaction of *N*,*N*-disubstituted hydrazinecarbothioamides with 2-bromo-2-substituted acetophenones furnished thiazole, bis-thiazole, pyrazole, and 1,3,4-thiadiazole derivatives in good yield [7]. 2-(Bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate show different reactivity, which is attributed to several electrophilic sites (C≡N, C=C, CO_2Et), towards different compounds, affording various heterocyclic compounds with biological activities [8–10]. Various mercaptopyrazoles were synthesized from the reaction of ethyl bis(methylthio)-2-cyanoacrylate with amidrazones in dry ethanol and triethylamine [11]. On the other hand, 1,3,4-thiadiazoles and 1,3-thiazines were obtained by reaction of 2-(bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)-acrylate with symmetrical N^1,N^2-disubstituted hydrazinecarbothioamides [12]. Pyrazoles are biologically active compounds that show a broad spectrum of biological activities, involving antifungal, antitubercular, and antiinflammatory activities [13, 14], analgesic effects [15], as well as antidepressant and anticonvulsant activities [16]. Synthesis of 3-amino-5-(methylthio)-1-phenyl-1*H*-pyrazole-4-carbonitrile [17] and ethyl-5-amino-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate [17] was achieved by reaction of phenylhydrazine with 2-(bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio) acrylate, respectively. 1,2,4-Triazole-5-thiones were prepared by refluxing either glycine hydrazide or hydrazine hydrate with different isothiocyanates in 10 % K_2CO_3 [18]. The N^2 of hydrazinecarbothioamides has greater nucleophilicity than the terminal N^1 [2, 6]. However, in the present investigation, all the nucleophilic sites on the hydrazinecarbothioamides (SH, ^{1}NH, ^{2}NH, ^{3}NH) play an important role in the heterocyclization and formation of the final products.

Experimental

Melting points are uncorrected and were recorded on a Gallenkamp melting point apparatus (Gallenkamp, UK) using open capillaries. NMR spectra were measured on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.54 MHz for ^{15}N). ^{1}H and ^{13}C chemical shifts are given relative to internal standard tetramethylsilane (TMS); ^{15}N shifts are reported versus ammonia. For preparative thin-layer chromatography (PLC), glass plates (20 × 48 cm^2) were covered with a slurry of silica gel Merck PF_{254}, air dried, and developed using the solvents

listed. Zones were detected by quenching of indicator fluorescence upon exposure to ultraviolet (UV) light at 254 nm. Elemental analyses were carried at Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Mass spectra were recorded on a Varian MAT 312 instrument in electrospray ionization (EI) mode (70 eV), at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. IR spectra were obtained from KBr pellets on a FT-IR (Bruker) at Minia University, El-Minia, Egypt.

Starting materials

N-Substituted hydrazinecarbothioamides **1a**–**d** were prepared according to literature procedures (**1a** [19], **1b** [19, 20], **1c** [21], and **1d** [22]).

Reaction of *N*-substituted hydrazinecarbothioamides 1a–d with 2a

General procedure

A solution of **1a**–**d** (1.0 mmol) and **2a** (1.0 mmol) was stirred with gentle heating at 50 °C in dry ethanol containing 0.5 mL triethylamine till consumption of starting materials. After reaction completion, the solvent was removed und vacuum and the residue was subjected to PLC using toluene/EtOAc (10:1) to give different zones.

5-Amino-4-cyano-3-(methylthio)-*N*-phenyl-1*H*-pyrazole-1-carbothioamide (3) Yield: (0.187 g, 65 %); colorless crystals (EtOH); M.p.: 160–162 °C.

IR (KBr): ν = 3303-3251 (NH's), 3090 (Ar–CH), 2215 (CN), 1633 (C=N), 1614 (Ar–C=C), 1358 (C=S) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.35 (s, 3H, SCH_3), 6.01 (br. s, 2H, NH_2), 6.91–6.94 (m, 3H, Ar–H), 6.98–7.00 (m, 2H, Ar–H), 11.55 (br. s, 1H, NH–Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 12.30 (SCH_3), 62.00 (pyrazole-C-4), 114.22 (CN), 127.50, 128.30 (Ar-2CH), 129.42 (Ar–CH), 138.60 (Ar–C), 148.52 (pyrazole-C-3), 164.00 (pyrazole-C-5), 170.00 (C=S).

MS: *m*/*z* (%) = 289 ($M^{\cdot+}$, 14), 153 (100), 136 (70), 106 (17).

Anal. Calcd. for $C_{12}H_{11}N_5S_2$ (289.38): C, 49.81; H, 3.83; N, 24.20; S, 22.16. Found: C, 49.83; H, 3.82; N, 24.18; S, 22.19.

5-Amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (4) Yield: (0.03 g, 20 %); colorless crystals (EtOH); m.p.: 150-151 °C; Lit. ([23, 24] 152 °C).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 12.60 (SCH_3), 72.30 (pyrazole-C-4), 114.70 (CN), 147.60 (pyrazole-C-3), 154.30 (pyrazole-C-5).

4-Phenyl-3-(phenylamino)-1*H*-1,2,4-triazole-5(4*H*)-thione (5aa) Yield: (0.03 g, 20 %); colorless crystals (EtOH); M.p.: 204–206 °C; Lit. (201–203 °C [18]).

4-(Pyridin-3-yl)-3-(pyridin-3-ylamino)-1*H*-1,2,4-triazole-5(4*H*)-thione (5ba) Yield: (0.175 g, 65 %); colorless crystals (EtOH); M.p.: 306–308 °C.

IR (KBr): ν = 3230 (NH), 3150 (Ar–CH), 1588 (Ar–C=C), 1315 (C=S) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.21–7.34 (m, 2H, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.63–7.65 (m, 1H, Ar–H), 8.15–8.17 (m, 1H, Ar–H), 8.18–8.20 (m, 1H, Ar–H), 8.75–8.77 (m, 1H, Ar–H), 10.19 (br. s, 1H, NH-pyridinyl), 13.53 (br. s, 1H, NH-triazole).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 129.50, 129.60, 130.40, 130.50, 137.10, 137.60, 141.90, 142.50 (Ar–CH), 147.90, 149.80 (Ar–C), 155.80 (C=N), 165.60 (C = S).

MS: *m/z* (%) = 270 ($M^{\cdot+}$) (17), 153 (100), 136 (67), 106 (17).

Anal. Calcd. for $C_{12}H_{10}N_6S$ (270.31): C, 53.32; H, 3.73; N, 31.09; S, 11.86. Found: C, 53.28; H, 3.79; N, 31.15; S, 11.81.

5-Amino-4-cyano-2-(2,2-dicyano-1,1-bis(methylthio)ethyl)-*N*-ethyl-3-(methylthio)-2,3-dihydro-1*H*-pyrazole-1-carbothioamide (12) Yield: (0.33 g, 80 %); colorless crystals (EtOH); M.p.: 158–159 °C.

The IR spectrum of **12** showed absorptions at ν 3425–3231; 2211; 1608 and 1359 for (NH's), C≡N, C=N and C=S, respectively.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.10 (t, 3H, CH_3, J = 7.0 Hz), 2.30 (s, 6H, $2SCH_3$), 2.40 (s, 3H, SCH_3), 3.33 (s, 1H, *C*H$(CN)_2$), 3.60 (q, CH_2, 2H, J = 7.0 Hz), 8.79 (br. s, 1H, NH), 9.99 (br. s, 1H, NH-Et).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 11.30 (CH_3-Et), 12.50 ($2SCH_3$), 12.70 (SCH_3), 22.30 (*C*H$(CN)_2$), 38.10 (CH_2-Et), 65.00 (pyrazole-C-4), 78.00 [*C*$(SCH_3)_2$], 113.30 (2CN), 116.60 (CN), 163.30 (pyrazole-C-3), 169.00 (pyrazole-C-5), 184.00 (C=S).

MS: *m/z* (%) = 411 ($M^{\cdot+}$) (6), 391 (10); 166 (22), 148 (100), 108 (24), 94 (43).

Anal. Calcd. for $C_{14}H_{17}N_7S_4$ (411.59): C, 40.86; H, 4.16; N, 23.82; S, 31.16. Found: C, 40.72; H, 4.18; N, 23.80; S, 31.19.

Reaction of *N*-substituted hydrazinecarbothioamides 1a–d with 2b

General procedure

A mixture of *N*-substituted hydrazinecarbothioamides **1a–d** (1 mmol) in abs. EtOH (30 mL) was heated gently at 50 °C with 2-cyano-3,3-bis(methylthio)acrylate **2b** (1 mmol) followed by thin-layer chromatography (TLC) analysis. A colorless precipitate of 1,3,4-thiadiazole **13** was formed, and this was filtered and washed with a small amount of EtOH. The filtrate was subjected to PLC [toluene:EtOAc (10:1)] to give two zones **15** and **16**.

(*Z*)-Ethyl 2-cyano-2-(5-(phenylamino)-1,3,4-thiadiazol-2(3*H*)-ylidene)-acetate (13ab) Yield: (0.173 g, 60 %); colorless crystals (DMF/EtOH), M.p.: 280–282 °C.

IR (KBr): ν = 3283 (NH's), 3146 (Ar–CH), 2976 (Ali-CH), 2196 (CN), 1647 (C=O), 1623 (C=N), 1595 (Ar–C=C) cm^{-1}.

NMR spectral data in Table 1.

MS: *m/z* (%) = 288 ($M^{\cdot+}$) (30), 153 (100), 135 (65), 106 (18), 76 (15).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$ (288.32): C, 54.16; H, 4.20; N, 19.43; S, 11.12. Found: C, 54.22; H, 4.27; N, 19.39; S, 11.07.

(*Z*)-Ethyl 2-cyano-2-(5-(pyridin-3-ylamino)-1,3,4-thiadiazol-2(3*H*)-ylidene)acetate (13bb) Yield: (0.13 g, 45 %); yellow crystals (DMF/EtOH); M.p.: 270-272 °C.

IR (KBr): ν = 3278 (NH), 3122 (Ar–CH), 2995 (Ali-CH), 2203 (CN), 1645 (C=O), 1622 (C=N), 1587 (Ar–C=C) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.21 (t, 3H, CH_3, J = 6.8 Hz), 4.19 (q, 2H, CH_2, J = 7.0 Hz), 7.40–7.42 (m, 1H, Ar–H), 7.93–7.95 (m, 1H, Ar–H), 8.23–8.24 (m, 1H, Ar–H), 8.68–8.69 (m, 1H, Ar–H), 10.46 (br. s, 1H, NH-pyridyl), 13.81 (br. s, 1H, thiadiazole-NH).

Table 1 NMR spectral data of **13ab**

^{1}H NMR		^{1}H-^{1}H COSY	Assignment
13.64 (b; 1H)			NH-3
10.24 (bs; 1H)			NH-5a
7.48 (d, J = 7.7; 2H)		7.36, 7.02	H–*o*
7.36 ("t", J = 7.4; 2H)		7.48, 7.02	H-*m*
7.02 (t, J = 7.1; 1H)		7.48, 7.36	H-*p*
4.16 (q, J = 6.8; 2H)		1.23	H-2c
1.23 (t, J = 6.8; 3H)		4.16	H-2d
^{13}C NMR	HSQC	HMBC	Assignment
166.42		4.16	C-2b
162.94			C-2/5
155.52			C-5/2
139.88		*7.48*, 7.36	C-*i*
129.15	7.36	7.36, *7.02*	C-*m*
122.12	7.02	7.48	C-*p*
117.32	7.48	10.24, 7.48, *7.36*, 7.02	C-*o*
116.68			C≡N
60.03	4.16	1.23	C-2c
58.69			C-2a
14.52	1.23	4.16	C-2d
^{15}N NMR	HSQC	HMBC	Assignment
257.10		10.24	N-4
95.40	10.24	7.48	N-5a

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 14.70 (CH_3), 59.10 (C-2a), 60.30 (CH_2), 117.00 (CN), 124.20, 125.00, 137.00, 139.10 (Ar–CH), 142.90 (Ar–C), 156.20 (C=N), 163.50 (thiadiazole-C-2), 166.20 (CO).

MS: *m*/*z* (%) = 289 ($M^{\cdot+}$) (18), 153 (100); 135 (64), 106 (18).

Anal. Calcd. for $C_{12}H_{11}N_5O_2S$ (289.31): C, 49.82; H, 3.83; N, 24.21; S, 11.08. Found: C, 49.97; H, 3.89; N, 24.09; S, 11.20.

(*Z*)-Ethyl 2-(5-(allylamino)-1,3,4-thiadiazol-2(3*H*)-ylidene)-2-cyanoacetate (13cb) Yield: (0.151 g, 60 %); colorless crystals; M.p.: 242–244 °C.

IR (KBr): ν = 3291 (NH's), 2970 (Ali-CH), 2192 (CN), 1644 (C=O), 1624 (C=N).

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.20 (t, 3H, CH_3, J = 6.8 Hz), 4.12 (q, 2H, CH_2, J = 7.0 Hz), 5.14 (m, 2H, allyl-CH_2), 5.22 (m. 2H, allyl-CH_2N), 5.86 (m, 1H, allyl-CH =), 7.70 (br. s, 1H, NH-allyl), 13.24 (br. s, 1H, thiadiazole-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 14.50 (CH_3), 46.00 (allyl-CH_2NH), 57.90 (C-2a), 59.70 (CH_2), 116.30 (allyl-CH_2=), 117.10 (CN), 134.00 (allyl-CH=), 159.50 (C=N), 163.20 (thiadiazole-C-2), 166.40 (CO).

MS: *m*/*z* (%) = 252 ($M^{\cdot+}$) (60), 153 (100); 136 (70), 106 (19), 92 (23).

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$ (252.29): C, 47.61; H, 4.79; N, 22.21; S, 12.71. Found: C, 47.50; H, 4.94; N, 22.33; S, 12.60.

4-Cyano-3-(methylthio)-5-oxo-*N*-phenyl-2,5-dihydro-1*H*-pyrazole-1-carbothioamide (14ab) Yield: (0.058 g, 20 %); colorless crystals (EtOH); M.p.: 262–264 °C.

IR (KBr): ν = 3250 (NH's), 3100 (Ar–CH), 2920 (Ali-CH), 2192 (CN), 1572 (CO), 1644 (C=O), 1494 (Ar–C=C), 1370 (C=S) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.50 (S, 3H, SCH_3), 7.00–7.22 (m, 3H, Ph-H), 7.40–7.52 (m, 2H, Ph-H), 11.60 (br. s, 1H, NH–Ph), 13.22 (br. s, 1H, NH-pyrazole).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 11.50 (SCH_3), 73.40 (pyrazole-C-4), 115.00 (CN), 127.30, 128.40 (Ar-2CH), 128.80 (Ar–CH), 137.60 (Ar–C), 147.60 (pyrazole-C-3), 164.30 (CO), 173.50 (C=S).

MS: *m*/*z* (%) = 290 ($M^{\cdot+}$) (22), 153 (16), 131 (100), 91 (15).

Anal. Calcd. for $C_{12}H_{10}N_4OS_2$ (290.36): C, 49.64; H, 3.47; N, 19.30; S, 22.08. Found: C, 49.49; H, 3.60; N, 19.42; S, 22.15.

Ethyl 5-amino-3-(methylthio)-1-(phenylcarbamothioyl)-1*H*-pyrazole-4-carboxylate (15ab) Yield: (0.04 g, 12 %); colorless crystals (EtOH); M.p.: 182–183 °C.

IR (KBr): ν = 3204 (NH's), 3112 (Ar–CH), 2923 (Ali-CH), 1648 (CO), 1620 (C=N), 1559 (Ar–C=C), 1357 (C=S) cm^{-1}.

^{1}H NMR: (400 MHz, DMSO-d_6): δ_H = 1.14 (t, 3H, CH_3, J = 7.0 Hz), 2.50 (s, 3H, SCH_3), 4.16 (q, 2H, CH_2, J = 6.8 Hz), 7.24–7.35 (m, 3H, Ar–H), 7.41–7.49 (m, 2H, Ar–H), 6.17 (br. s, 2H, NH_2), 11.70 (br. s, 1H, NH–Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 11.10 (CH_3-Et), 11.40 (SCH_3), 58.60 (CH_2-Et), 92.50 (pyrazole-C-4), 127.50, 128.10 (Ar-2CH), 128.90 (Ar–CH), 130.03 (Ar-C), 140.70 (pyrazole-C-3), 149.80 (pyrazole-C-5), 155.50 (C=N), 163.30 (CO), 173.80 (C=S).

MS: *m/z* (%) = 336 ($M^{\cdot+}$) (5 %), 201 (56), 153 (87), 148 (77), 135 (80), 116 (49), 90 (100).

Anal. Calcd. for $C_{14}H_{16}N_4O_2S_2$ (336.43): C, 49.98; H, 4.79; N, 16.65; S, 19.06. Found: C, 49.93; H, 4.90; N, 16.75; S, 19.15.

Ethyl 1-(allylcarbamothioyl)-5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate (15cb) Yield: (0.06 g, 20 %); colorless crystals (EtOH); M.p.: 92 °C.

IR (KBr): ν = 3365-3338 (NH's); 2920 (Ali-CH), 1671 (CO), 1615 (C=N), 1354 (C=S) cm^{-1}.

NMR spectral data in Table 2.

MS: *m/z* (%) = 300 ($M^{\cdot+}$) (17), 252 (17), 201 (88), 155 (100), 90 (15).

Anal. Calcd. for $C_{11}H_{16}N_4O_2S_2$ (300.07): C, 43.98; H, 5.37; N, 18.65; S, 21.35. Found: C, 44.10; H, 5.42; N, 18.59; S, 21.46.

Ethyl 5-amino-1-(ethylcarbamothioyl)-3-(methylthio)-1*H*-pyrazole-4-carboxylate (15db) Yield: (0.158 g, 55 %); colorless crystals (EtOH); M.p.: 96 °C.

IR (KBr): ν = 3371–3336 (NH's), 2986–2840 (Ali-CH), 1670 (CO), 1615 (C=N), 1354 (C=S) cm^{-1}.

Table 2 NMR spectral data of **15cb**

^{1}H NMR	^{1}H-^{1}H COSY	Assignment
10.02 (bs; 1H)	4.26	NH-2b
8.27 (b; 2H)		NH-3a
5.91 (ddt, J_d = 17.1, 10.4, J_t = 5.2; 1H)	5.21, 5.18, 4.26	H-2d
5.21 (d, J = 16.6; 1H)	5.91, 5.18, 4.26	H-2e
5.18 (d, J = 9.9; 1H)	5.91, 5.21, 4.26	H-2e
4.26 (bm; 2H)	10.02, 5.91, 5.21, 5.18	H-2c
4.22 (q, J = 7.2; 2H)	1.28	H-4b
2.51 (s; 3H)		H-5a
1.28 (t, J = 7.1; 3H)	4.22	H-4c

^{13}C NMR	HSQC	HMBC	Assignment
172.97			C-2a
161.65		4.22	C-4a
153.36		2.51	C-5
150.46			C-3
131.73	5.91	4.26	C-2d
115.70	5.21, 5.18		C-2e
91.27			C-4
58.46	4.22	1.28	C-4b
44.54	4.26		C-2c
13.33	1.28	4.22	C-4c
11.46	2.51		C-5a

^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 0.87 (t, 3H, CH_3, J = 7.0 Hz), 1.10 (t, 3H, CH_3, J = 6.8 Hz), 2.49 (S, 3H, SCH_3), 3.64 (q, 2H, CH_2, J = 7.0 Hz), 4.20 (q, 2H, CH_2, J = 7.0 Hz), 8.27 (br. s, 2H, NH_2), 9.88 (br. s, 1H, NH-ethyl).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 11.10 (CH_3-Et), 11.60 (SCH_3), 13.00 (CH_3-Et), 42.50 59.40 (CH_2-Et), 92.40 (pyrazole-C-4), 139.8 (pyrazole-C-3), 151.30 (pyrazole-C-5), 162.60 (CO), 173.40 (C=S).

MS: m/z (%) = 288 ($M^{\cdot+}$) (30), 201 (100), 200 (54), 154 (92), 147 (21).

Anal. Calcd. For $C_{10}H_{16}N_4O_2S_2$ (288.38): C, 41.65; H, 5.59; N, 19.43; 10; S, 7.00. Found: C, 41.63; H, 5.60; N, 19.45; S, 6.91.

Ethyl 5-amino-3-(methylthio)-1-(phenylcarbamothioyl)-1*H*-pyrazole-4-carboxylate (16) Yield: (0.016 g, 8 %); colorless crystals (EtOH); M.p.: 136–137 °C; lit [25, 26] 135–136 °C.

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 11.40 (SCH_3), 14.4 (CH_3), 58.6 (OCH_2), 91.5 (pyrazole-C-4), 149.5 (C=N), 152.9 (pyrazole-C-3), 163.3 (CO).

Crystal structure determination of 3, 4, and 15cb

Single-crystal X-ray diffraction studies were carried out on a Bruker D8 Venture diffractometer with Photon100 or PhotonII detector at 123(2) K using Cu K_α radiation (λ = 1.54178 Å). Direct methods (SHELXS-97) or dual-space methods (SHELXT) [27, 28] were used for structure solution, and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [29]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model H(N). Semiempirical absorption corrections were applied. Due to the poor quality of the data and the (not to be resolved) disorder of the thiomethane substituents for **4**, only the constitution could be determined. Therefor the data of **4** were not deposited with The Cambridge Crystallographic Data Centre.

Compound **3**: Colorless crystals, $C_{12}H_{11}N_5S_2$, M_r = 289.38, crystal size 0.22 × 0.16 × 0.10 mm, monoclinic, space group *C2/c* (no. 15), a = 22.0120(7) Å, b = 19.5237(6) Å, c = 13.8667(5) Å, β = 118.775(1)°, V = 5223.4(3) Å^3, Z = 16, ρ = 1.472 Mg/m^{-3}, μ(Cu K_α) = 3.642 mm^{-1}, F(000) = 2400, $2\theta_{max}$ = 144.4°, 46,945 reflections, of which 5138 were independent (R_{int} = 0.025), 363 parameters, 6 restraints, R_1 = 0.028 [for 5056 $I > 2\sigma(I)$], wR_2 = 0.075 (all data), S = 1.03, largest diff. peak/hole = 0.416/−0.364 e Å^{-3}.

Compound **4**: Colorless crystals, $C_5H_6N_4S$, M_r = 154.20, crystal size 0.26 × 0.14 × 0.12 mm, monoclinic, space group *C2/c* (no. 15), a = 30.5762(10) Å, b = 11.7594(4) Å, c = 16.8216(5) Å, β = 107.038(2)°, V = 5782.9(3) Å^3, Z = 32, ρ = 1.417 Mg/m^{-3}, μ(Cu K_α) = 3.384 mm^{-1}, F(000) = 2560.

Compound **15cb**: Colorless crystals, $C_{11}H_{16}N_4O_2S_2$, M_r = 300.40, crystal size 0.16 × 0.10 × 0.04 mm, monoclinic, space group *P2$_1$/c* (no. 14), a = 9.3909(4) Å, b = 19.3892(8) Å, c = 7.9959(4) Å, β = 98.096(2)°, V = 1441.40(11) Å^3, Z = 4, ρ = 1.384 Mg/m^{-3}, μ(Cu K_α) = 3.397 mm^{-1}, F(000) = 632, $2\theta_{max}$ = 144.4°, 11,575 reflections, of which 2833 were independent (R_{int} = 0.033), 182 parameters, 3

restraints, $R_1 = 0.034$ [for 2462 $I > 2\sigma(I)$], $wR_2 = 0.091$ (all data), $S = 1.05$, largest diff. peak/hole = 0.459/−0.282 e Å^{-3}.

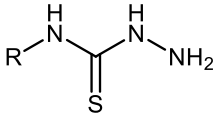
CCDC 1856010 (**3**) and 1840929 (**15cb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Due to their poor quality, the data for **4** were not deposited with The Cambridge Crystallographic Data Centre.

Results and discussion

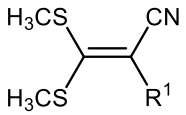
The reactions of different hydrazinecarbothioamides **1a**–**d** with 2-(bis(methylthio) methylene)malononitrile (**2a**) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**) were successfully achieved, giving different heterocyclic rings under reaction conditions. The structures of the starting substances under investigation are shown in Fig. 1.

Gentle heating (at 50 °C) of equimolar solutions of **1a** and **2a** in absolute ethanol containing 0.5 mL Et_3N for 3 h gave compound **3** in 45 % yield together with 5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (**4**) [23, 24] in 5 % yield and 4-phenyl-3-(phenylamino)1*H*-1,2,4-triazole-5(4*H*)-thione (**5aa**) [18] in 20 % yield (Scheme 1). The side products **4** and **5aa** were separated by preparative thin-layer chromatography (PLC) using toluene/EtOAc (10:1). To optimize the yield of the pyrazole derivative **3**, we carried out the reaction between equal equivalents of the two starting materials at room temperature. 5-Amino-4-cyano-3-(methylthio)-*N*-phenyl-1*H*-pyrazole-1-carbothioamide (**3**) was successfully obtained as the major product in 65 % yield (Scheme 1).

The IR spectrum of compound **3** showed absorptions at 3303–3251, 2215, 1633, and 1358 due to (NH's), (CN), (C=N), and C=S, respectively. In the ^{1}H NMR spectrum, a singlet appeared at $\delta = 2.35$ due to methylthio protons, two broadened singlets at $\delta = 6.01$ and 11.55 related to NH_2 and HN-Ph, respectively, in addition to aromatic protons. The ^{13}C NMR spectrum also supported the structure due to $\delta = 12.30$ (SCH_3), 62.00 (pyrazole-C-4), 114.22 (CN), 148.52 (C=N), 164.00 (pyrazole-C-5), and 170.00 related to C=S. The mass spectrum also confirmed the result of elemental analysis due to the appearance of a molecular ion peak at $m/z = 289$.



1a-d

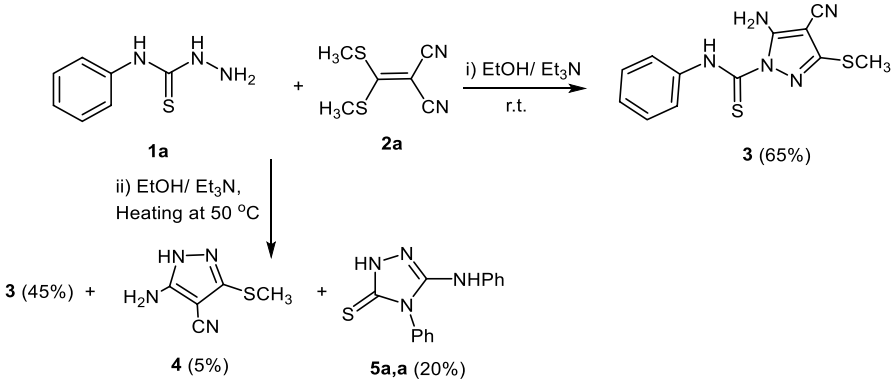


2a,b

a; R = C_6H_5
b; = 3-C_6H_3N
c; = $CH_2CH{=}CH_2$
d; = CH_2CH_3

a; R^1 = CN
b; = CO_2Et

Fig. 1 Starting substances **1a**–**d** and **2a**, **b**



Scheme 1 Reaction of *N*-phenyl hydrazinecarbothioamide **1a** with **2a**

The structure of compound **3** was, ultimately, proved by X-ray structure analysis (Fig. 2).

The formation of compound **3** can be explained due to nucleophilic attack of the terminal N^1 lone pair in **1a** on the ethylenic carbon in **2a**, to form intermediate **6a** accompanied by elimination of methanethiol to form intermediate **6a** (Scheme 2). Nucleophilic addition of nitrogen lone pair-N^2 on the nitrile carbon would lead to salt **7a**. Subsequently, neutralization of **6a** followed by aromatization would then give compound **3**. Meanwhile, elimination of phenyl

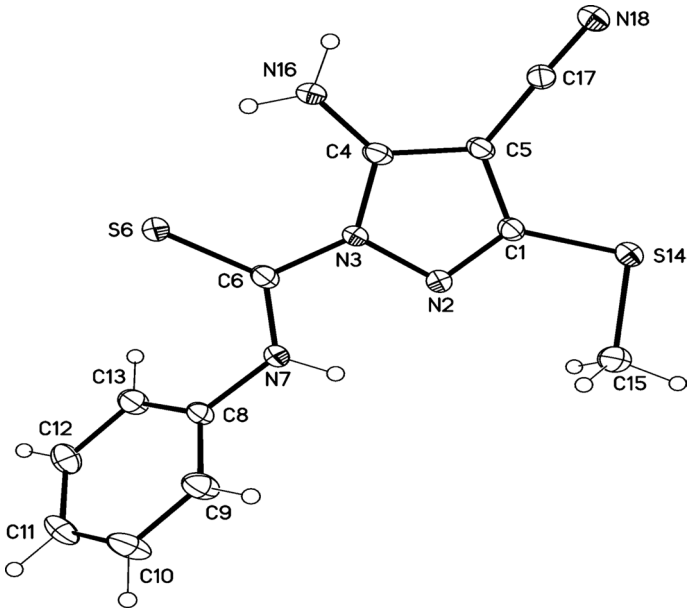
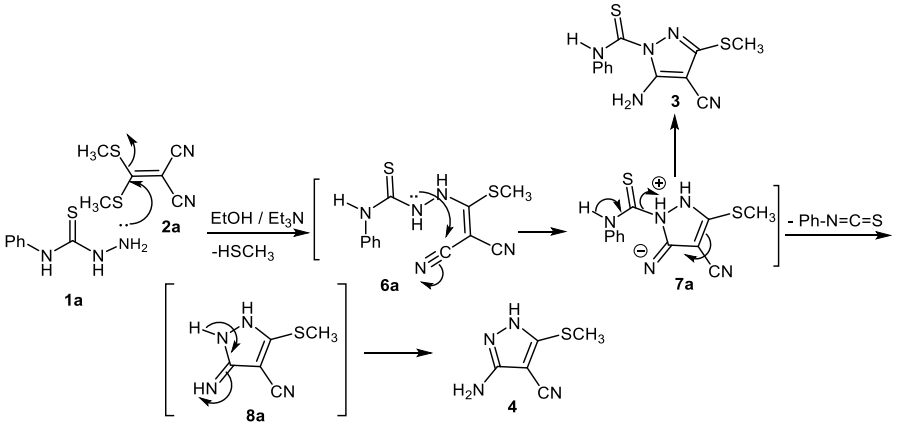


Fig. 2 Molecular structure analysis of one of the crystallographic independent molecules of **3** (displacement parameters drawn at 50 % probability level)



Scheme 2 Mechanism describing formation of compounds **3** and **4**

isothiocyanate from **7a** would give intermediate **8a** (Scheme 2). Aromatization of **8** would directly give **4** (Scheme 2).

Meanwhile, the formation of the side product **4** can be explained as a result of the loss of phenyl isothiocyanate molecule from compound **3** (Scheme 2). The structure of **4** was elucidated by different spectral data (i.e., IR, NMR, and mass spectra). In addition, single-crystal X-ray structure analysis of **4** was also obtained (Fig. 3).

The formation of the product **5aa** may be rationalized via tautomerism between thione and thiol, followed by formation of salt **8.** Elimination of hydrazine molecule from the Zwitter ion **A** would form isothiocyanate intermediate (Scheme 3). Nucleophilic attack of the hydrazinyl-*N* lone pair of **1a** on thiocarbonyl of isothiocyanate intermediate would result in amidine-like reaction to the thione-C as in **9**, accompanied by elimination of H_2S molecule to give **5aa** (Scheme 3). Such a

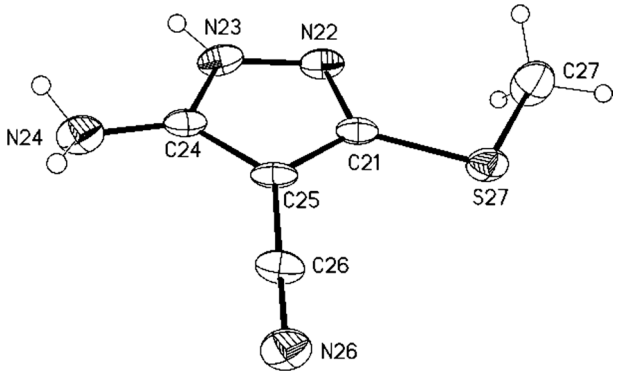
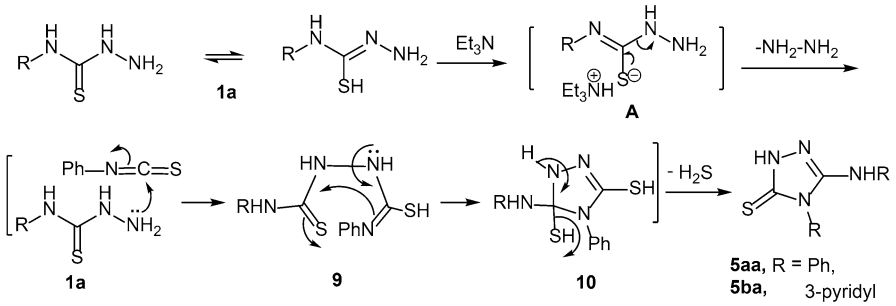


Fig. 3 Molecular structure of one of the four independent molecules of **4** (displacement parameters drawn at 50 % probability level)



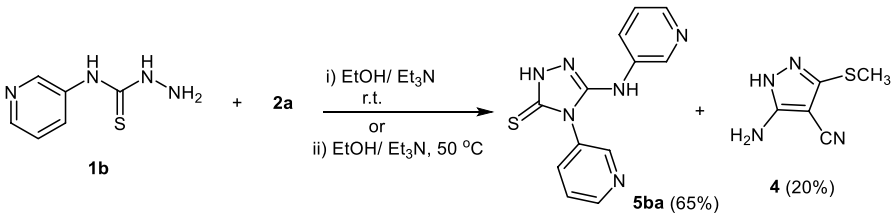
Scheme 3 Plausible mechanism describing formation of **5aa** and **5ba**

route was also noted with pyridinyl substituent of hydrazinecarbothioamides, and compound **5ba** was also obtained.

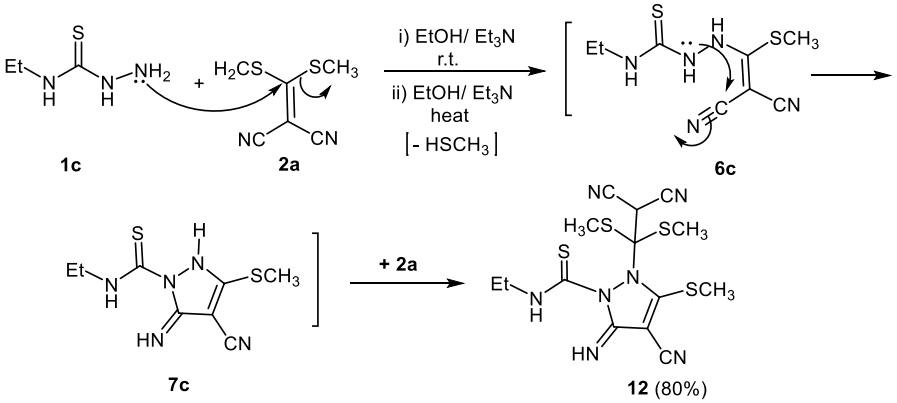
In a different manner, reaction of compound **1b** with **2a** produced, either at room temperature or in heating condition (50 °C), two products: **4** in 20 % yield and 4-pyridyl-3-(pyridylamino)-1*H*-1,2,4-triazole-5(4*H*)-thione (**5ba**) in 65 % yield (Scheme 4). The different behavior of **1a** towards **2a** compared with that between **1b** and **2a** might be explained by the high reactivity of the 3-pyrindyl substituent and the instability of its reaction products even at room temperature.

The molecular formula of **5ba** ($C_{12}H_{10}N_6S$) was confirmed from its mass spectrum due to the presence of a molecular ion peak at $m/z = 270$. The ^{1}H NMR spectrum of compound **5ba** showed two broad exchangeable (with D_2O) singlets at $\delta = 10.19$ and 13.53 due to (NH-pyridyl) and (NH-triazole), respectively, as well as aromatic protons in aromatic region. The ^{13}C NMR spectrum showed the presence of aromatic carbons at $\delta = 129.50$, 129.60, 130.40, 130.50, 137.10, 137.60, 141.90, 142.50, 147.90, and 149.80 in addition to 155.80 and 165.60 due to carbon signals of C=N and C=S, respectively.

In a different manner, *N*-ethyl hydrazinecarbothioamide (**1c**) reacted with **2a** to provide compound **12** in 80 % yield. The structure of **12** was confirmed by different spectroscopic data and was identified as 5-amino-4-cyano-2-(2,2-dicyano-1,1-bis(methylthio)ethyl)-*N*-ethyl-3-(methylthio)-2,3-dihydro-1*H*-pyrazole-1-carbothioamide (Scheme 5). The mechanism could be explained as due to nucleophilic attack of the hydrazine-lone pair in **1c** on the electrophilic carbon in **2a**. That was followed by elimination of one molecule of methanethiol to give **6c**. Thereafter, cyclization would then occur due to another nucleophilic attack on the carbon of nitrile group



Scheme 4 Reaction of 3-*N*-pyridyl hydrazinecarbothioamide **1b** with **2a**



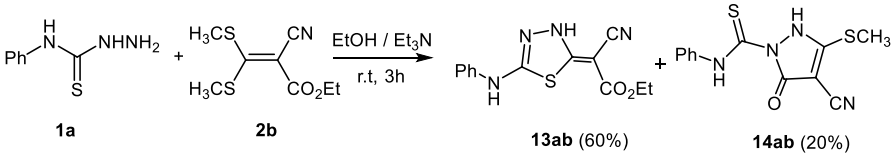
Scheme 5 Mechanism describing formation of compound **12**

to give intermediate **7c**. Addition of a second molecule of **2a** to **7c** would produce compound **12** (Scheme 5).

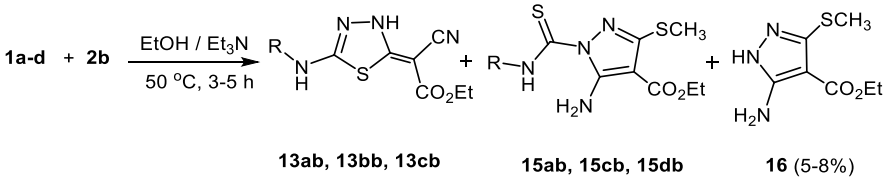
The ^{1}H NMR spectrum of compound **12** showed three singlets at δ_H = 2.30 (6H), 2.40 (3H), and 3.33 (1H) for $2SCH_3$, SCH_3, and $CH(CN)_2$, respectively (see "Experimental" section). The *N*-ethyl protons resonated in the ^{1}H NMR spectrum as a quartet and triplet at δ_H = 3.60 (CH_2, J = 7.0 Hz) and 1.10 (CH_3, J = 7.0 Hz). Two additional broad singlets were observed for NH and NHEt at δ_H = 8.79 and 9.99, respectively. The presence of methylthiol carbon signals was also confirmed by ^{13}C NMR at δ_C = 12.50 (2C) and 12.70 (C). respectively. Pyrazole C-5, C-4, and C-3 resonated at δ_C = 169.00, 65.00, and 163.30. The low δ value of pyrazole-C-4 is attributed to the presence of a push–pull system. In addition, the δ_C = 11.30, 22.30, 38.10, 78.00, and 184.00 ppm signals are attributed to CH_3–Et, *C*H$(CN)_2$, CH_2–Et, (*C*$(SCH_3)_2$), and C=S, respectively (see "Experimental" section). Finally, elemental analysis proved that compound **12** has molecular formula $C_{14}H_{17}N_7S_4$, as also confirmed by the mass spectrum due to the appearance of the molecular ion peak at m/z = 411. The aforementioned behavior between *N*-substituted hydrazinecarbothioamides **1a**–**d** with **2a** encouraged us to study the behavior of **1a**–**d** towards ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**). Reaction of *N*-phenyl hydrazinecarbothioamide **1a** with **2b** at room temperature in dry ethanol containing 0.5 mL triethylamine gave a colorless precipitate of (*Z*)-ethyl 2-cyano-2-(5-(phenylamino)-1,3,4-thiadiazol-2(3*H*)-ylidene)-acetate (**13ab**) in 60 % yield, then the filtrate was subjected to PLC to separate another zone, identified as 4-cyano-3-(methylthio)-5-oxo-*N*-phenyl-2,5-dihydro-1*H*-pyrazole-1-carbothioamide (**14ab**), in 20 % yield (Scheme 6). The structures of **13ab** and **14ab** were detected using various spectral data (IR; ^{1}H, ^{13}C, and 2D NMR; MS) as well as elemental analyses.

In a different manner, reactions of **1a**–**d** with **2b** under heating at 50 °C in dry ethanol containing 0.5 mL triethylamine yielded three structures **13**, **15**, and **16** (Scheme 7).

Compound **13** was separated as a precipitate, whereas the filtrate contained the other two zones, which were separated out using PLC. The fast-migrating



Scheme 6 Reaction of *N*-phenylhydrazinecarbothioamides **1a** and **2b** at room temperature



Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
13ab	50	**15ab**	12	**16**	6
13bb	45	**15cb**	20	**16**	8
13cb	60	**15db**	55	**16**	7

Scheme 7 Reaction of *N*-substituted hydrazinecarbothioamides **1a–d** and **2b** under gentle heating condition

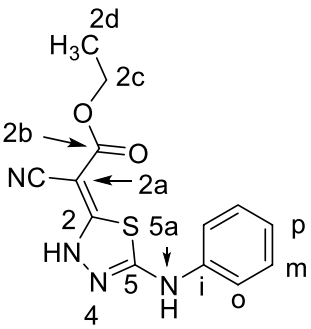


Fig. 4 The distinctive carbons in compound **13ab**

zone contained **15** while the slowest-migrating zone contained ethyl 5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate **16** [25, 26] (Scheme 7).

Figure 4 shows distinctive carbon atoms in compound **13a**, **b**. The ^{1}H spectral data of **13ab** showed two broadened singlets downfield, both having integrals of 1H, at δ_H = 13.64, 10.24 ppm due to thiadiazole NH and (NH–Ph), respectively (Table 1). The methyl singlet is absent due to loss of two methanethiol molecules. The ethoxy 3H triplet (H-2d) is distinctive at δ_H = 1.23; its attached carbon (C-2d) appears at δ_C = 14.52; H-2d gives COSY correlation, and C-2d gives HMBC correlation, with the 2H quartet at δ_H = 4.16, assigned as H-2c; the attached carbon

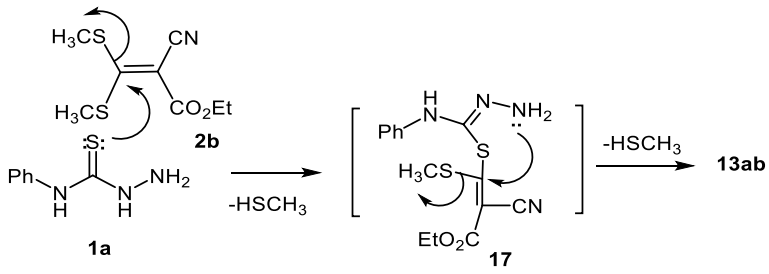
(C-2c) appears at $\delta_C = 60.03$. The H-2c also gives HMBC correlation with a carbon at $\delta_C = 166.42$, assigned as the ester carbonyl C-2b (Fig. 4). The phenyl protons are assigned straightforwardly as H-*p* ($\delta = 7.02$), H-*m* ($\delta_H = 7.36$), and H–*o* ($\delta_H = 7.48$); the attached carbons appear at $\delta_C = 122.12$ (C-*p*), 129.15 (C-*m*), and 117.32 (C-*o*). H-*m* and (weakly) H–*o* give HMBC correlation with a carbon at $\delta_C = 139.88$, assigned as C-*i*. H-*o* also gives HMBC correlation with a nitrogen at $\delta_N = 95.40$, assigned as N-5a; this nitrogen gives HSQC correlation with its attached proton at $\delta_H = 10.24$.

The H-5a gives HMBC correlation with C-*o* and with a nitrogen at $\delta_N = 257.10$, assigned as N-4 (Table 1). The carbon signal at $\delta_C = 116.68$ is assigned as the nitrile carbon, and the carbon signal at $\delta_C = 58.69$ is assigned as C-2a, the upfield shift arising because of its position in a push–pull system. The carbons at $\delta_C = 162.94$ and 155.52 must be C-2 and C-5.

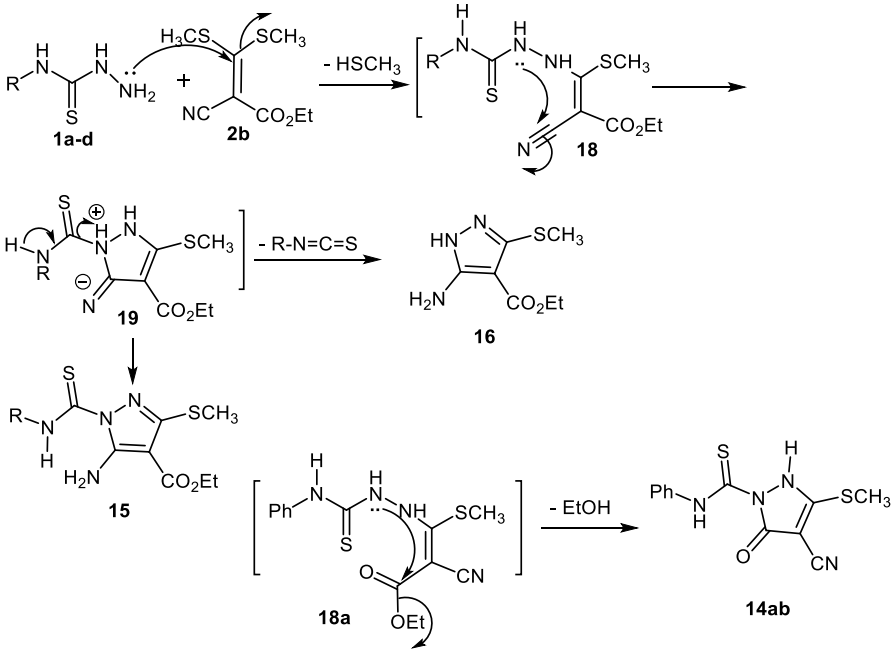
The mass spectrum of **13ab** also supported the proposed structure, showing a molecular ion peak at (*m*/*z* = 288, 30 %) corresponding to the molecular formula $C_{13}H_{12}N_4O_2S$.

The mechanism describing the formation of **13ab** is presented in Scheme 8. Nucleophilic attack of the thione lone pair **1a** on C-2 of **2b** accompanied by elimination of a molecule of methanethiol followed by another nucleophilic attack from terminal hydrazine-NH_2 on the same carbon leading to loss of another molecule of methanethiol forms the target compounds **13ab** (Scheme 8).

The mechanism for the formation of **14ab**, **15**, and **16** can be explained as nucleophilic attack of the more powerful terminal nitrogen N^1 lone pair in **1a**–**d** on C-3 of **2b** accompanied by loss of a molecule of methanethiol giving intermediate **18**, followed by a second nucleophilic attack from N^2 of hydrazinecarbothioamides on the carbonitrile group, forming intermediate **19** (Scheme 9). Subsequently, nucleophilic addition of N^2-lone pair on the nitrile carbon would give zwitterion **19** (Scheme 9). Neutralization of **19** followed by aromatization would give **15** (Scheme 9). Rearrangement to **19** accompanied by elimination of substituted isothiocyanate molecule would give the pyrazole derivatives **16** (i.e., occurring easily under heating) [25, 26]. On the other hand, loss of ethanol molecule from **18a** would occur at room temperature due to nucleophilic attack from N^2 of hydrazinecarbothioamide **1a** on the carbonyl of ester group to give **14ab** (Scheme 9). Compound **14ab** was identified as 4-cyano-3-(methylthio)-5-oxo-*N*-phenyl-2,5-dihydro-1*H*-pyrazole-1-carbothioamide



Scheme 8 Plausible mechanism for formation of **13ab**

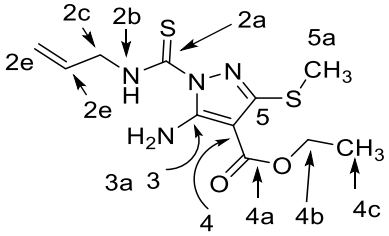


Scheme 9 Rationale for the formation of products **14ab**, **15**, and **16**

using different spectroscopic data. Formation of compound **16** was further confirmed from the reaction of **2b** with hydrazine hydrate to give ethyl 5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate (**16**). Generally, the structure of ethyl 1-(allylcarbamothioyl)-5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate (**15cb**) was confirmed via different spectral data as follows: IR spectra of compound **15cb** showed characteristic absorptions at ν = 3365–3338, 2920, 1671, 1615, and 1354 cm^{-1} relating to (NH's), (Ali-CH), CO, C=N, and C=S. The ethoxy 3H triplet (H-4c) is distinctive at δ_H = 1.28; its attached carbon (C-4c) appears at δ_C = 13.33. The H-4c gives COSY correlation, and C-4c gives HBC correlation, with the 2H quartet at δ_H = 4.22, assigned as H-4b; the attached carbon (C-4b) appears at δ_C = 58.46. The H-4b also gives HMBC correlation with a carbon at δ_C = 161.7, assigned to the ester carbonyl C-4a. Distinctive carbon atoms of compound **15cb** are shown in Fig. 5.

The ^{1}H double–double-triplet at δ_H = 5.91 is assigned as H-2d; the attached carbon C-2d appears at δ_C = 131.73. H-2d gives COSY correlation with the broadened doublets at δ_H = 5.21 and 5.18, assigned to the terminal vinylic protons H-2e; their attached carbon C-2e appears at δ_C = 115.70. Protons H-2e and H-2d all give COSY correlation with a 2H broad multiplet at δ_H = 4.26, assigned as H-2c. The fine structure of this signal is not resolved, even though the coupling constant with H-2d is over 5 Hz; H-2c gives HSQC correlation with the carbon at δ_C = 44.54, assigned as C-2c. H-2c also gives COSY correlation with the broad 1H singlet at δ_H = 10.02, assigned as NH-2b. The broad 2H signal at δ_H = 8.27 is assigned as

Fig. 5 Distinctive carbons of **15cb**



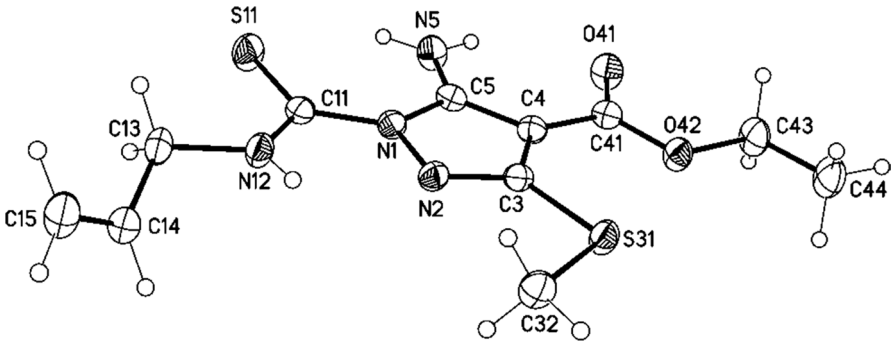


Fig. 6 Molecular structure analysis of **15cb** (displacement parameters drawn at 50 % probability level)

NH-3a. The ^{13}C spectrum has 11 signals; four are in the normal sp^3 region upfield of $\delta_C = 58.46$, while the other seven are downfield of $\delta_C = 91.27$ (Table 2). The carbon at $\delta_C = 11.46$ gives HSQC correlation with a signal at $\delta_H = 2.51$, which is not resolved from the DMSO signal but must be a 3H singlet given by H-5a; the carbon just mentioned is assigned as C-5a. H-5a gives HMBC correlation with a carbon at $\delta = 153.36$, assigned as C-5. The remaining three carbons at $\delta_C = 172.97$, 150.46, and 91.27 give no correlations; based on their chemical shifts, they are assigned as C-2a, C-3, and C-4, respectively. The structure of **15cb** was determined also by single-crystal X-ray structure analysis, which confirmed the loss of a molecule of methanethiol (Fig. 6). The bond lengths of C11–S11, N2–C3, C4–C5, and C41–O41 are 1.6727 (17) Å, 1.311 (2) Å, 1.395 (2) Å, and 1.219 (2) Å, respectively, relating to C=S, C=N, C=C, and C=O double bond character, whereas the bond lengths of N1–N2 [1.4105 (18) Å], N1-C11 [1.401 (2) Å], and C41-O42 [1.343(2) Å] suggest that they have single bond character when compared with N–N, C–N, and C–O single bonds.

Conclusions

Hydrazinecarbothioamides have attracted much attention due to the presence of many active nucleophilic centers. The reactivity of substituents of hydrazinecarbothioamides depends upon their electronic structure (i.e., aliphatic or aromatic), as well

as their stability towards reaction with electrophiles. To date, many efforts have been made in this field, especially for construction of new simple classes of sulfur and/or nitrogen heterocycles.

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