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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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Abstract

The reaction of *N*-substituted hydrazinecarbothioamides to 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 is fully characterized using different spectral data IR, NMR, Mass spectrometry together with elemental analysis as well as single crystal X-ray analyses.

Keywords: *N*-Substituted hydrazinecarbothioamides . 2-bis(methylthio)methylene)malononitriles . reactive intermediates . various heterocycles . X-ray structure analyses

Introduction

Hydrazinecarbothioamides were usually used as building blocks with several π -deficient compounds for the synthesis of different heterocycles such as 1,3,4-

1 thiadiazoles and 1,3,4-thiadiazepines,¹ pyridazinethiones and triazolopyridazine-
2 thiones,² oxathidiazoles and benzothiadiazines,³ thiadiazepine, thiadiazole, dithiadiazole
3 and oxathiadiazole derivatives.⁴ Recently, spiro(indolone-3,2'-[1,3,4-thiadiazol])-2-
4 ones⁵ and 1,2,4-triazepinethiones⁶ have been synthesized *via* refluxing of substituted
5 hydrazinecarbothioamides with 3-(dicyanomethylene)-2-indolone and dimethyl
6 acetylenedicarboxylate or dibenzoylacetylene, respectively. Aly et al.⁷ reported that the
7 reaction of *N,N*-disubstituted hydrazinecarbothioamides with 2-bromo-2-substituted
8 acetophenones furnished the formation of thiazole, bis-thiazol, pyrazole and 1,3,4-
9 thiadiazole derivatives in good yields. 2-Bis(methylthio)-methylene)malononitrile and
10 ethyl 2-cyano-3,3-bis(methylthio)acrylate showing different reactivities attributing to
11 several electrophilic sites (C≡N, C=C, CO₂Et) towards different compounds and afford
12 various heterocyclic compounds with biological activities.^{8,9,10} Various
13 mercaptopyrazoles were synthesized from the reaction of ethyl bis(methylthio)-2-
14 cyanoacrylate with amidrazones in dry ethanol and triethylamine.¹¹ On the other hand,
15 1,3,4-thiadiazoles and 1,3-thiazines were obtained *via* reacting of 2-bis(methylthio)-
16 methylene)-malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate with
17 symmetrical *N*¹,*N*²-disubstituted hydrazinecarbothioamides.¹² Pyrazoles are biologically
18 active compounds which have a broad spectrum of biological activities involving
19 antifungal, antitubercular, anti-inflammatory activities,^{13,14} analgesic agents¹⁵ as well as
20 their antidepressant and anticonvulsant activities.¹⁶ The synthesis of 3-amino-5-
21 (methylthio)-1-phenyl-1*H*-pyrazole-4-carbonitrile and ethyl-5-amino-3-(methylthio)-1-
22 phenyl-1*H*-pyrazole-4-carboxylate¹⁷ were achieved from the reaction of phenyl
23 hydrazine with 2-bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-
24 bis(methylthio)acrylate, respectively. 1,2,4-Triazole-5-thiones were prepared from

refluxing either glycine hydrazide or hydrazine hydrate with different isothiocyanates in 10% K₂CO₃.¹⁸ The N² of hydrazinecarbothioamides has more nucleophilicity than the terminal ¹N^{2,6}. However, in the present investigation all nucleophilic sites on hydrazine-carbothioamides (SH, ¹NH, ²NH, ³NH) play an important role in heterocyclization and formation of the final products.

Experimental Section

Melting points are uncorrected and were recorded on a Gallenkamp melting point apparatus (Gallenkamp, UK), by using open capillaries. NMR spectra were measured on a Bruker AV-400 spectrometer (400 MHz for ¹H, 100 MHz for ¹³C, and 40.54 MHz for ¹⁵N). The ¹H and ¹³C chemical shifts are given relative to internal standard TMS; ¹⁵N shifts are reported vs. ammonia. For preparative thin layer chromatography (plc), glass plates (20 × 48 cm) were covered with a slurry of silica gel Merck PF₂₅₄ and air dried and developed using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in the at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Mass spectra were recorded on a Varian MAT 312 instrument in EI mode (70 eV), at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. IR spectra using KBr pellets were run on a FT-IR (Bruker), Minia University, El-Minia, Egypt.

Starting materials

N-Substituted hydrazinecarbothioamides **1a-d** were prepared according to the published procedures in literatures (**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 of triethylamine till consummation of starting materials. After completion of the reaction, the mixture was subjected to PLC using Toluene/ EtOAc (10:1) to give different zones.

5-Amino-4-cyano-3-(methylthio)-N-phenyl-1H-pyrazole-1-carbothioamide (3)

Yield: (0.187 g, 65%); colorless crystals (EtOH); M.p: 162-163 °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} .

^1H NMR (400 MHz, DMSO- d_6): δ_{H} = 2.35 (s, 3H, SCH₃), 6.01 (br. s, 2H, NH₂), 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 (SCH₃), 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^+ , 14), 153 (100), 136 (70), 106 (17).

Anal. Calcd. for C₁₂H₁₁N₅S₂ (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)-1H-pyrazole-4-carbonitrile (4)

Yield: (0.03 g, 20%); colorless crystals (EtOH); m.p: 150-151 °C; Lit. 152 °C)^{23,24}

^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} = 12.60 (SCH₃), 72.30 (Pyrazole-C-4), 114.70 (CN), 147.60 (Pyrazole-C-3), 154.30 (Pyrazole-C-5).

4-Phenyl-3-(phenylamino)-1H-1,2,4-triazole-5(4H)-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)-1H-1,2,4-triazole-5(4H)-thione (5ba)

1 Yield: (0.175 g, 65%); colorless crystals (EtOH); M.p: 306-308°C.

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

3 ^1H NMR (400 MHz, DMSO- d_6): δ_{H} = 7.21-7.34 (m, 2H, Ar-H), 7.36-7.40 (m, 2H, Ar-

4 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-

5 8.77 (m, 1H, Ar-H), 10.19 (br. s, 1H, NH-pyridinyl), 13.53 (br. s, 1H, NH-triazole).

6 ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} = 129.50, 129.60, 130.40, 130.50, 137.10, 137.60,

7 141.90, 142.50 (Ar-CH), 147.90, 149.70 (Ar-C), 155.80 (C=N), 165.60 (C=S).

8 MS: m/z (%) = 270 (M^+) (17), 153 (100), 136 (67), 106 (17).

9 *Anal. Calcd. for* $\text{C}_{12}\text{H}_{10}\text{N}_6\text{S}$ (270.31): C, 53.32; H, 3.73; N, 31.09; S, 11.86. Found: C,

10 53.28; H, 3.79; N, 31.15; S, 11.81.

11 **5-Amino-4-cyano-2-(2,2-dicyano-1,1-bis(methylthio)ethyl)-N-ethyl-3-(methylthio)-**

12 **2,3-dihydro-1H-pyrazole-1-carbothioamide (12)**

13 Yield: (0.33g, 80%); colourless crystals (EtOH); M.p: 158-159 °C

14 The IR spectrum of **12** showed absorptions at ν 3425-3231; 2211; 1608 and 1359 for

15 (NH's), $\text{C}\equiv\text{N}$, $\text{C}=\text{N}$ and $\text{C}=\text{S}$, respectively.

16 ^1H NMR (400 MHz, DMSO- d_6): δ_{H} = 1.10 (t, 3H, CH_3 , J = 7.0 Hz), 2.30 (s, 6H,

17 2SCH_3), 2.40 (s, 3H, SCH_3), 3.33 (s, 1H, $\text{CH}(\text{CN})_2$), 3.60 (q, CH_2 , 2H, J = 7.0 Hz), 8.79

18 (br. s, 1H, NH), 9.99 (br. s, 1H, NH-Et).

19 ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} = 11.30 (CH_3 -Et), 12.50 (2SCH_3), 12.70 (SCH_3),

20 22.30 ($\text{CH}(\text{CN})_2$), 38.10 (CH_2 -Et), 65.00 (Pyrazole-C-4), 78.00 ($\text{C}(\text{SCH}_3)_2$), 113.30

21 (2CN), 116.60 (CN), 163.30 (Pyrazole-C-3), 169.00 (Pyrazole-C-5), 184.00 ($\text{C}=\text{S}$).

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

23 *Anal. Calcd. for* $\text{C}_{14}\text{H}_{17}\text{N}_7\text{S}_4$ (411.59): C, 40.86; H, 4.16; N, 23.82; S, 31.16. Found: C,

24 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) and followed by 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(*3H*)-ylidene)-acetate (13ab)

Yield: (0.173 g, 60%); colorless crystals (DMF / EtOH), Mp: 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⁺) (30), 153 (100), 135 (65), 106 (18), 76 (15).

Anal. Calcd. for C₁₃H₁₂N₄O₂S (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(*3H*)-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.

¹H NMR (400 MHz, DMSO-*d*₆): δ_H = 1.21 (t, 3H, CH₃, *J* = 6.8 Hz), 4.19 (q, 2H, CH₂, *J* = 7.0 Hz), 7.40-7.43 (m, 1H, Ar-H), 7.93-7.96 (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).

¹³C NMR (100 MHz, DMSO-*d*₆): δ_C = 14.70 (CH₃), 59.10 (C-2a), 60.30 (CH₂), 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⁺) (18), 153 (100); 135 (64), 106 (18).

Anal. Calcd. for C₁₂H₁₁N₅O₂S (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(3H)-ylidene)-2-cyanoacetate (13cb)

Yield: (0.151g, 60%); colorless crystals; M.p: 242-244 °C.

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

¹H NMR (400 MHz, DMSO-*d*₆): δ_H = 1.20 (t, 3H, CH₃, *J* = 6.8 Hz), 4.12 (q, 2H, CH₂, *J* = 7.0 Hz), 5.14 (m, 2H, allyl-CH₂), 5.22 (m, 2H, allyl-CH₂N), 5.86 (m, 1H, allyl-CH=), 7.70 (br. s, 1H, NH-allyl), 13.24 (br. s, 1H, thiadiazole-NH).

¹³C NMR (100 MHz, DMSO-*d*₆): δ_C = 14.50 (CH₃), 46.00 (allyl-CH₂NH), 57.90 (C-2a), 59.70 (CH₂), 116.30 (allyl-CH₂=), 117.10 (CN), 134.00 (allyl-CH=), 159.50 (C=N), 163.20 (thiadiazole-C-2), 166.40 (CO).

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

Anal. Calcd. for C₁₀H₁₂N₄O₂S (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-1H-pyrazole-1-carbothio-
amide (14ab)**

Yield: (0.058 g, 20%); colorless crystals (EtOH); Mp: 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} .

^1H NMR (400 MHz, DMSO- d_6): δ_{H} = 2.50 (s, 3H, SCH₃), 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 (SCH₃), 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^+) (22), 153 (16), 131 (100), 91 (15).

Anal. Calcd. for C₁₂H₁₀N₄OS₂ (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)-1H-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} .

^1H NMR: (400 MHz, DMSO- d_6): δ_{H} = 1.14 (t, 3H, CH₃, J = 7.0 Hz), 2.50 (s, 3H,
SCH₃), 4.16 (q, 2H, CH₂, 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, NH₂), 11.70 (br. s, 1H, NH-Ph).

¹³C NMR (100 MHz, DMSO-*d*₆): δ_C = 11.10 (CH₃-Et), 11.40 (SCH₃), 58.60 (CH₂-Et), 92.50 (Pyrazole-C-4), 127.50, 128.10 (Ar-2CH), 128.90 (Ar-CH), 130.02 (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⁺) (5%), 201 (56), 153 (87), 148 (77), 135 (80), 116 (49), 90 (100).

Anal. Calcd. for C₁₄H₁₆N₄O₂S₂ (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 (Alk-CH), 1671 (CO), 1615 (C=N), 1354 (C=S) cm⁻¹.

NMR spectral data in Table 2.

MS: m/z (%) = 300 (M⁺) (17), 252 (17), 201 (88), 155 (100), 90 (15).

Anal. Calcd. for C₁₁H₁₆N₄O₂S₂ (300.40): 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 (Alk-CH), 1670 (CO), 1615 (C=N), 1354 (C=S) cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ_H = 0.87 (t, 3H, CH₃, *J* = 7.0 Hz), 1.10 (t, 3H, CH₃, *J* = 6.8 Hz), 2.49 (s, 3H, SCH₃), 3.64 (q, 2H, CH₂, *J* = 7.0 Hz), 4.20 (q, 2H, CH₂, *J* = 7.0 Hz), 8.27 (br. s, 2H, NH₂), 9.88 (br. s, 1H, NH-Ethyl).

¹³C NMR (100 MHz, DMSO-*d*₆): δ_C = 11.10 (CH₃-Et), 11.60 (SCH₃), 13.00 (CH₃-Et), 42.50 59.40 (CH₂-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⁺) (30), 201 (100), 200 (54), 154 (92), 147 (21).

Anal. Calcd. For C₁₀H₁₆N₄O₂S₂ (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. (135-136 °C)^{25,26}.

¹³C NMR (100 MHz, DMSO-*d*₆): δ_C = 11.40 (SCH₃), 14.4 (CH₃), 58.6 (OCH₂), 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

The 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)). Semi-empirical absorption corrections were applied. Due to the bad quality of the data and the (not to be resolved) disorder of the thiomethane substituents for **4** only the constitution could

be determined. Therefore 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 $0.22 \times 0.16 \times 0.10$ mm, monoclinic, space group $C2/c$ (No. 15), $a = 22.0120(7)$ Å, $b = 19.5237(6)$ Å, $c = 13.8667(5)$ Å, $\beta = 118.775(1)^\circ$, $V = 5223.4(3)$ Å³, $Z = 16$, $\rho = 1.472$ Mg/m³, $\mu(\text{Cu-K}\alpha) = 3.642$ mm⁻¹, $F(000) = 2400$, $2\theta_{\text{max}} = 144.4^\circ$, 46945 reflections, of which 5138 were independent ($R_{\text{int}} = 0.025$), 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 $0.26 \times 0.14 \times 0.12$ mm, monoclinic, space group $C2/c$ (No. 15), $a = 30.5762(10)$ Å, $b = 11.7594(4)$ Å, $c = 16.8216(5)$ Å, $\beta = 107.038(2)^\circ$, $V = 5782.9(3)$ Å³, $Z = 32$, $\rho = 1.417$ Mg/m³, $\mu(\text{Cu-K}\alpha) = 3.384$ mm⁻¹, $F(000) = 2560$.

Compound 15cb: Colorless crystals, $C_{11}H_{16}N_4O_2S_2$, $M_r = 300.40$, crystal size $0.16 \times 0.10 \times 0.04$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 9.3909(4)$ Å, $b = 19.3892(8)$ Å, $c = 7.9959(4)$ Å, $\beta = 98.096(2)^\circ$, $V = 1441.40(11)$ Å³, $Z = 4$, $\rho = 1.384$ Mg/m³, $\mu(\text{Cu-K}\alpha) = 3.397$ mm⁻¹, $F(000) = 632$, $2\theta_{\text{max}} = 144.4^\circ$, 11575 reflections, of which 2833 were independent ($R_{\text{int}} = 0.033$), 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 the bad quality of the data of **4** the data were not deposited with The Cambridge Crystallographic Data Centre.

Results and Discussion

In this paper, the reaction 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 starting substances under investigation are shown in Figure 1.

Figure 1. Starting substances **1a-d** and **2a,b**.

Gentle heating (at 50 °C) of equimolar solutions of **1a** and **2a** in absolute ethanol containing 0.5 mL of Et₃N for 3 h, the reaction gave compound **3** in 45% yield together with 5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (**4**)^{22,23} 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). In order to optimize the yield of the pyrazole derivative **3**, we carried the reaction between of 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 structure of compound **3** was, ultimately, proved by X-ray structure analysis (Figure 2).

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 to the high reactivity of the 3-pyridyl substituent and the instability of its reaction products even at room temperature.

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

The molecular formula of **5ba** (C₁₂H₁₀N₆S) was confirmed from mass spectrum due to presence of a molecular ion peak at $m/z = 270$. The ¹H NMR of compound **5ba** showed broad exchangeable (with D₂O) two 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 ¹³C NMR spectrum showed the presence of aromatic carbons at $\delta = 129.50, 129.60, 130.40, 130.50, 137.10, 137.60, 141.90, 142.50, 147.90, 149.80$ in addition to 155.70 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** to 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 to the carbon of nitrile group to give intermediate **7c**. Addition of a second molecule of **2a** to **7c** would produce compound **12** (Scheme 5).

Scheme 5. Mechanism describes the formation of compound **12**.

The ¹H NMR of compound **12** showed three singlets at $\delta_H = 2.30$ (6H), 2.40 (3H), and 3.33 (1H) for 2SCH₃, SCH₃, and CH(CN)₂, respectively (see the Experimental Section). The *N*-ethyl protons resonated in the ¹H NMR spectrum as a quartet and triplet at $\delta_H = 3.60$ (CH₂, *J* = 7.0 Hz) and 1.10 (CH₃, *J* = 7.0 Hz). Additional two broad singlets for NH and NH₂Et at $\delta_H = 8.79$ and 9.99, respectively. The presence of methylthiol carbon signals were also confirmed through ¹³C NMR at $\delta_C = 12.50$ (2C) and 12.70 (C), respectively. Pyrazole C-5, C-4 and C-3 resonated at $\delta_C = 169.00$, 65.00 and 163.30. The low δ value of pyrazole-C-4 is attributed to presence of push-pull system. In addition, $\delta_C = 11.30$, 22.30, 38.10, 78.00 and 184.00 ppm attributing to CH₃-Et, CH(CN)₂, CH₂-Et, (C(SCH₃)₂) and C=S, respectively (see the experimental section). Finally, elemental analysis proved that compound **12** has a molecular formula C₁₄H₁₇N₇S₄, which was confirmed *via* 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*-phenylhydrazinecarbothioamide **1a** with **2b** at room temperature in dry ethanol containing 0.5 mL of triethylamine giving 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 which 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; ¹H NMR, ¹³C NMR and 2D- NMR; MS) and elemental analyses as well.

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

In different manner, reactions of **1a-d** with **2b** under heating at 50 °C in dry ethanol containing 0.5 mL of triethylamine yielded three structures **13**, **15** and **16** (Scheme 7). Compound **13** was separated as a precipitate, whereas the filtrate contains the other two zones, which were separated out using (plc). The fast migrating zone containing **15** and the lowest migrating zone containing ethyl 5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate **16** [24,25] (Scheme 7).

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.

Figure 4 showed distinctive carbon atoms in compound **13a,b**. The ^1H spectral data of **13ab** showed two broadened singlets downfield both have integrals of 1H at $\delta_H = 13.64$, 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 $\delta_H = 1.23$; its attached carbon (C-2d) appears at $\delta_C = 14.52$; H-2d gives COSY correlation, and C-2d gives HMBC correlation, with the 2H quartet at $\delta_H = 4.16$, 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 (Figure 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 $\delta_H = 10.24$.

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

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.

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, <i>J</i> = 7.7; 2H)	7.36, 7.02	H- <i>o</i>
7.36 (“t”, <i>J</i> = 7.4; 2H)	7.48, 7.02	H- <i>m</i>
7.02 (t, <i>J</i> = 7.1; 1H)	7.48, 7.36	H- <i>p</i>
4.16 (q, <i>J</i> = 6.8; 2H)	1.23	H-2c
1.23 (t, <i>J</i> = 6.8; 3H)	4.16	H-2d
¹³ C NMR	HSQC	HMBC
		Assignment

166.42		4.16	C-2b	1
162.94			C-2/5	
155.52			C-5/2	2
139.88		7.48, 7.36	C-i	
129.15	7.36	7.36, 7.02	C-m	3
122.12	7.02	7.48	C-p	
117.32	7.48	10.24, 7.48, 7.36, 7.02	C-o	4
116.68			C≡N	
60.03	4.16	1.23	C-2c	5
58.69			C-2a	
14.52	1.23	4.16	C-2d	6
¹⁵ N NMR	HSQC	HMBC	Assignment	7
257.10		10.24	N-4	8
95.40	10.24	7.48	N-5a

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

The mechanism describing the formation of **13ab** was presented in Scheme 8. As nucleophilic attack of the thione lone pair **1a** to C-2 of **2b** accompanied with elimination of a molecule of methanethiol followed by another nucleophilic attack from terminal hydrazine-NH₂ to the same carbon leading to loss another molecule of methanethiol and forming the target compounds **13ab** (Scheme 8).

The mechanism describes the formation of **14ab**, **15** and **16** can be explained as nucleophilic attack of the more powerful terminal nitrogen N¹ lone pair in **1a-d** to C-3

of **2b** accompanied by loss of a molecule of methanethiol giving intermediate **18** which followed by a second nucleophilic attack from N^2 of hydrazinecarbothioamides to the carbonitrile group forming intermediate **19** (Scheme 9). Subsequently, nucleophilic addition of N^2 -lone pair to the nitrile carbon would give Zwitterion **19** (Scheme 9). Neutralization of **19** followed by aromatization would give **15** (Scheme 9). Rearrangement to **19** accompanied with elimination of substituted isothiocyanate molecule would give the pyrazole derivatives **16** (i.e. easily occurred under heating

Scheme 9. A rationale for the formation of products **14ab**, **15** and **16**.

temperature).^{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** to 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 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 $\nu = 3365\text{--}3338$, 2920, 1671, 1615, 1354 cm^{-1} relating to (NH's), (Al-CH), CO, C=N and C=S. The ethoxy 3H triplet (H-4c) is distinctive at $\delta_H = 1.28$; its attached carbon (C-4c) appears at $\delta_C = 13.33$. The H-4c gives COSY correlation, and C-4c gives HBC correlation, with the 2H quartet at $\delta_H = 4.22$, assigned as H-4b; the attached carbon (C-4b) appears at $\delta_C = 58.46$. The H-4b also gives HMBC correlation with a carbon at $\delta_C = 161.7$, assigned as the ester carbonyl C-4a. Distinctive carbon atoms of compound **15cb** are as shown in Figure 5.

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

The ^1H double-double-triplet at $\delta_H = 5.91$ is assigned as H-2d; the attached carbon C-2d appears at $\delta_C = 131.73$. H-2d gives COSY correlation with the broadened doublets at $\delta_H = 5.21$ and 5.18 , assigned as the terminal vinylic protons H-2e; their attached carbon C-2e appears at $\delta_C = 115.70$. Protons H-2e and H-2d all give COSY correlation with a 2H broad multiplet at $\delta_H = 4.26$, 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 $\delta_C = 44.54$, assigned as C-2c. H-2c also gives COSY correlation with the broad 1H singlet at $\delta_H = 10.02$, assigned as NH-2b. The broad 2H

signal at $\delta_H = 8.27$ is assigned as NH-3a. The ^{13}C spectrum has 11 signals; four are in the normal sp^3 region upfield of $\delta_C = 58.46$, 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 (Figure 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 bonds 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 as they compared to N-N, C-N, C-O single bonds.

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

^1H NMR	^1H - ^1H 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:
172.97		C-2a
161.65		C-4a
153.36		C-5
150.46		C-3

1	131.73	5.91	4.26	C-2d
2	115.70	5.21, 5.18		C-2e
3	91.27			C-4
4	58.46	4.22	1.28	C-4b
5	44.54	4.26		C-2c
6	13.33	1.28	4.22	C-4c
7	11.46	2.51		C-5a
8

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

Conclusion

Hydrazinecarbothioamides have still shed attention due to the presence of many active nucleophilic centers. Reactivity of substituent of hydrazinecarbothioamides depends upon its electronic structure (i.e. aliphatic or aromatic), besides its stability towards reactions with electrophiles. So far, many efforts must be done, especially for the construction of new simple classes of sulfur and/or nitrogen heterocycles.

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