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A New Approach for the Synthesis of Some Novel Sulphur Bridged Pyrazoles and their Characterization

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ABSTRACT

Reaction of derivatives of ethyl vinyl ether or ketene dithioacetal substituted with alkyl and aryl groups with hydrazine hydrate afforded respective pyrazole derivatives. This on subsequent treatment with α-halosubstituted acyl halide resulted in the respective N-acylated derivative. Reaction of N-acylated derivative with mercaptoheterocyclic compounds in the presence of base resulted in the formation of Sulphur bridged pyrazole derivatives.

Keywords: pyrazole, ethyl vinyl ether, ketene dithioacetal, mercaptoheterocycles, chloroacetyl chloride, bromopropionyl bromide.

INTRODUCTION

In recent years pyrazole derivatives have received significant attention owing to their diverse range of biological properties particularly being antifungal, antitubercular, antibacterial, antiviral, anticancer and antioxidant [1-4]. Heterocycles bearing nitrogen, sulphur, oxygen and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Some of them are tetrazoles, fused thiazoles, thiadiazoles, oxadiazoles, triazoles, which are structural subunits of several biologically active compounds [5-7]. In our recent communication we reported some of the novel sulphur bridged pyrazole derivatives having thiomethyl substituent at the 3-position of pyrazole ring, their characterization and biological activities [8].

EXPERIMENTAL SECTION

General

Melting points were determined on a Buchi Melting point B-540 instrument and are uncorrected. The purity of the compounds was analyzed by thin layer chromatography (pre-coated silica gel, Merck, chloroform/methanol, 8:2). The mass spectra were recorded in PE-SCIEX API-3000 LC/MS/MS with Turbo ion spray. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 on a Bruker Avance 400 MHz Spectrometer with multinuclear BBO Probe and TMS as an internal standard.

(1-Ethoxyethylidene)malononitrile (1a):

A mixture of malononitrile (10 g; 151 mmol), triethyl orthoacetate (24.56; 151 mmol) and acetic anhydride (37.09 g; 363 mmol) was heated under reflux for 8-10 hours. The by-product such as acetic acid, ethyl acetate and ethanol were removed by distillation under vacuum. To the residue chilled water was added. The solid product was filtered and washed with chilled water. Drying the product under vacuum afforded (1-ethoxyethylidene)malononitrile. (Yield 16.2 g, 78.60 %).

[Ethoxy(phenyl)methylene]malononitrile (1b):

By following the procedure disclosed for **1a,** use of triethyl orthobenzoate instead of triethyl orthoacetate afforded [ethoxy(phenyl)methylene]malononitrile. (Yield 27.4 g, 91.31 %)

[Bis(methylthio)methylene]malononitrile (1c):

To a solution of potassium hydroxide (114.09 g; 2033 mmol) in water (80 mL) N,N-dimethylformamide (150 mL) was added at ice cold temperature. To the reaction mixture malononitrile (58.4 g; 884 mmol) was added and stirred for 10 minutes at ice cold temperature. Carbon disulphide (67.31 g; 884 mmol) was added slowly by controlling the temperature at 0-5 °C. The reaction temperature was raised slowly to 30 °C and stirred for 30 minutes at the same temperature. The reaction mixture was cooled to 10 °C and dimethylsulphate (209.62 g; 1662 mmol) was added slowly. The reaction mixture was quenched by adding crushed ice with stirring. The precipitated product was filtered and washed with ice cold water. Drying the product under vacuum to afford ethyl 2-cyano-3,3-bis(methylthio)acrylate.

5-Amino-3-methyl-1H-pyrazole-4-carbonitrile (2a):

A mixture of (1-ethoxyethylidene)malononitrile (20 g; 147 mmol) and hydrazine hydrate (14.72 g; 294 mmol) in methanol (30 mL) was heated under reflux till completion of reaction. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, methanol was removed by distillation under vacuum. To the residue chilled water was added. The crystallized product was filtered and washed with chilled water. Drying the product under vacuum afforded 5-amino-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 10.3 g, 57.41 %). *m/z* 123.2 $(M+H)^{+}$; ^{1}H NMR 2.12 (3H, s, CH_3), 6.21 (2H, s, NH_2) 11.64 (1H, s, NH)

5-Amino-3-phenyl-1H-pyrazole-4-carbonitrile (2b):

By following the procedure disclosed for **2a,** use of [ethoxy(phenyl)methylene]malononitrile instead of (1-ethoxyethylidene)malononitrile afforded 5-amino-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 14.6 g, 78.56 %). *m/z* 185.1 $(M+H)^{+}$; ^{1}H NMR 6.50-7.53 (5H, m, Ar), 7.83 (2H, s, NH_2) 12.17 (1H, s, NH)

5-Amino-3-(methylthio)-1H-pyrazole-4-carbonitrile (2c):
By following the procedure disclosed for **2a,** use [bis(methylthio)methylene]malononitrile instead of (1-ethoxyethylidene)malononitrile afforded 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 16.2 g, 71.52 %). *m/z* 155.2 $(M+H)^+$; ^{1}H NMR 2.43 (3H, s, SCH_3), 6.47 (2H, s, NH_2) 11.97 (1H, s, NH)

5-Amino-1-(chloroacetyl)-3-methyl-1H-pyrazole-4-carbonitrile (3a):
To a suspension of 5-amino-3-methyl-1H-pyrazole-4-carbonitrile (8 g; 66 mmol) in acetone (80 mL) chloroacetyl chloride (8.89 g; 79 mmol) was added at ice cold temperature. To the reaction mixture, triethylamine (9.95 g; 98 mmol) was slowly added. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, ice cold water was slowly added to the reaction mixture. The precipitated product was filtered and washed with ice cold water. Drying the product under vacuum afforded 5-amino-1-(chloroacetyl)-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 6.7 g, 51.50 %). *m/z* 199.5, 216.2, 218.2 $(M-H)^-$; ^{1}H NMR 2.23 (3H, s, CH_3), 5.07 (2H, s, SCH_2), 8.16 (2H, s, NH_2)

5-Amino-1-(chloroacetyl)-3-phenyl-1H-pyrazole-4-carbonitrile (3b):
By following the procedure disclosed for **3a,** use of 5-amino-3-phenyl-1H-pyrazole-4-carbonitrile instead of 5-amino-3-methyl-1H-pyrazole-4-carbonitrile afforded 5-amino-1-(chloroacetyl)-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 7.1 g, 62.71 %). *m/z* 261.4 $(M+H)^+$; ^{1}H NMR 5.13 (2H, s, SCH_2), 7.54-7.90 (5H, m, Ar), 8.16 (2H, s, NH_2)

5-Amino-1-(2-bromopropanoyl)-3-(methylthio)-1H-pyrazole-4-carbonitrile (3c):
To a suspension of 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile (3 g; 19.5 mmol) in acetone (30 mL) 2-bromopropionyl bromide (5.05 g; 23.4 mmol) was added at ice cold temperature. Triethylamine (2.96 g; 29.2 mmol) was added slowly to the reaction mixture. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, ice cold water was slowly added to the reaction mixture. The precipitated product was filtered and washed with ice cold water. Drying the product under vacuum to afford 5-amino-1-(2-bromopropanoyl)-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 3.6 g, 63.99 %). *m/z* 289.3, 291.3 $(M+H)^+$; ^{1}H NMR 1.69 (3H, d, $CH\underline{CH_3}$), 2.52 (3H, s, SCH_3), 5.25 (1H, q, $\underline{CH}CH_3$), 8.13 (2H, s, NH_2)

5-Amino-1-(2-bromopropanoyl)-3-methyl-1H-pyrazole-4-carbonitrile (3d):
By following the procedure disclosed in **3c,** use of 5-amino-3-methyl-1H-pyrazole-4-carbonitrile instead of 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile afforded 5-amino-1-(2-bromopropanoyl)-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 3.9 g, 61.76 %). *m/z* 255.2, 257.2 $(M-H)^-$; ^{1}H NMR 1.81 (3H, d, $CH\underline{CH_3}$), 2.18 (3H, s, CH_3), 5.47 (1H, q, $\underline{CH}CH_3$), 8.06 (2H, s, NH_2)

5-Amino-1-(2-bromopropanoyl)-3-phenyl-1H-pyrazole-4-carbonitrile (3e):
By following the procedure disclosed in **3c,** use of 5-amino-3-phenyl-1H-pyrazole-4-carbonitrile instead of 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile afforded 5-amino-1-(2-bromopropanoyl)-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 3.5 g, 67.33 %). *m/z* 317.1, 319.0 $(M-H)^-$; ^{1}H NMR 1.77 (3H, d, $CH\underline{CH_3}$), 5.63 (1H, q, $\underline{CH}CH_3$), 7.41-7.91 (5H, m, Ar), 8.20 (2H, s, NH_2)

5-Amino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-methyl-1H-pyrazole-4-carbonitrile (5a):
To a mixture of 5-amino-1-(chloroacetyl)-3-methyl-1H-pyrazole-4-carbonitrile (500 mg; 2.52 mmol) and 1,3-benzothiazole-2-thiol (440 mg; 2.63 mmol) in acetone (15 mL) triethylamine (306 mg; 3.03 mmol) was added slowly under ice cold temperature. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, chilled water was added to the reaction mixture. The precipitated product was filtered and washed with chilled water to afford 5-amino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 520 mg, 62.71 %). *m/z* 330.0 $(M+H)^+$; mp 172.4 °C(dec); ^{1}H NMR 2.21 (3H, s, CH_3), 4.97 (2H, s, SCH_2), 7.35-8.01 (4H, m, Ar), 8.03 (2H, s, NH_2)

5-Amino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbonitrile (5b):
To a mixture of 5-amino-1-(chloroacetyl)-3-phenyl-1H-pyrazole-4-carbonitrile (500 mg; 1.92 mmol) and 1,3-benzothiazole-2-thiol (340 mg; 2.03 mmol) in acetone (15 mL) triethylamine (233 mg; 2.31 mmol) was added slowly under ice cold temperature. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, chilled water was added to the reaction mixture. The crystallized product was filtered and washed with chilled water to afford 5-amino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 610 mg, 81.24 %). *m/z* 392.1 $(M+H)^+$; mp 179.6 °C(dec); ^{1}H NMR 5.09 (2H, s, SCH_2), 7.35-8.04 (10H, m, Ar), 8.16 (2H, s, NH_2)

5-Amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-methyl-1H-pyrazole-4-carbonitrile (5c):
To a mixture of 5-amino-1-(2-bromopropanoyl)-3-methyl-1H-pyrazole-4-carbonitrile (500 mg; 1.95 mmol) and 1,3-benzothiazole-2-thiol (340 mg; 2.03 mmol) in acetone (10 mL) triethylamine (251 mg; 2.48 mmol) was added slowly under ice cold temperature. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, chilled water was added to the reaction mixture. The precipitated product was filtered and washed with chilled water to afford 5-amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 390 mg, 58.39 %). *m/z* 344.0 $(M+H)^+$; mp 135.9 °C; ^{1}H NMR 1.69 (3H, d, $CH\underline{CH_3}$), 2.12 and 2.35 (3H, s, CH_3), 4.90 and 5.59 (1H, q, $\underline{CH}CH_3$), 7.38-8.03 (4H, m, Ar), 8.05 (2H, s, NH_2)

5-Amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-phenyl-1H-pyrazole-4-carbonitrile (5d):
To a mixture of 5-amino-1-(2-bromopropanoyl)-3-phenyl-1H-pyrazole-4-carbonitrile (500 mg; 1.57 mmol) and 1,3-benzothiazole-2-thiol (280 mg; 1.67 mmol) in acetone (10 mL) triethylamine (198 mg; 2.04 mmol) was added slowly under ice cold temperature. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, chilled water was added to the reaction mixture. The precipitated product was filtered and washed with chilled water to afford 5-amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 380 mg, 59.82 %). *m/z* 406.1 $(M+H)^+$; mp 178.2 °C; ^{1}H NMR 1.71 (3H, d, $CH\underline{CH_3}$), 4.95 and 5.80 (1H, q, $\underline{CH}CH_3$), 7.33-8.05 (9H, m, Ar), 8.16 (2H, s, NH_2)

5-Amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-(methylthio)-1H-pyrazole-4-carbonitrile (5e):
To a mixture of 5-amino-1-(2-bromopropanoyl)-3-(methylthio)-1H-pyrazole-4-carbonitrile (500 mg; 1.73 mmol) and 1,3-benzothiazole-2-thiol (310 mg; 1.85 mmol) in acetone (10 mL)

triethylamine (228 mg; 2.25 mmol) was added slowly under ice cold temperature. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). After completion of reaction, chilled water was added to the reaction mixture. The precipitated product was filtered and washed with chilled water to afford 5-amino-1-[2-(1,3-benzothiazol-2-ylthio)propanoyl]-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 420 mg, 64.69 %). *m/z* 376.0 $(M+H)^+$; mp 174.6 °C; ^{1}H NMR 1.70 (3H, d, CH<u>CH$_3$</u>), 2.31 (3H, s, SCH_3), 5.65 (1H, q, <u>CH</u>CH_3), 7.38-8.05 (4H, m, Ar), 8.18 (2H, s, NH_2)

5-Amino-1-{[(1-methyl-1H-tetrazol-5-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile (6a):
By following the procedure disclosed for **5a,** use of 1-methyl-1H-tetrazole-5-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(1-methyl-1H-tetrazol-5-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 420 mg, 59.95 %). *m/z* 330.0 $(M+H)^+$; mp 146.3 °C; ^{1}H NMR 2.18 (3H, s, CH_3), 3.99 (3H, s, NCH_3), 4.85 (2H, s, SCH_2), 8.03 (2H, s, NH_2)

5-Amino-1-{[(1-methyl-1H-tetrazol-5-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile (6b):
By following the procedure disclosed for **5b,** use of 1-methyl-1H-tetrazole-5-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(1-methyl-1H-tetrazol-5-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 490 mg, 75.06 %). *m/z* 341.1 $(M+H)^+$; mp 214.4 °C; ^{1}H NMR 4.01 (3H, s, NCH_3), 4.98 (2H, s, SCH_2), 7.55-7.91 (5H, m, Ar), 8.15 (2H, s, NH_2)

5-Amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile (6c):
By following the procedure disclosed for **5c,** use of 1-methyl-1H-tetrazole-5-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 330 mg, 58.05 %). *m/z* 293.1 $(M+H)^+$; mp 168.5 °C; ^{1}H NMR 1.59 (3H, d, CH<u>CH$_3$</u>), 2.11 (3H, s, SCH_3), 3.97 (3H, s, NCH_3), 5.23 (1H, q, <u>CH</u>CH_3), 8.04 (2H, s, NH_2)

5-Amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile (6d):
By following the procedure disclosed for **5d,** use of 1-methyl-1H-tetrazole-5-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-Amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 370 mg, 66.64 %). *m/z* 355.1 $(M+H)^+$; mp 173.1 °C; ^{1}H NMR 1.54 (3H, d, CH<u>CH$_3$</u>), 3.96 (3H, s, NCH_3), 4.63 and 5.39 (1H, q, <u>CH</u>CH_3), 7.42-7.84 (5H, m, Ar), 8.19 (2H, s, NH_2)

5-Amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile (6e):
By following the procedure disclosed for **5e,** use of 1-methyl-1H-tetrazole-5-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(1-methyl-1H-tetrazol-5-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 360 mg, 64.18 %). *m/z* 325.1 $(M+H)^+$; mp 205.2 °C; ^{1}H NMR 1.61 (3H, d, CH<u>CH$_3$</u>), 2.44 (3H, s, SCH_3), 3.96 (3H, s, NCH_3), 5.26 (1H, q, <u>CH</u>CH_3), 8.18 (2H, s, NH_2)

5-Amino-1-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile (7a):

By following the procedure disclosed for **5a,** use of 5-methyl-1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 450 mg, 60.72 %). *m/z* 295.0 $(M+H)^+$; mp 189.6 °C(dec); ^{1}H NMR 2.18 (3H, s, pyrazole $\underline{CH_3}$), 2.67 (3H, s, thiadiazole $\underline{CH_3}$), 4.86 (2H, s, SCH_2), 8.00 (2H, s, NH_2)

5-Amino-1-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile (7b):

By following the procedure disclosed for **5b,** use of 5-methyl-1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 390 mg, 57.05 %). *m/z* 357.0 $(M+H)^+$; mp 159.4 °C(dec); ^{1}H NMR 2.63 (3H, s, thiadiazole $\underline{CH_3}$), 4.98 (2H, s, SCH_2), 7.54-7.92 (5H, m, Ar), 8.14 (2H, s, NH_2)

5-Amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile (7c):

By following the procedure disclosed for **5c,** use of 5-methyl-1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 350 mg, 58.36 %). *m/z* 309.1 $(M+H)^+$; mp 174.3 °C; ^{1}H NMR 1.58 (3H, d, $CH\underline{CH_3}$), 2.15 (3H, s, pyrazole CH_3), 2.69 (3H, s, thiadiazole CH_3), 5.34 (1H, q, $\underline{CH}CH_3$), 8.02 (2H, s, NH_2); Anal. Calcd. for $C_{11}H_{12}N_6OS_2$: C, 42.84; H, 3.92; N, 27.25. Found: C, 42.56; H, 4.10; N, 27.48

5-Amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile (7d):

By following the procedure disclosed for **5d,** use of 5-methyl-1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 400 mg, 68.92 %). *m/z* 371.1 $(M+H)^+$; mp 191.8 °C; ^{1}H NMR 1.62 (3H, d, $CH\underline{CH_3}$), 2.62 (3H, s, thiadiazole CH_3), 5.48 (1H, q, $\underline{CH}CH_3$), 7.53-7.84 (5H, m, Ar), 8.16 (2H, s, NH_2)

5-Amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile (7e):

By following the procedure disclosed for **5e,** use of 5-methyl-1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 330 mg, 56.05 %). *m/z* 341.1 $(M+H)^+$; mp 181.1 °C; ^{1}H NMR 1.60 (3H, d, $CH\underline{CH_3}$), 2.45 (3H, s, SCH_3), 2.69 (3H, s, CH_3), 5.37 (1H, q, $\underline{CH}CH_3$), 8.16 (2H, s, NH_2)

5-Amino-1-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile (8a):

By following the procedure disclosed for **5a,** use of 5-phenyl-1,3,4-oxadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 470 mg, 54.85 %). *m/z* 341.1 $(M+H)^+$; mp 196.6 °C;

^{1}H NMR 2.17 (3H, s, pyrazole $\underline{CH_3}$), 4.94 (2H, s, SCH_2), 7.58-7.96 (5H, m, Ar), 8.04 (2H, s, NH_2)

5-Amino-1-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile (8b):

By following the procedure disclosed for **5b,** use of 5-phenyl-1,3,4-oxadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 410 mg, 53.12 %). *m/z* 403.1 $(M+H)^+$; mp 213.3 °C; ^{1}H NMR 5.03 (2H, s, SCH_2), 7.53-7.96 (10H, m, Ar), 8.19 (2H, s, NH_2)

5-Amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile (8c):

By following the procedure disclosed for **5c,** use of 5-phenyl-1,3,4-oxadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 360 mg, 52.23 %). *m/z* 355.1 $(M+H)^+$; mp 175.0 °C; ^{1}H NMR 1.65 (3H, d, $CH\underline{CH_3}$), 2.02 (3H, s, CH_3), 5.32 (1H, q, $\underline{CH}CH_3$), 7.59-7.96 (5H, m, Ar), 8.08 (2H, s, NH_2)

5-Amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile (8d):

By following the procedure disclosed for **5d,** use of 5-phenyl-1,3,4-oxadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 380 mg, 58.24 %). *m/z* 417.2 $(M+H)^+$; mp 181.2 °C; ^{1}H NMR 1.71 (3H, d, $CH\underline{CH_3}$), 4.75 & 5.48 (1H, q, $\underline{CH}CH_3$), 7.38-8.00 (10H, m, Ar), 8.22 (2H, s, NH_2)

5-Amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile (8e):

By following the procedure disclosed for **5e,** use of 5-phenyl-1,3,4-oxadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 370 mg, 55.37 %). *m/z* 387.1 $(M+H)^+$; mp 198.6 °C; ^{1}H NMR 1.66 (3H, d, $CH\underline{CH_3}$), 2.42 (3H, s, SCH_3), 5.33 (1H, q, $\underline{CH}CH_3$), 7.58-7.94 (5H, m, Ar), 8.22 (2H, s, NH_2)

5-Amino-1-[(1,3,4-thiadiazol-2-ylthio)acetyl]-3-methyl-1H-pyrazole-4-carbonitrile (9a):

By following the procedure disclosed for **5a,** use of 1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-[(1,3,4-thiadiazol-2-ylthio)acetyl]-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 380 mg, 53.84 %). *m/z* 281.1 $(M+H)^+$; mp 177.8 °C(dec); ^{1}H NMR 2.19 (3H, s, pyrazole $\underline{CH_3}$), 4.96 (2H, s, SCH_2), 8.01 (2H, s, NH_2), 9.51 (1H, s, thiadiazole $\underline{CH}$)

5-Amino-1-[(1,3,4-thiadiazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbonitrile (9b):

By following the procedure disclosed for **5b,** use of 1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-[(1,3,4-thiadiazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 360 mg, 54.82 %). *m/z* 343.0 $(M+H)^+$; mp 176.3 °C(dec); ^{1}H NMR 5.06 (2H, s, SCH_2), 7.55-7.93 (5H, m, Ar), 8.15 (2H, s, NH_2), 9.53 (1H, s, thiadiazole $\underline{CH}$)

5-Amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-methyl-1H-pyrazole-4-carbonitrile (9c):
By following the procedure disclosed for **5c,** use of 1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 330 mg, 57.64 %). *m/z* 295.0 $(M+H)^+$; mp 133.4 °C; ^{1}H NMR 1.61 (3H, d, CH$\underline{CH_3}$), 2.16 (3H, s, CH_3), 5.43 (1H, q, $\underline{CH}CH_3$), 8.03 (2H, s, NH_2), 9.58 (1H, s, thiadiazole CH)

5-Amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-phenyl-1H-pyrazole-4-carbonitrile (9d):
By following the procedure disclosed for **5d,** use of 1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 310 mg, 55.52 %). *m/z* 357.1 $(M+H)^+$; mp 186.6 °C; ^{1}H NMR 1.69 (3H, d, CH$\underline{CH_3}$), 4.80 & 5.59 (1H, q, $\underline{CH}CH_3$), 7.53-7.85 (5H, m, Ar), 8.17 (2H, s, NH_2), 9.58 (1H, s, thiadiazole CH)

5-Amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-(methylthio)-1H-pyrazole-4-carbonitrile (9e):
By following the procedure disclosed for **5e,** use of 1,3,4-thiadiazole-2-thiol instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-[2-(1,3,4-thiadiazol-2-ylthio)propanoyl]-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 340 mg, 60.24 %). *m/z* 327.0 $(M+H)^+$; mp 170.7 °C; ^{1}H NMR 1.64 (3H, d, CH$\underline{CH_3}$), 2.45 (3H, s, SCH_3), 5.45 (1H, q, $\underline{CH}CH_3$), 8.22 (2H, s, NH_2), 9.59 (1H, s, thiadiazole CH)

5-Amino-1-{[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile (10a):
By following the procedure disclosed for **5a,** use of 3-mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]acetyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 280 mg, 34.61 %). *m/z* 322.0 $(M+H)^+$; mp 188.2 °C(dec); ^{1}H NMR 2.16 (3H, s, pyrazole $\underline{CH_3}$), 2.51 (3H, s, N$\underline{CH_3}$), 4.96 (2H, s, SCH_2), 8.01 (2H, s, NH_2)

5-Amino-1-{[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile (10b):
By following the procedure disclosed for **5b,** use of 3-mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]acetyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 310 mg, 42.16 %). *m/z* 384.1 $(M+H)^+$; mp 227.9 °C(dec); ^{1}H NMR 2.51 (3H, s, N$\underline{CH_3}$), 5.12 (2H, s, SCH_2), 7.53-7.89 (5H, m, Ar), 8.15 (2H, s, NH_2); Anal. Calcd. for $C_{16}H_{13}N_7O_3S$: C, 50.12; H, 3.42; N, 25.57. Found: C, 50.03; H, 3.50; N, 25.76

5-Amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile (10c):
By following the procedure disclosed for **5c,** use of 3-mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-methyl-1H-pyrazole-4-carbonitrile. (Yield 300 mg, 46.00 %). *m/z* 336.5 $(M+H)^+$; mp 158.1 °C; ^{1}H NMR 1.69 (3H, d, CH$\underline{CH_3}$), 2.22 (3H, s, CH_3), 2.48 (3H, s, NCH_3), 5.46 (1H, q, $\underline{CH}CH_3$), 8.08 (2H, s, NH_2)

5-Amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile (10d):

By following the procedure disclosed for **5d,** use of 3-mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-phenyl-1H-pyrazole-4-carbonitrile. (Yield 310 mg, 49.79 %). *m/z* 398.3 $(M+H)^+$; mp 229.4 °C(dec); ^{1}H NMR 1.66 (3H, d, CH<u>CH$_3$</u>), 2.55 (3H, s, NCH$_3$), 5.41 (1H, q, <u>CH</u>CH$_3$), 7.59-7.96 (5H, m, Ar), 8.19 (2H, s, NH$_2$)

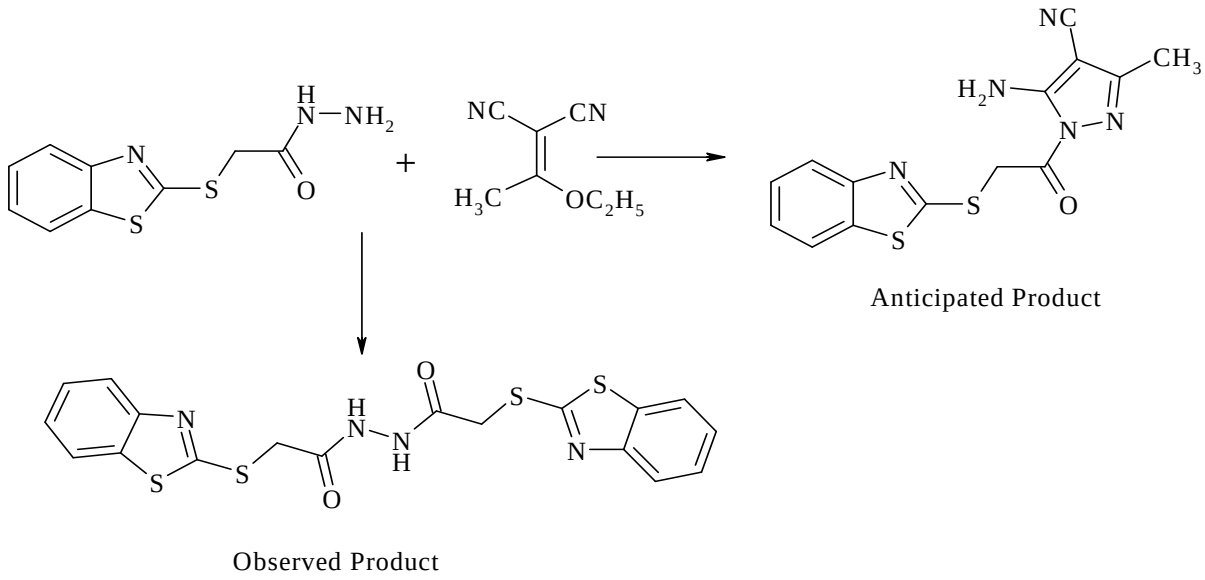
5-Amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile (10e):

By following the procedure disclosed for **5e,** use of 3-mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione instead of 1,3-benzothiazole-2-thiol afforded 5-amino-1-{2-[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]propanoyl}-3-(methylthio)-1H-pyrazole-4-carbonitrile. (Yield 290 mg, 45.65 %). *m/z* 368.0 $(M+H)^+$; mp 190.0 °C; ^{1}H NMR 1.79 (3H, d, CH<u>CH$_3$</u>), 2.49 (3H, s, SCH$_3$), 2.50 (3H, s, NCH$_3$), 5.47 (1H, q, <u>CH</u>CH$_3$), 8.19 (2H, s, NH$_2$)

RESULTS AND DISCUSSION

In our continued research, we have attempted to synthesize Sulphur bridged pyrazole having alkyl and aryl substitution in addition to thiomethyl at the 3-position of pyrazole ring by replacing ketene dithioacetal with alkyl and aryl substituted ethyl vinyl ethers as per the procedure described in our earlier communication [8]. Hence, the ethyl vinyl ether derivative having methyl substituent prepared from malononitrile using triethyl orthoacetate and acetic anhydride [9] on treatment with acylated hydrazine derivative of 2-mercaptobenzothiazole did not resulted in the anticipated 5-aminopyrazole derivative having methyl substituent at the 3-position, but formed the dimer of acylated hydrazine derivative of 2-mercaptobenzothiazole as represented in **Scheme-1**.

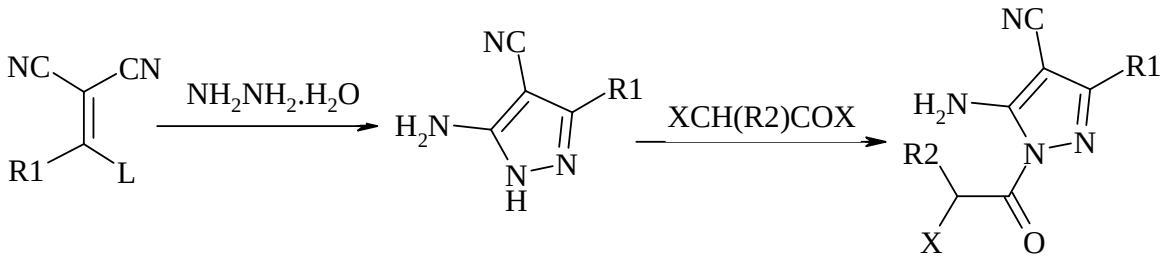
Scheme-1. Synthesis of sulphur bridged pyrazoles by classical method



The above reaction was carried out in the presence of acetic acid as well as in the presence of triethylamine [10]. In all the attempts, the observed product was dimer of acylated hydrazine derivative of 2-mercaptobenzothiazole.

An alternate route was attempted in order to achieve the target 3-alky and 3-aryl in addition to 3-thiomethyl substituted [8] 5-aminopyrazole derivatives of mercaptoheterocyclic compounds. Hence the ethyl vinyl ether having alkyl and aryl substitutent on treatment hydrazine hydrate [10-11] resulted in the formation of simple pyrazole derivatives having alkyl and aryl substituent. This on treatment with α-halosubstituted acyl halide in the presence of base in acetone resulted in the formation of N-haloacetyl derivatives as represented in **Scheme-2**.

Scheme-2. Preparation of simple pyrazoles and their Acylation



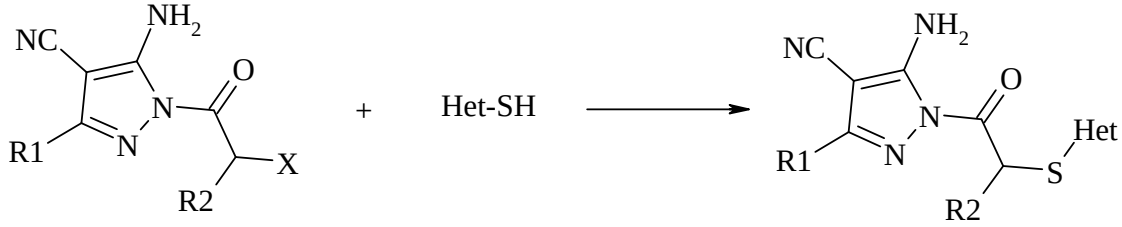
1a-c **2a-c** **3a-e**

Table-1. Representation of R^1, L, R^2 and X in scheme-2

Compound No	R^1	L	R^2	X
1a	CH_3	OC_2H_5	-	-
1b	C_6H_5	OC_2H_5	-	-
1c	SCH_3	SCH_3	-	-
2a	CH_3	-	-	-
2b	C_6H_5	-	-	-
2c	SCH_3	-	-	-
3a	CH_3	-	H	Cl
3b	C_6H_5	-	H	Cl
3c	SCH_3	-	CH_3	Br
3d	CH_3	-	CH_3	Br
3e	C_6H_5	-	CH_3	Br

The above synthesized N-haloacetyl derivatives of thiomethyl, alkyl and aryl substituted 5-aminopyrazole on treatment with mercaptoheterocyclic compound in the presence of base resulted in the formation of target alkyl and aryl in addition to thiomethyl substituted 5-aminopyrazole derivatives of mercaptoheterocyclic compounds.

Scheme-3. Condensation of acylated pyrazoles with mercaptoheterocyclic compounds.



3a-e **4a-f** **5a-e; 6a-e; 7a-e; 8a-e; 9a-e; 10a-e**

Table-2. Representation of Het-SH in scheme-3

Compound No	Het-SH
4a	2-mercapto-1,3-benzothiazol
4b	5-mercapto-1-methyltetrazol
4c	2-mercapto-5-methylthiadiazol
4d	5-phenyl-2-mercapto-oxadiazol
4e	2-mercaptothiadiazol
4f	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazine

Table-3. Representation of R^1, R^2 and Het in scheme-3

Compound No	R^1	R^2	Het
5a	CH_3	H	2-mercapto-1,3-benzothiazolyl
5b	C_6H_5	H	2-mercapto-1,3-benzothiazolyl
5c	CH_3	CH_3	2-mercapto-1,3-benzothiazolyl
5d	C_6H_5	CH_3	2-mercapto-1,3-benzothiazolyl
5e	SCH_3	CH_3	2-mercapto-1,3-benzothiazolyl
6a	CH_3	H	5-mercapto-1-methyltetrazolyl
6b	C_6H_5	H	5-mercapto-1-methyltetrazolyl
6c	CH_3	CH_3	5-mercapto-1-methyltetrazolyl
6d	C_6H_5	CH_3	5-mercapto-1-methyltetrazolyl
6e	SCH_3	CH_3	5-mercapto-1-methyltetrazolyl
7a	CH_3	H	2-mercapto-5-methylthiadiazolyl
7b	C_6H_5	H	2-mercapto-5-methylthiadiazolyl
7c	CH_3	CH_3	2-mercapto-5-methylthiadiazolyl
7d	C_6H_5	CH_3	2-mercapto-5-methylthiadiazolyl
7e	SCH_3	CH_3	2-mercapto-5-methylthiadiazolyl
8a	CH_3	H	5-phenyl-2-mercapto-oxadiazolyl
8b	C_6H_5	H	5-phenyl-2-mercapto-oxadiazolyl
8c	CH_3	CH_3	5-phenyl-2-mercapto-oxadiazolyl
8d	C_6H_5	CH_3	5-phenyl-2-mercapto-oxadiazolyl
8e	SCH_3	CH_3	5-phenyl-2-mercapto-oxadiazolyl
9a	CH_3	H	2-mercaptothiadiazolyl
9b	C_6H_5	H	2-mercaptothiadiazolyl
9c	CH_3	CH_3	2-mercaptothiadiazolyl
9d	C_6H_5	CH_3	2-mercaptothiadiazolyl
9e	SCH_3	CH_3	2-mercaptothiadiazolyl
10a	CH_3	H	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazinyl
10b	C_6H_5	H	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazinyl
10c	CH_3	CH_3	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazinyl
10d	C_6H_5	CH_3	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazinyl
10e	SCH_3	CH_3	3-mercapto-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazinyl

CONCLUSION

Various pyrazole derivatives were prepared by an alternate route through acylation of pyrazoles followed by condensation with mercaptoheterocyclic compounds. The synthesized compounds were confirmed by various analytical techniques. The alkyl and aryl substituted ethyl vinyl ether and ketene dithioacetal derivatives (**1a-c**) used for the synthesis of pyrazole derivatives were prepared according to the procedure reported in the literature [9,12].

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