Convenient Synthesis of Some New Substituted Pyrazolyl-1,3,4-oxadiazoles and Pyrazolyl-1,2,4-triazoles

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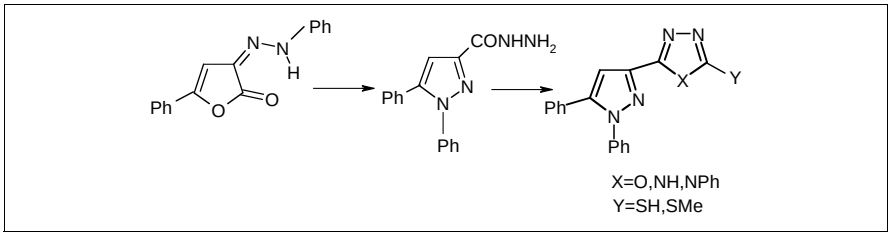

A simple and versatile method for the synthesis of pyrazol-3-yl-1,3,4-oxadiazole, pyrazol-3-yl-1,2,4-triazole, (1,5-diphenylpyrazol-3-yl)-(3,5-dimethyl-1-carbonyl)pyrazole and (1,5-diphenylpyrazol-3-yl)-(5-hydroxy-3-metheyl-1-carbonyl)pyrazole derivatives from 1,5-diphenylpyrazole-3-carboxylic acid hydrazide has been developed..

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Introduction.

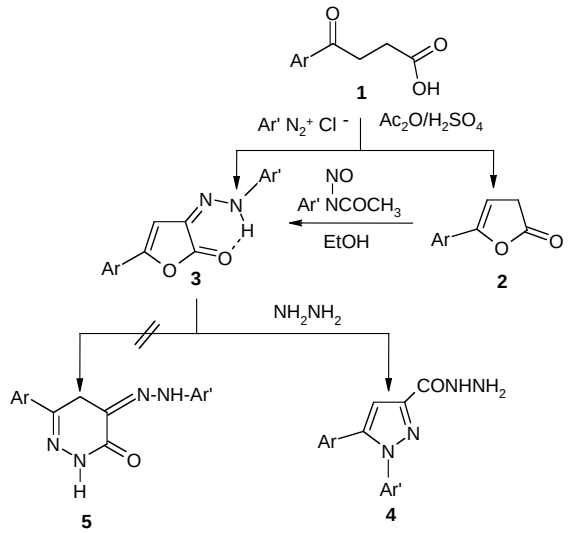
Many substituted 1,3,4-oxadiazoles have a wide variety of applications as biologically active compounds in medicine and agriculture. For example, they are used as antiperipheral vasomotility [1], central nervous system (CNS) stimulant, anti-inflammatory, hypotensive [2], hypoglycemic [3,4], analgesic, anticonvulsant, antiemetic, diuretic [5], muscle relaxant [6,7], bactericidal [8], pesticidal [9], insecticidal [10], herbicidal [11,12] and fungicidal agents [13,14]. On the other hand, the therapeutic effects of 1,2,4-triazoles have been well documented [15-17]. Several 1,2,4-triazole derivatives show anti-inflammatory [18], vasodilatory [19] and psychotropic properties [20]. Recently, our interest in the synthesis of various substituted heterocyclic systems, which could be adapted for the preparation of small libraries, has been the subject of several publications from our laboratory [21-31]. During our investigation, we have found that acid hydrazides can be used as useful intermediates leading to the formation of several heterocycles of potential biological activity such as 1,2,4-triazoles, 1,3,4-oxadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines [23,32].

In this context, we report a convenient rout to some new pyrazolyl-1,2,4-triazole, pyrazolyl-1,3,4-oxadiazole, (1,5-diphenyl-1*H*-pyrazol-3-yl)-(3,5-dimethyl-1-carbonyl)pyrazole and (1,5-diphenyl-1*H*-pyrazol-3-yl)-(5-hydroxy-3-metheyl-1-carbonyl)pyrazole starting from a readily accessible 1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid hydrazide.

Results and Discussion.

Treatment of 5-aryl-3*H*-furan-2-ones (**2a,b**) [33,35] (formed in situ by cyclization of 4-oxo-4-arylbutyric acid **1** by the action of acetic anhydride-sulfuric acid mixture) with aromatic diazonium salts, afforded colored products that were identified as 3-arylhydrazono-5-aryl-3*H*-furan-2-one derivatives (**3a,b**). The structures of the latter products were confirmed by the appearance of hydrazone NH and carbonyl bands near 3280 and 1750 cm^{-1}, respectively in their IR spectra and the lack of the characteristic signals due to methylene protons in their ^1H NMR spectra. Compounds (**3a,b**) were also obtained from the reaction of intermediate 5-aryl-3*H*-furan-2-one derivatives (**2a,b**) with *N*-nitrosoacylarylamine [34], in ethanol at room temperature (Scheme 1).

Scheme 1



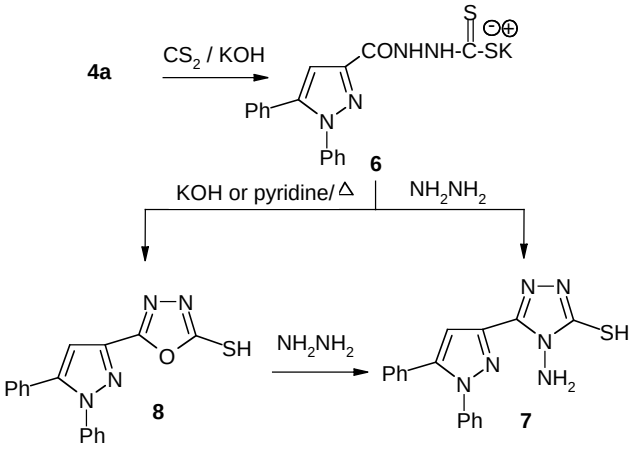
2, 3, 4, 5 **a**: Ar = Ar'= Ph
b: Ar = Ar'= 4-$CH_3C_6H_4$

When the 3-arylhydrazono-5-aryl-3*H*-furan-2-one derivatives (**3a,b**) were treated with hydrazine hydrate, they afforded products identified as the 1,5-diaryl-1*H*-pyrazole-3-carboxylic acid hydrazide derivatives (**4a,b**), respectively (Scheme 1). The structures of the isolated products were assigned on the basis of their elemental analysis and spectral data. For example, the IR spectra of the isolated products showed three bands in each case, in the region 3286-3210 cm^{-1} corresponding to NH and NH_2 groups and a carbonyl absorption band near 1689 cm^{-1}. The ^1H NMR spectrum of (**4a**), as an example, showed a singlet signal at δ 6.81 corresponding to 4-CH of the pyrazole ring and two broad bands (D_2O-exchangeable) at δ 4.34 and 8.73 due to NH_2 and NH protons, respectively, in addition to a multiplet signal in the region δ 7.13-7.53 due to aromatic protons. Moreover, the mass spectrum of the same product revealed a peak corresponding to its molecular ion at *m/z* 278. The other possible 3-aryl-5-arylhydrazono-1*H*-pyridazine-6-one structure (**5**) was ruled out on the basis of the IR and ^1H NMR spectra of the reaction products (see experimental part).

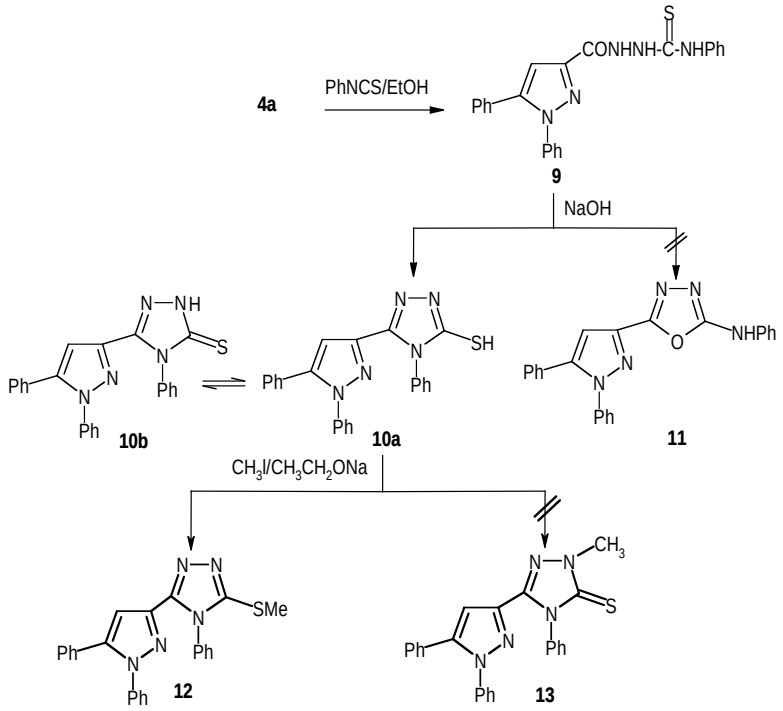
Treatment of 1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid hydrazide (**4a**) with carbon disulphide in ethanolic potassium hydroxide solution afforded the corresponding potassium 2-[(1,5-diphenyl-1*H*-pyrazole-3-yl)carbonyl]-hydrazinecarbodithioate intermediate (**6**) (Scheme 2). Treatment of the potassium salt (**6**) with hydrazine hydrate, afforded a single product (as tested by TLC) identified as 4-amino-5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**7**) according to its elemental analysis and spectral data. For example, its IR spectrum revealed absorption band in the region 3147 cm^{-1} characteristic for NH_2 group. Its mass spectrum revealed a peak at m/z 334 corresponding to its molecular ion.

When the potassium salt (**6**) was heated in pyridine, it gave only one isolable product that was identified as 5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2-thiol

Scheme 2



Scheme 3



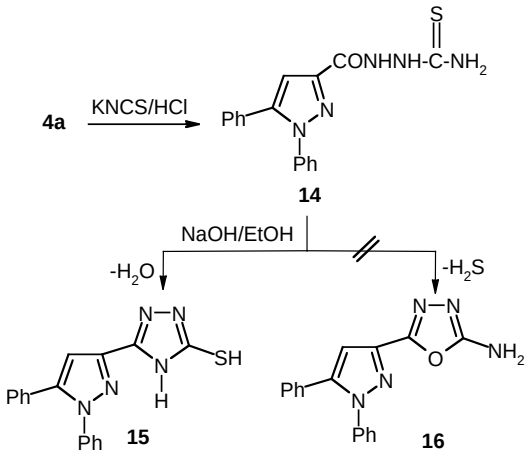
(**8**) according to its elemental analysis and spectral data. This conclusion was further supported by the chemical transformation of the latter product into 4-amino-5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**7**) by reaction with hydrazine hydrate (Scheme 2).

When the pyrazole-3-carboxylic acid hydrazide (**4a**) was treated with phenyl isothiocyanate, it afforded a single product identified as 1-(1,5-diphenyl-1*H*-pyrazole-3-carbonyl)-4-phenyl-thiosemicarbazide (**9**). Treatment of a suspension of the latter product with sodium hydroxide solution, under reflux, afforded 5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole (**10**) (Scheme 3). The structures of the isolated products were established on the basis of their elemental analysis and spectral data (see experimental part).

Treatment of the 1,2,4-triazole-3-thiol (**10**) with ethanolic solution of sodium ethoxide followed by the addition of an equimolar amount of methyl iodide, afforded 5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4-phenyl-3-methylthio-4*H*-1,2,4-triazole (**12**) (Scheme 3).

On the other hand, when the pyrazole-3-carboxylic acid hydrazide (**4a**) was treated with a solution of potassium thiocyanate in the presence of hydrochloric acid, it afforded 1-(1,5-diphenyl-1*H*-pyrazole-3-carbonyl)thio-semicarbazide (**14**) (Scheme 4). The latter product underwent an intramolecular cyclization upon treatment with sodium hydroxide to afford a single product (TLC analysis), for which the 5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiole structure (**15**) was assigned. The mass spectrum of the reaction product revealed a peak at *m/z* 319. This indicates that the thiosemicarbazide (**14**) undergoes intramolecular cyclization *via* the loss of a water molecule which supports the assigned structure (**15**) and ruled out the other possible structure (**16**) (Scheme 4).

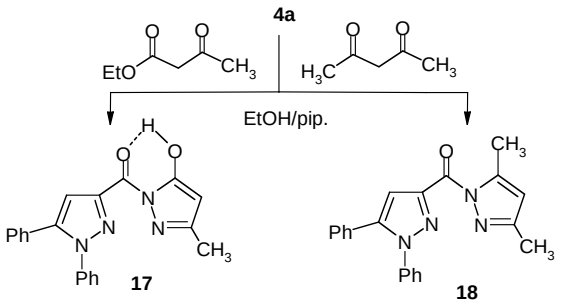
Scheme 4



Next, when the pyrazole-3-carboxylic acid hydrazide (**4a**) was treated with ethyl acetoacetate, in the presence of a catalytic amount of piperidine, it afforded a product identified as (1,5-diphenyl-1*H*-pyrazol-3-yl)-(5-hydroxy-3-metheyl-1-carbonyl)pyrazole (**17**) (Scheme 5). The IR spectrum of the isolated product revealed a characteristic carbonyl absorption band at 1650 cm^{-1}, whereas its mass spectrum revealed a peak corresponding to its molecular ion at *m/z* 344.

Similarly, the pyrazole-3-carboxylic acid hydrazide (**4a**) reacts with acetylacetone, under the same reaction condition, to afford the corresponding (1,5-diphenyl-1*H*-pyrazol-3-yl)-(3,5-dimethyl-1-carbonyl)pyrazole (**18**) (Scheme 5). The structure of the latter product was established on the basis of its elemental analysis and spectral data (see experimental part).

Scheme 5



EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP-3-300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d_6). Chemical shifts are quoted in δ and were related to that of the solvents. The mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Center of Cairo University. 5-Aryl-3*H*-furan-2-ones (**2a,b**) were prepared according to literature procedure [33,35].

3-Arylhydrazono-5-aryl-3*H*-furan-2-ones (**3a,b**).

Method A.

General Procedure: The appropriate 4-oxo-4-arylbutyric acid (**1**) (40 mmol) was added to acetic anhydride (40 mL) containing few drops (0.5 mL) of sulfuric acid and the mixture was heated on a water bath for 70 min. then allowed to cool to room temperature [33]. This solution was added dropwise with stirring to solution of the appropriate aromatic diazonium salt (40 mmol) at 0-5°C over a period of 30 min. After complete addition, the reaction mixture was allowed to stand overnight on a refrigerator and the precipitated solid was collected by filtration, washed with water and finally crystallized from ethanol/DMF to afford the corresponding hydrazone derivatives (**3a,b**).

Method B.

General Procedure: To the appropriate 5-aryl-3*H*-furan-2-one (**2**) [33,35] (10 mmol) (prepared *in situ* according to procedure A above) was added the appropriate *N*-nitrosoacylarylamine (10 mmol) [34,35]. The reaction mixture was shaken to effect complete dissolution of the reactants and then left to stand overnight at room temperature. The precipitated solid was collected by filtration, washed with water and finally crystallized from ethanol/DMF to afford products identical in all respects (mp, mixture mp and IR spectra) with those obtained from Method A above.

5-Phenyl-3-phenylhydrazono-3*H*-furan-2-one (**3a**).

Yield 67%; mp 227-228°C (lit. [35] mp 227).

5-(4-Methylphenyl)-3-(4-methylphenylhydrazono)-3*H*-furan-2-one (**3b**).

Yield 89%; mp 230-231°C; IR (KBr) ν cm^{-1} 3263 (NH), 1743 (C=O); MS, *m/z* 292 (M^+), 200, 106, 93, 77; ^{1}H NMR)DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.17-7.61 (m, 9H, furan-4CH and ArHs), 11.19 (s, br., D_2O-exchangable 1H, NH); ^{13}C NMR (DMSO-d_6): δ 164.23, 154.45, 140.84, 140.67, 131.94, 129.89, 129.43,128.88, 125.31, 124.75, 114.39, 94.80, 21.13, 20.43.

Anal. Calcd. For $C_{18}H_{16}N_2O_2$ (292.33): C, 73.96 H, 5.52; N, 9.58. Found: C, 73.6; H, 5.5; N, 9.6.

1,5-Diaryl-1*H*-pyrazole-3-carboxylic acid hydrazides (**4a,b**).

General Procedure: Hydrazine hydrate (80%, 3 mL) was added to a suspension of the appropriate 3-arylhydrazono-furanone derivative (**3**) (10 mmol) in ethanol (20 mL) and the reaction mixture was stirred at room temperature for 1 h. The color of the arylhydrazone derivative disappeared and a white deposit was formed. It was allowed to stand overnight, poured into water and the precipitate was collected by filtration, washed with water and crystallized from ethanol-water.

1,5-Diphenyl-1*H*-pyrazole-3-carboxylic acid hydrazide (**4a**).

Yield 72%; m.p. 153°C (lit. [35] mp 149-150°C).; IR (KBr) ν cm^{-1} 3286 (NH), 3210 (NH_2), 1689 (C=O); ^{1}H NMR ($CDCl_3$): δ 4.34 (s, 2H, NH_2), 8.73 (s, 1H, NH); 6.81 (s, 1H, pyrazole-4CH), 7.13-7.53 (m, 10H, ArHs); ^{13}C NMR (DMSO-d_6): δ 156.2, 148.17, 147.12, 145.3, 136.56, 129.78, 129.69, 129.45, 126.33, 120.16, 112.96, 98.48; MS *m/z* 278 (M^+), 187, 130, 93, 77.

Anal. Calcd. for $C_{16}H_{14}N_4O$ (278.31): C, 69.09; H, 5.07; N, 20.13. Found: C, 69.1; H, 5.2; N, 20.2.

1,5-Di(4-methylphenyl)-1*H*-pyrazole-3-carboxylic acid hydrazide (**4b**).

Yield 83%; mp 160°C; IR (KBr) ν cm^{-1} 3301 (NH), 3210 (NH_2), 1690 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 4.85 (s, br., D_2O-exchangable, 2H, NH_2), 8.78 (s, 1H, NH), 6.93 (s, 1H, pyrazole-4CH), 7.11-7.28 (m, 8H, ArHs); ^{13}C NMR (DMSO-d_6): 156.20, 148.17, 147.12, 145.31, 137.09, 136.56, 129.88, 129.78, 129.69, 129.45, 126.33, 120.16, 22.20, 21.52.

Anal. Calcd. for $C_{18}H_{18}N_4O$ (306.36): C, 70.57; H, 5.92; N, 18.29. Found: C, 70.6; H, 6.0; N, 18.3.

Reaction of 1,5-Diphenyl-1*H*-pyrazole-3-carboxylic acid hydrazide (**4a**) with Carbon disulfide.

A solution of potassium hydroxide (0.78 g, 20 mmol), in absolute ethanol (20 mL) and the appropriate acid hydrazide (**4a**) (2.78 g, 10 mmol) was treated by the addition of carbon disulfide (1.14 g, 15 mmol) and the mixture was stirred for 16 hours. It was then diluted with 20 mL of dry ether and the precipitated solid was collected by filtration, washed with 20 mL of ether and dried under vacuum at 65°C to afford potassium 2-[(1,5-diphenyl-1*H*-pyrazole-3-yl)carbonyl]hydrazinecarbodithioate (**6**). The latter salt was obtained in nearly quantitative yield and was used for the next reactions without further purification. Its characteristic spectral feature: IR (KBr) ν cm^{-1} 1658 (C=O), 3363 (NH).

4-Amino-5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4H-1,2,4-triazole-3-thiol (**7**).

Method A.

A suspension of the potassium salt (**6**) (3.76 g, 10 mmol), hydrazine hydrate (20 mmol, 95%) and water (2 mL) was refluxed with stirring for 3 hours. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odor) and a homogeneous solution resulted. Dilution with cold water (100 mL) and acidification with concentrated hydrochloric acid precipitated a white solid. This product was collected by filtration, washed with cold water and recrystallized from ethanol-water to afford 4-amino-5-(1,5-diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**7**); Yield 40%, mp 129°C, IR (KBr) ν cm^{-1} 3147 (NH_2), 2677 (SH); MS *m/z* 334 (M^+), 252, 170, 140, 115, 77; ^{1}H NMR ($CDCl_3$): δ 5.91 (s, br., D_2O-exchangable 2H, NH_2), 6.63 (s, 1H, pyrazole-4CH), 7.00-7.86 (m, 10H, ArHs), 13.78 (s, br, D_2O-exchangable 1H, SH); ^{13}C NMR (DMSO-d_6): δ 148.07, 144.96, 129.94, 129.33, 129.26, 129.11, 128.99, 128.73, 125.60, 118.93, 112.23, 109.36, 107.24.

Anal. Calcd. for $C_{17}H_{14}N_6S$ (334.40): C, 61.06; H, 4.22; N, 25.13; S, 9.59. Found: C, 61.1; H, 4.3; N, 25.3; S, 9.6.

Method B.

A mixture of the pyrazolyl-oxadiazole (**8**) (3.20 g, 10 mmole), and hydrazine hydrate (5 ml, 95%) in water (20 mL) was refluxed with stirring for 4 hours then diluted with cold water (200 mL), acidified by the dropwise addition of concentrated hydrochloric acid, and the solid that formed was collected by filtration. The solid that formed was washed with the least amount of cold water and recrystallization from ethanol-water (1:1). The spectra of pyrazolyl-triazole obtained by this route are superimposed on those for the same substance obtained by Method A above.

5-(1, 5-Diphenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2-thiole (**8**).

Method A.

To a solution of the hydrazide (**4a**) (2.78 g, 10 mmol) in ethanol (10 mL), a solution of carbon disulphide (1.14 g, 15 mmol) in water (3 mL) and potassium hydroxide (1 g) was added and the mixture was refluxed until the evolution of H_2S ceased (7-8 hours). The reaction mixture was allowed to cool and then acidified with dilute hydrochloric acid. The solid obtained was collected by filtration, washed with the least amount of water and recrystallized from ethanol-water (1:1).

Method B.

A mixture of the potassium salt (**6**) (3.76 g, 10 mmol) and a solution of potassium hydroxide solution (50 mL, 20%) was

refluxed for 2 hours, then allowed to cool and acidified with concentrated hydrochloric acid. The precipitate that formed was collected by filtration and washed with cold water and recrystallization from ethanol-water (1:1). Yield 50%; mp 110°C; IR (KBr) ν cm^{-1} 1600 (C=N); 2650 (SH); ^{1}H NMR (DMSO-d6): δ 6.66 (s, 1H, pyrazole-4CH), 7.11-7.42 (m, 10H, ArHs), 12.71 (s, 1H, SH); ^{13}C NMR (DMSO-d6): δ 169.07, 148.02, 145.81, 139.42, 136.95, 129.95, 129.88, 129.80, 129.62, 129.44, 129.36, 129.21, 129.97; MS *m/z* 320 (M^+), 278, 187, 130, 93, 77.

Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.37): C, 63.73; H, 3.77; N, 17.48; S, 9.99. Found: C, 63.7; H, 3.8; N, 17.5; S, 10.0.

1-(1,5-Diphenyl-1*H*-pyrazole-3-carbonyl)-4-phenylthiosemicarbazide (**9**).

A mixture of an equimolar quantity of the pyrazole acid hydrazide (**4a**) (2.78 g, 10 mmol) and phenyl isothiocyanate (10 mmol), in absolute ethanol (40 mL) was refluxed for 6 hours. On cooling to room temperature, fine crystals deposited which were collected by filtration and recrystallized from ethanol. Yield 75%; mp 198°C; IR (KBr) ν cm^{-1} 3310, 3201 (NH, NH), 1658 (C=O); ^{1}H NMR (DMSO-d_6): δ 6.8 (s, 1H, pyrazole-4CH), 7.12-7.51 (m, 15H, ArHs), 9.6 (s, br., D_2O-exchangable, 2H, 2NH), 10.5 (s, br., D_2O-exchangable, 1H, NH).

Anal. Calcd. for $C_{23}H_{19}N_5OS$ (413.50): C, 66.81; H, 4.63; N, 16.94; S, 7.75. Found: C, 66.8; H, 4.7; N, 17.0; S, 7.7.

5-(1, 5-Diphenyl-1*H*-pyrazol-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiole (**10**).

A suspension of the thiosemicarbazide (**9**) (2.07, 5 mmol) in sodium hydroxide solution (25 mL, 5%) was heated under reflux for one hour. The reaction mixture was allowed to cool, and then adjusted to pH 6 with 10% hydrochloric acid. The precipitate that formed was collected by filtration, washed with water, dried and finally recrystallized from ethanol. Yield 83%; mp 210°C; IR (KBr) ν cm^{-1} 2650 (SH), 1589 (C=N), 1496 (C=C); ^{1}H NMR (DMSO-d6): δ 6.61 (s, 1H, pyrazole-4CH), 6.99-7.54 (m, 15H, ArHs), 14.10 (s, br., D_2O-exchangable, 1H, SH). MS *m/z* 395 (M^+), 246, 198, 149, 116, 77; ^{13}C NMR (DMSO-d_6): δ 168.75, 145.22, 144.65, 143.49, 138.91, 134.93, 129.33, 129.05, 128.99, 128.95, 128.72, 128.56, 128.18, 124.70, 119.00, 113.27, 107.82.

Anal. Calcd. for $C_{23}H_{17}N_5S$ (395.49): C, 69.85; H, 4.33; N, 17.71, .S, 8.11. Found: C, 69.9; H, 4.4; N, 17.8; S, 8.2.

5-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-4-phenyl-3-methylthio-4*H*-1,2,4-triazole (**12**).

The triazole-thiol (**10**) (0.4 g, 1 mmol) was dissolved in an ethanolic solution of sodium ethoxide [prepared from sodium metal (0.023 g) in ethanol (15 mL)], then methyl iodide (0.3 g, 2 mmol) was added gradually to the resulting solution. The reaction mixture was heated under reflux for 2 hours, concentrated, cooled, diluted with water and left overnight. The precipitate obtained was collected by filtration, washed with water and recrystallized from ethanol. Yield 65%; mp 149°C; IR (KBr) ν cm^{-1} 1600 (C=N), 1498 (C=C).^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 6.74 (s, 1H, pyrazole-4CH), 6.9-7.56 (m, 15H, ArH's); ^{13}C NMR (DMSO-d_6): δ 168.52, 146.02, 145.92, 144.79, 129.13, 129.07, 128.82, 128.54, 128.35, 126.85, 126.57, 126.28, 126.12, 123.99, 123.64, 123.63.

Anal. Calcd. for $C_{24}H_{19}N_5S$ (409.51): C, 70.40; H, 4.68; N, 17.10; S, 7.83. Found: C, 70.9; H, 4.7; N, 17.2; S, 7.6.

1-(1,5-Diphenyl-1*H*-pyrazole-3-carbonyl)thiosemicarbazide (**14**).

To a solution of the hydrazide (**4a**) (2.78 g, 10 mmol) in methanol (50 mL), a solution of potassium thiocyanate (20 mmol) and hydrochloric acid (3 mL) was added with constant stirring. The mixture was immediately evaporated to dryness on a steam bath and heated for an additional hour with another 50 mL methanol. The resulting solid was treated with water and with little ethanol and finally recrystallized from ethanol. Yield 75%, mp. 150°C, IR (KBr) ν cm^{-1} 3250 (NH_2), 3310 (NH, NH) 1681 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.81 (s, br, 2H, NH_2), 6.71 (s, 1H, pyrazole-4CH), 7.05-7.37 (m, 10H, ArHs), 9.21 (s, br, 1H, NH), 10.24 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 169.81, 161.03, 142.33, 142.29, 139.99, 135.15, 129.07, 128.92, 127.86, 127.44, 126.51, 125.96, 107.87.

Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337.40): C, 60.52; H, 4.48; N, 20.76, S, 9.50. Found: C, 60.6; H, 5.0; N, 20.8; S, 9.6

5-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiole (**15**)

A suspension of the thiosemicarbazid derivative (**14**) (0.34 g, 1 mmol) in sodium hydroxide solution (10 mL, 10%) was heated under reflux for one hour. The reaction mixture was allowed to cool then adjusted to pH 6 with 10% hydrochloric acid. The precipitate that formed was collected by filtration, washed with water, dried and recrystallized from ethanol. Yield 78%; mp 173°C; IR (KBr) ν cm^{-1} 1598 (C=N); ^{1}H NMR (DMSO-d_6): δ 6.9 (s, 1H, pyrazole-4CH), 7.05-7.47(m, 10H, ArHs), 13.7 (s, 1H, NH), 13.8 (s, 1H, SH). MS *m/z* 319 (M^+), 264, 246, 116, 77, 51; ^{13}C NMR (DMSO-d_6): δ 169.31, 149.75, 146.50, 144.50, 129.22, 129.10, 128.94, 128.73, 126.77, 125.64, 124.68, 109.63, 106.46.

Anal. Calcd. for $C_{17}H_{13}N_5S$ (319.40): C, 63.93; H, 4.10; N, 21.92; S, 10.04. Found: C, 64.0; H, 4.2; N , 22.0; S, 10.0.

(1,5-Diphenyl-1*H*-pyrazol-3-yl)-(5-hydroxy-3-metheyl-1-carbonyl)-pyrazole (**17**).

To a mixture of 1,5-diphenylpyrazol-3-carboxylic acid hydrazide (**4a**) (2.78 g, 10 mmol) and ethyl acetoacetate (10 mmol) in ethanol (20 mL), piperidine (0.4 mL) was added, and the mixture was refluxed for 10 hours. The precipitated solid was collected by filtration and recrystallized from 95% ethanol. Yield 42%; mp 166°C IR (KBr) ν cm^{-1} 1650 (C=O). MS *m/z* 344 (M^+), 303, 264, 247, 105, 77. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 6.23 (s, 1H, CH pyrazole), 6.74 (s, 1H, pyrazole-4CH), 7.09-7.59 (m, 10H, ArH's), 10.8 (s, br., D_2O-exchangeable 1H, OH); ^{13}C NMR (DMSO-d_6): δ 169.47, 144.41, 143.48, 141.27, 139.79, 139.25, 133.46, 129.21, 128.67, 128.52, 128.32, 127.78, 125.50, 107.99, 95.25, 16.60.

Anal. Calcd. for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.75; H, 4.68; N, 16.27. Found: C, 69.8; H, 4.7; N, 16.3.

(1,5-Diphenyl-1*H*-pyrazol-3-yl)-(3,5-dimethyl-1-carbonyl)-pyrazole (**18**).

To a mixture of 1,5-diphenylpyrazol-3-yl-carboxylic acid hydrazide (**4a**) (2.78 g, 10 mmol) and acetylacetone (10 mmol) in ethanol (20 mL), piperidine (0.4 mL) was added, and the mixture was refluxed for 8 hours. The precipitated solid was collected by filtration and recrystallized from 95% ethanol. Yield 43%; mp 130°C; IR (KBr) ν cm^{-1} 1676 (C=O); MS *m/z* 342 (M^+), 266, 247, 219, 171, 116, 77, 51. ^{1}H NMR ($CDCl_3$): δ

2.45 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 6.61 (s, 1H, pyrazole-4CH), 6.68 (s, 1H, CH pyrazole), 7.10-7.83 (m, 10H, ArH's); ^{13}C NMR (DMSO-d_6): δ 190.02, 148.06, 145.74, 144.96, 143.30, 139.61, 133.20, 129.27, 128.99, 128.73, 128.50, 127.50.

Anal. Calcd. for $C_{21}H_{18}N4O$ (342.40): C, 73.66; H, 5.30; N, 16.36. Found: C, 73.6; H, 5.3; N, 16.4.

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