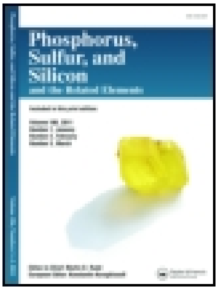


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Studies With Pyrazol-3-Carboxylic Acid Hydrazide: The Synthesis of New Pyrazolyloxadiazole and Pyrazolyltriazole Derivatives

Yehya M. Elkholy [a], Korany A. Ali [b] & Ahmad M. Farag [b]
[a] Department of Chemistry, Helwan University, Ain-Helwan, Cairo, Egypt
[b] Department of Chemistry, Cairo University, Giza, Egypt
Published online: 21 Sep 2006.

Phosphorus, Sulfur, and Silicon, 181:2037–2049, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500600605731

Studies With Pyrazol-3-Carboxylic Acid Hydrazide: The Synthesis of New Pyrazolyloxadiazole and Pyrazolyltriazole Derivatives

Yehya M. Elkholy
Department of Chemistry, Helwan University, Ain-Helwan, Cairo, Egypt

Korany A. Ali
Ahmad M. Farag
Department of Chemistry, Cairo University, Giza, Egypt

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.

Keywords 1,5-disubstituted-pyrazole-3-carboxylic acid hydrazide; pyrazolyl-1,2,4-triazoles; pyrazolyl-1,3,4-oxadiazoles

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] a CNS stimulant, antiinflammatory, hypertensive,[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 antinflammatory,[18] vasodilators[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

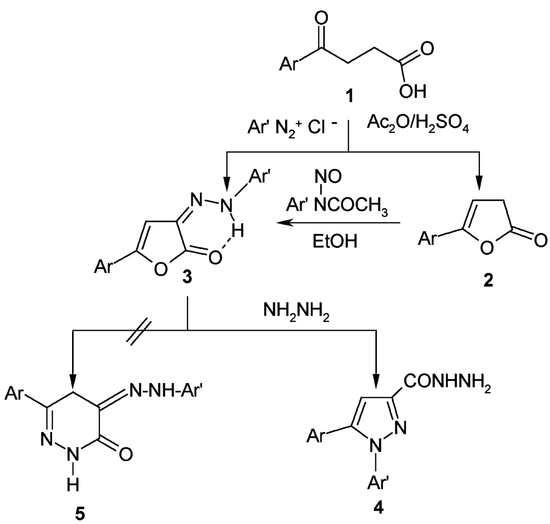
Received November 14, 2005; accepted December 9, 2005.
Address correspondence to Yehya M. Elkholy, Helwan University, Department of Chemistry, Faculty of Science, Ain-Helwan, Cairo, Egypt. E-mail: y_elkholy@yahoo.com

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 route to some new pyrazolyl-1,2,4-triazole, pyrazoly-1,3,4-oxadiazole, (1,5-diphenyl-1H-pyrazol-3-yl)-(3,5-dimethyl-1-carbonyl) pyrazole, and (1,5-diphenyl-1H-pyrazol-3-yl)-(5-hydroxy-3-metheyl-1-carbonyl) pyrazoles starting from a readily accessible 1,5-diphenyl-1H-pyrazole-3-carboxylicacidhydrazide.

RESULTS AND DISCUSSION

The treatment of 5-aryl-3H-furan-2-ones (**2a**, **b**)[33,35] (formed in situ by the 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-3H-furan-2-one derivatives (**3a**, **b**). Structures of the latter products were confirmed by the appearance of hydrazones 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 ^{1}H NMR spectra. Compounds (**3a**, **b**) were also obtained from the reaction of intermediate 5-aryl-3H-furan-2-one derivatives (**2a**, **b**) with N-nitrosoacylarylamine[34] in ethanol at r.t. (Scheme 1).

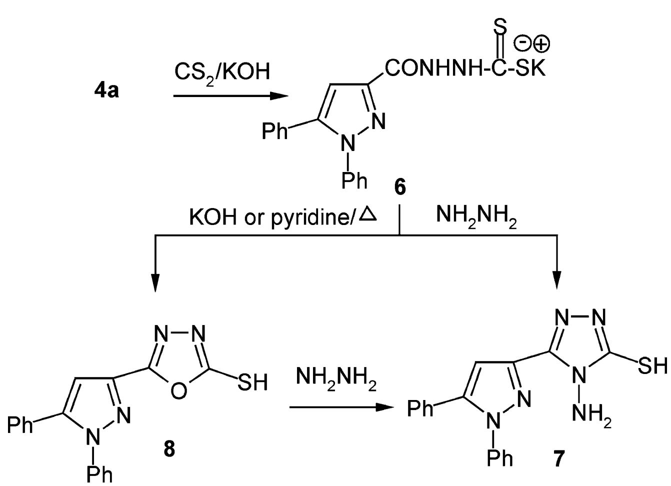


2, 3, 4, 5 a: Ar = Ar'= Ph
b: Ar = Ar'= 4-$CH_3C_6H_4$

SCHEME 1

When 3-arylhydrazono-5-aryl-3H-furan-2-one derivatives (**3a**, **b**) were treated with hydrazine hydrate, they afforded products identified as the 1,5-diaryl-1H-pyrazole-3-carboxylic acid hydrazide derivatives (**4a**, **b**), respectively (Scheme 1). Structures of the isolated products were assigned on the basis of their elemental analysis and spectral data. For example, IR spectra of the isolated products showed in each case three bands in the region 3286–3210 cm^{-1} corresponding to the NH and NH_2 groups and a carbonyl absorption band near 1689 cm^{-1}. The ^{1}H NMR spectrum of (**4a**), as an example, showed a singlet signal at δ 5.1 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 multiple 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-1H-pyridazine-6-one structure (**5**) was ruled out on the basis of IR and ^{1}H NMR spectra of the reaction products (see Experimental section).

The treatment of 1,5-diphenyl-1H-pyrazole-3-carboxylic acid hydrazide (**4a**) with carbon disulphide in ethanolic potassium hydroxide solution afforded the corresponding potassium N-(1,5-diphenyl-1H-pyrazole-3-carbonyl)-hydrazinecarbo dithioate intermediate (**6**) (Scheme 2). The treatment of the potassium salt (**6**) with hydrazine hydrate afforded a single product (as tested by TLC) identified as 4-amino-3-(1,5-diphenyl-1H-pyrazol-3-yl)-1,2,4-triazole-5-thiol (**7**) according to its elemental analysis and spectral data. For example, its IR spectrum revealed an absorption band in the region 3147 cm^{-1} characteristic

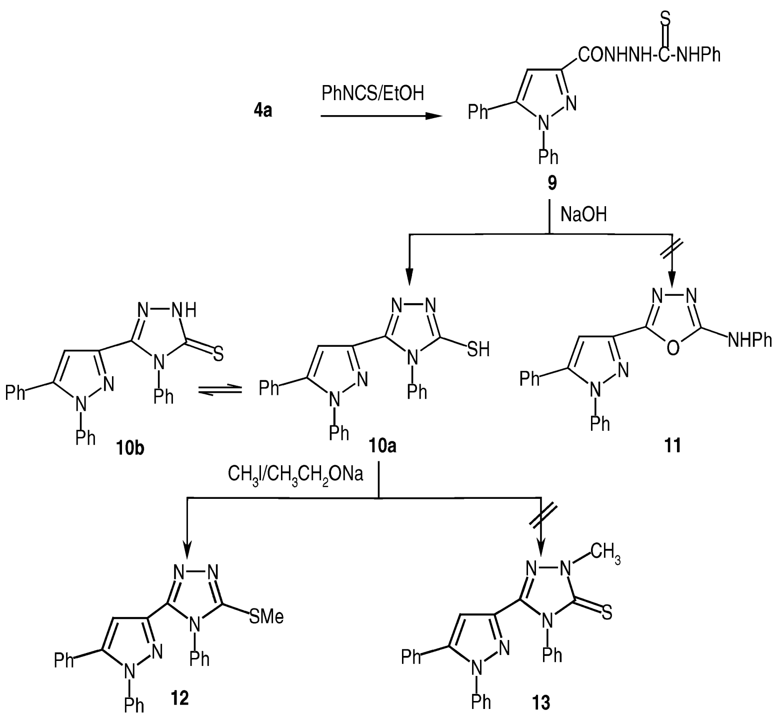


SCHEME 2

for a 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-1H-pyrazol-3-yl)-1,3,4-oxadiazole-2-thiol (**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-3-(1,5-diphenyl-1H-pyrazol-3-yl)-1,2,4-triazole-5-thiol (**7**) by a reaction with hydrazine hydrate (Scheme 2).

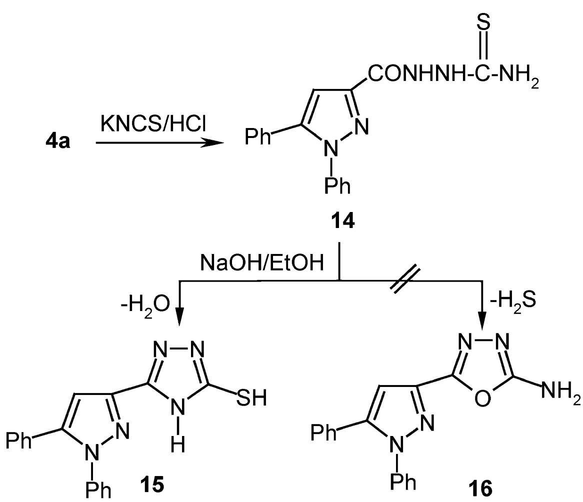
When pyrazole-3-carboxylic acid hydrazide (**4a**) was treated with phenyl isothiocyanate, it afforded a single product identified as 1-(1,5-diphenyl-1H-pyrazole-3-carbonyl)-4-phenylthiosemicarbazide (**9**). The treatment of a suspension of the latter product with sodium hydroxide solution, under reflux,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



SCHEME 3

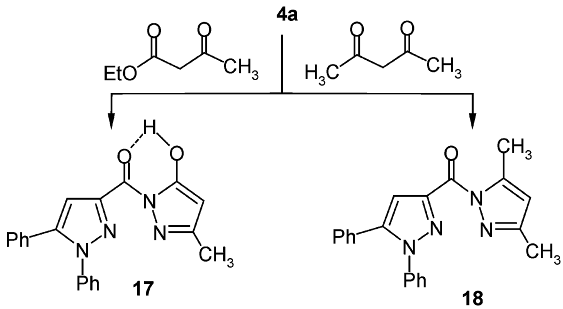
The treatment of the 1,2,4-triazole-5-thiol (**10**) with ethanolic solution of sodium ethoxide followed by the addition of an equimolar amount of methyl iodide afforded 3-(1,5-diphenyl-1H-pyrazol-3-yl)-4-phenyl-5-methylthio-4H-1,2,4-triazole (**12**) (Scheme 3).

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-1H-pyrazole-3-carbonyl)thiosemicarbazide (**14**) (Scheme 4). The latter product underwent an intermolecular cyclization upon treatment with sodium hydroxide to afford a single product (TLC analysis) for which the 3-(1,5-diphenyl-1H-pyrazol-3-yl)-4H-1,2,4-triazole-5-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 intermolecular 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 piper dine, it afforded a product identified as (1,5-diphenyl-1H-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 345.



SCHEME 5

Similarly, the pyrazole-3-carboxylic acid hydrazide (**4a**) reacts with acetyl acetone, under the same reaction condition, to afford the corresponding (1,5-diphenyl-1H-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 section).

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 spectrophotometers. NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{1}H NMR 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. Mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Micro-Analytical Center of Cairo University, Egypt. 5-aryl-3H-furan-2-ones (**2a**, **b**) were prepared according to the literature procedure.[33,35]

3-Arylhydrazono-5-aryl-3H-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 a few drops (0.5 mL) of sulfuric acid, and the mixture was heated on a water bath for 70 min and then allowed to cool to r.t.[33] This solution was added dropwise with stirring to a solution of the appropriate aromatic diazonium salt (40 mmol) at 0–5°C over a period of 30 min. After the 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-3H-furan-2-one (**2**)[33,35] 10 mmol (prepared in situ according to method A) the appropriate N-nitrosoacylarylamine[34,35] (10 mmol) was added. The reaction mixture was shaken to effect a complete dissolution of the reactants and then left to stand overnight at r.t. The precipitated solid was collected by filtration, washed with water, and finally crystallized from ethanol/DMF to afford products identical in all respects (m.p., mixture m.p., and IR spectra) with those obtained from Method A. 5-phenyl-3-phenylhydrazono-3H-furan-2-one (3a): Yield 67%; m.p. 227–228°C (lit.[35] m.p. 227).

5-(4-Methylphenyl)-3-(4-methylphenylhydrazono)-3H-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) CDCl3): δ 3.07 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 5.76 (s, 1H, furan-H-4), 7.17–7.61 (m, 8H, ArHs), 10.92 (s, br, D_2O-exchangable 1H, NH). Calcd. for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.52; H, 5.52; N, 9.58. Found: C, 73.6; H, 5.5; N, 9.6.

1,5-Diaryl-1H-pyrazole-3-carboxylic Acid Hydrazides (4a,b)

General Procedure

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

1,5 -Diphenyl-1H-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); 5.1 (s, 1H, 4-CH pyrazole), 7.13–7.53 (m, 10H, ArHs); ^{13}C NMR (DMSO-d6): δ 156.2, 148.17, 147.12,145.3, 136.56, 129.78, 129.69, 129.45, 126.33, 120.16; MS m/z 278 (M^+), 187, 130, 93, 77. Calcd. for $C_{16}H_{14}N_4O$ (278.31): C, 69.09; H, 5.07; N, 20.1. Found: C, 69.1; H, 5.2; N, 20.2.

1,5-Di(4-methylphenyl)-1H-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, CH3), 3.12 (s, 3H, CH3), 4.85 (s, br. D_2O-exchangable, 2H, NH_2), 8.78(s, 1H, NH), 6.93 (s, 1H, 4-CH pyrazole), 7.11–7.28 (m, 8H, ArHs); ^{13}C NMR (DMSO-d6): 156.2, 148.17, 147.12, 145.3, 136.56, 129.78, 129.69, 129.45, 126.33, 120.16, 40.20, 38.52. 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.

The Reaction of 1,5-Diphenyl-1H-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 h. It was then diluted with 20 mL of dry ether, and the precipitated solid was filtered off, washed with 20 mL of ether, and dried under vacuum at 65°C to afford potassium N′-(1,5-diphenyl-1H-pyrazole-3-carbonyl)-hydrazine carbodithioate (6). The latter salt was obtained in a nearly quantitative yield and was used for the next reactions without further purification. Its characteristic spectral feature: IR (K Br) ν cm^{-1} 1658 (C=O), 3363 (NH).

4-Amino-3-(1,5-diphenyl-1H-pyrazol-3-yl)-1,2,4-triazole-5-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 h. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odder), and a homogeneous solution resulted. Dilution with cold water (100 mL) and acidification with concentrated hydrochloric acid precipitated a white solid. This product was filtered off, washed with cold water, and recrystallized from ethanol-water to afford 4-amino-3-(1,5-diphenyl-1H-pyrazol-3-yl)-1,2,4-triazole-5-thiol (**7**).

Yield 40%, mp 129°C, IR (KBr) ν cm^{-1} 3147 (NH_2); MS m/z 334 (M^+), 252, 170, 140, 115, 77; ^{1}H NMR ($CDCl_3$): δ 3.81 (s, br, D_2O-exchangable 2H, NH_2), 5.71 (s, 1H, CH pyrazole), 7.20–7.18 (m, 10H, ArHs), 13.78 (s, br, D_2O-exchangable 1H, SH). Calcd. for $C_{17}H_{14}N_6S$ (334.44): 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 pyrazolo-oxadiazole (**8**) (3.20 g, 10 mmole), and hydrazine hydrate (5 mL, 95%) in water (20 mL) was refluxed with stirring for 4 h, diluted with cold water (200 mL), acidified by the dropwise addition of concentrated hydrochloric acid, and filtered off. The solid that formed was washed with the least amount of cold water and recrystallization from ethanol-water (1:1). The spectra of pyrazolotriazole obtained by this route were superimposed on those for the same substance obtained by Method A.

5-(1,5-Diphenyl-1H-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 evaluation of H_2S ceased (7–8 h). The reaction mixture was allowed to cool and then acidified with dilute hydrochloric acid. The solid that was 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 h, 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-4-H), 7.11–7.42 (m, 10H, ArHs), 12.71 (s, 1H, SH); ^{13}C NMR (DMSO-d6): δ148.02, 147.42, 145.81, 139.42, 136.95, 129.95, 129.88, 129.80, 129.62, 129.44, 129.36, 129.21, 129.97, 129.70, 126.36; MS m/z 320 (M^+), 278, 187, 130, 93, 77. 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-1H-pyrazole-3-carbonyl)-4-phenylthiosemicarbazide (9)

A mixture of an equimolecular 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 h. On cooling to r.t., fine crystals deposited that were filtered off 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, CH-pyrazole), 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). 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.

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

A suspension of the thiosemicarbazide (**9**) (2.07, 5 mmol) in sodium hydroxide solution (25 mL, 5%) was heated under reflux for 1 h. The reaction mixture was allowed to cool and then adjusted to pH 6 with 10% hydrochloric acid. The precipitate that formed was filtered off, washed with water, dried, and finally recrystallized from ethanol.

Yield 83%; mp 210°C; IR (KBr) ν cm^{-1} 1589 (C=N), 1496 (C=C), 2650 (SH);^{1}H NMR (DMSO-d6): δ 6.61 (s, 1H, CH-pyrazole), 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. 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.

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

The mercaptotriazole (**10**) (0.4 g, 1 mmol) was dissolved in an ethanolic solution of sodium ethoxide [prepared from sodium metal (0.023 g, 1 mg atom) in ethanol (15 mL)]; then methyl iodide (0.3 gm, 2 mmol) was added gradually to the resulting solution. The reaction mixture was heated under reflux for 2 h, concentrated, cooled, diluted with water, and left overnight. The precipitate that obtained was filtered off, 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 2.7 (s, 3H, CH_3), 4.8 (s, 1H, CH), 6.9–7.35 (m, 15H, ArH's). Calcd. for $C_{24}H_{19}N_5S$ (409.45): 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-1H-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 of 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} 3310 (NH,NH), 3250 (NH_2), 1681 (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.81 (s, br, 2H, NH_2), 5.51 (s, 1H, CH pyrazole), 6.63 (s, 1H, NH), 7.05–7.37 (m, 10H, ArHs), 9.21 (s, br, 1H, NH). Calcd. for $C_{17}H_{15}N_5OS$ (337.40): C, 60.52; H, 4.98; N, 20.76, S, 9.50. Found: C, 60.6; H, 5.0; N, 20.8; S, 9.6.

3(1,5-Diphenyl-1H-pyrazol-3-yl)-4H-1,2,4-triazole-5-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 1 h. The reaction mixture was allowed to cool and then adjusted to pH 6 with 10% hydrochloric acid. The precipitate that formed was filtered off, 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, CH-pyrazole), 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. 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-1H-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), piperdine (0.4 mL) catalysis (basic medium) was added, and the mixture was refluxed for 10 h. The precipitated solid was filtered off and recrystallized from dilute ethanol 95%.

Yield 42%; mp 166°C IR (KBr) ν cm^{-1} 1695 (C=O). MS m/z 344 (M^+), 303, 264, 247, 105, 77. ^{1}H-NMR ($CDCl_3$): δ 1.68 (s, 3H, CH_3), 4.48 (s, 1H, 4-H pyrazole), 5.4 (s, 1H, CH pyrazole), 7.09–7.59 (m, 10H, ArH's), 10.8 (s, br, D_2O-exchangeable 1H, OH). 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-1H-pyrazol-3-yl)-(3,5-dimethyl-1-carbonyl)pyrazole (18)

To a mixture of 1,5-diphenylpyrazol-3yl-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 h. The precipitated solid was filtered off and recrystallized from dilute 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. 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.

CONCLUSION

A simple method for the synthesis of some new 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 of potential biological activity has been developed.

REFERENCES

[1] C. Derappe, R. Rips, O. Albert, and M. Aurousseau, *Chim. Ther.*, **3,** 181 (1968). *Chem. Abstr.* **69,** 106626y (1968).
[2] A. A. Deshmukh, P. B. Sattur, and U. K. Sheth, *Indian. J. Exp. Biol.*, **4,** 166 (1976).
[3] J. B. Ó Neal, H. Rosen, P. B. Russel, A. C. Adams, and A. Blumenthal, *J. Med. Pharm. Chem.*, **5,** 617 (1962). *Chem. Abstr.*, **57,** 9168c (1962).
[4] F. Kurzer, *Org. Compd. Sulphur, Selenium, Tellurium*, **4,** 417 (1974).
[5] J. Thomas, *Ger. Pat.* **2,** 403, 357 (1974); *Chem. Abstr.*, **81**, 136153g (1974).
[6] H. L. Yale and K. Losee, *J. Med. Chem.*, **9,** 478–483 (1966).
[7] S. Turner, Reckitt and Colman Products Ltd., Ger. Pat. 2, 727,146 (1978); *Chem. Abstr.*, **88,** 105357, (1978).
[8] I. Chiyomaru, K. Takita, and H. Ito, Kumiai Chem. Ind. Co. Ltd., Jap. Pat. 72; 07, 549 (1972); *Chem. Abstr.*, **77,** 549 (1972).
[9] K. Hiroshi, H. Isaq, and O. Shigeki, *Zassokenkyn* ,**8**, 46 (1969); *Chem. Abstr.*, **73,** 108544b (1970).
[10] A. K. Sen Gupta, M. Garg, and U. Chandra, *J. Indian Chem. Soc.*, **56,** 1230 (1979).
[11] Hodogaya Chemical Co. Ltd., Jap. Pat. **1980**, 80 27,024; *Chem. Abstr.*, **93,** 232719q (1980).
[12] Hakko Chem. Ind. Co. Ltd., Brit. Pat. 1,266,542 (1972); *Chem. Abstr.***77,** 5474g (1972).
[13] H. Singh, and L. D. S. Yadav, *Agric. Biol. Chem.*, **40,** 759 (1976).
[14] T. Misato, K. Ko, Y. Honma, K. Konno, and E. Taniyama, *Inst. Phys. Chem. Res. Jap. Pat.* 772 508 (1977); *Chem. Abstr.* **87,** 147054 (1977).
[15] B. Tozkoparan, N. Gökhan, G. Aktay, E. Yelilada, and M. Ertan, *Eur. J. Med. Chem.*, **35,** 743 (2000).
[16] N. Demirbas, R. Ugurluoglu, and A. Demirbas, *Bioorg Med Chem.*, **10,** 3717 (2002).

[17] G. Turan-Zitouni, M. Sıvacı, F. S. Kelıç, and K. Erol, *Eur. J. Med. Chem.*, **36,** 685 (2001).

[18] M. Tandon, J. P. Bartwal, T. N. Bahalla, and K. P. Bhargava, *Indian J. Chem.*, **20,** 1017 (1981).

[19] E. Tenor, and R. Ludwig, *Pharmazie*, 534, (1971).

[20] A. Baiocchi, A. Chiari A. Frigerio, and P. Ridolfi, *Arzneim-Forsch*, 400 (1973).

[21] K. M. Dawood, A. M. Farag, and H. A. Abdelaziz, *J. Chem. Res.*, 378 (2005).

[22] Y. M. Elkholy, *Heterocyclic Commun.*, **11,** 89 (2005).

[23] K. M. Dawood, A. M. Farag, and H. A. Abdelaziz, *Heteroatom Chem*. **16,** (2005).

[24] A. M. Farag, K. M. Dawood, and H. A. Elmenoufy *Heteroatom Chem.*, **15,** 508 (2004).

[25] A. M. Farag, K. M. Dawood, and H. A. Abdel-Aziz, *J. Chem. Res.*, 808 (2004).

[26] K. M. Dawood, E. A. Ragab, and A. M. Farag, *J. Chem. Res.*, **(S), 685,** 1151 (2003).

[27] K. M. Dawood, M. A. Raslan, and A. M., Farag, *Synth. Commun.*, **33,** 4095 (2003).

[28] A. Z. Elassar and Y. M. Elkholy, *Heteroatom Chem.*, **14,** 427 (2003).

[29] Z. E. Kandeel, K. M. Dawood, E. A. Ragab, and A. M. Farag, *Heteroatom Chem.*, **13,** 248 (2002).

[30] Y. M. Elkholy, *Phosph., Sulfur, and Silicon.*, **177,** 2661 (2002).

[31] K. M. Dawood, A. M. Farag, E. A. Ragab, and Z. E. Kandeel, *J. Chem. Res*. (S) **206,** 622 (2000).

[32] P. Vainilavicius, R. Smicius, and V. Jakubkiene, *Monatsch. Chem.*, **132,** 825 (2001).

[33] A. Tsolomitis and C. Sandris, *J. Heterocyclic Chem.*, **20,** 1253 (1983).

[34] W. Hickinbottom, *J. Reactions of Organic Compounds*, p 336 (Wiley, New York, 1962).

[35] S. A. Khattab, A. S. Shawali, and A. M. Farag, *J. Chem. Eng. Data*, **22,** 104 (1977).