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2-Cyano-*N*′-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]acetohydrazide in the Synthesis of Nitrogen Heterocycles

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Abstract—Some interesting nitrogen heterocycles, as well as other products, were synthesized by reactions of 2-cyano-*N*′-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]acetohydrazide with phenyl isothiocyanate/elemental sulfur, 3,4,5-trimethoxybenzaldehyde, 4-hydroxy-1,1′-biphenyl-3-carbaldehyde, 2-oxoquinoline-3-caraldehyde, triethyl orthoformate, ethyl cyanoacetate, and thiosemicarbazide. The structures of all isolated compounds were established from their analytical and spectral data.

Keywords: 1,3-diphenylpyrazole, thiazolidine, chromene, pyridine, quinolinone.

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Pyrazoles are synthetically versatile substrates that display diverse biological and pharmacological properties [1–6]. Several compounds containing a pyrazole moiety have been reported to possess antibacterial, antifungal, anticonvulsant, anti-inflammatory, and anti-HIV activities. Among a number of commercially availble substituted hydrazines, 2-cyanoacetohydrazide is a versatile and convenient intermediate product for the synthesis of a wide variety of heterocyclic compounds. Herein, we report the synthesis of some nitrogen heterocycles containing a pyrazole moiety starting from cyanoacetohydrazide and 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde.

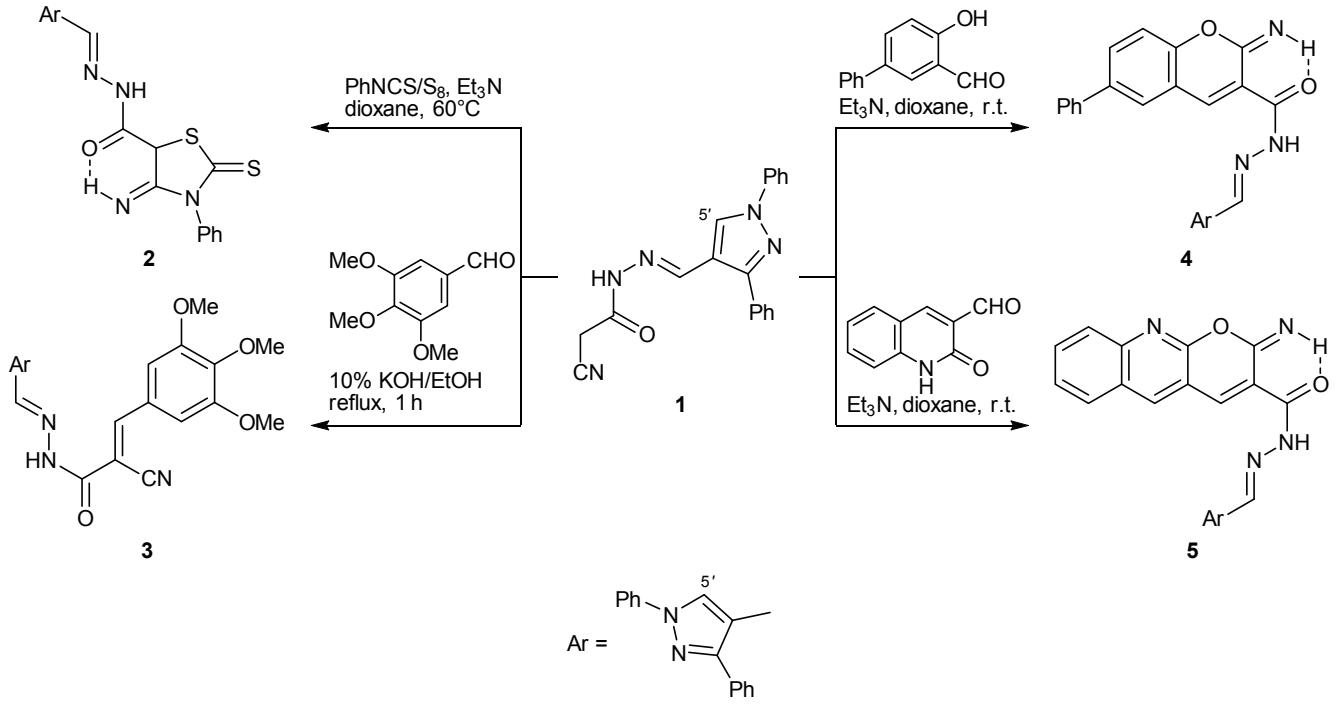
In continuation of our previous work [1–3, 5–10] and as a part of our program focusing on the synthesis of some valuable heterocyclic compounds with anticipated biological activity, 2-cyano-*N*′-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]acetohydrazide (**1**) [11] was selected as starting material to build up some biologically active *N*-heterocycles. The carbonyl and cyano functions in molecule **1** are suitably situated to enable reactions with common reagents to construct a variety of *N*-heterocyclic compounds. In addition, the active methylene group of **1** can be involved in condensation and substitution reactions.

Indeed, the cyclocondensation of **1** with phenyl isothiocyanate and elemental sulfur in the presence of triethylamine as a base led to the formation of thiazolidine derivative **2** (Scheme 1). The structure of **2** was inferred from its analytical and spectral data. The IR spectrum revealed the absence of C≡N group and the presence of characteristic absorption bands due to C=O, C=N, and C=S stretchings. The ^{1}H NMR spectrum of **2** was consistent with the assigned structure. The Knoevenagel condensation of **1** with 3,4,5-trimethoxybenzaldehyde in 10% ethanolic potassium hydroxide under reflux afforded α,β-unsaturated carbonyl compound **3** (Scheme 1). The IR spectrum of **3** exhibited absorption bands due to NH, C≡N, and C=O groups. The reduced C≡N stretching frequency (in comparison to **1**) was attributed to conjugation with the C=C double bond. Treatment of **1** with 5-phenylsalicylaldehyde and 2-oxoquinoline-3-carbaldehyde in the presence of triethylamine led to the formation of chromenone **4** and pyranoquinoline derivative **5**, respectively (Scheme 1). The IR spectra of compounds **4** and **5** lacked C≡N stretching band (see Experimental).

It seemed interesting that the reaction of **1** with triethyl orthoformate led to the formation of triazepinone derivative **7** instead of expected condensation product **6** (Scheme 2). The structure of **7** was deduced from its analytical and spectral data. The IR spectrum of **7** showed OH, C≡N, C=O, and C=N absorption bands. The ^{1}H NMR spectrum displayed an upfield singlet from the methine proton and was devoid of triplet and quartet signals typical of ethyl group, which ruled out structure **6**. Scheme 3 outlines a plausible mechanism for the formation of compound **7**.

The reaction of **1** with ethyl cyanoacetate in boiling DMF in the presence of triethylamine furnished dihy-

Scheme 1.

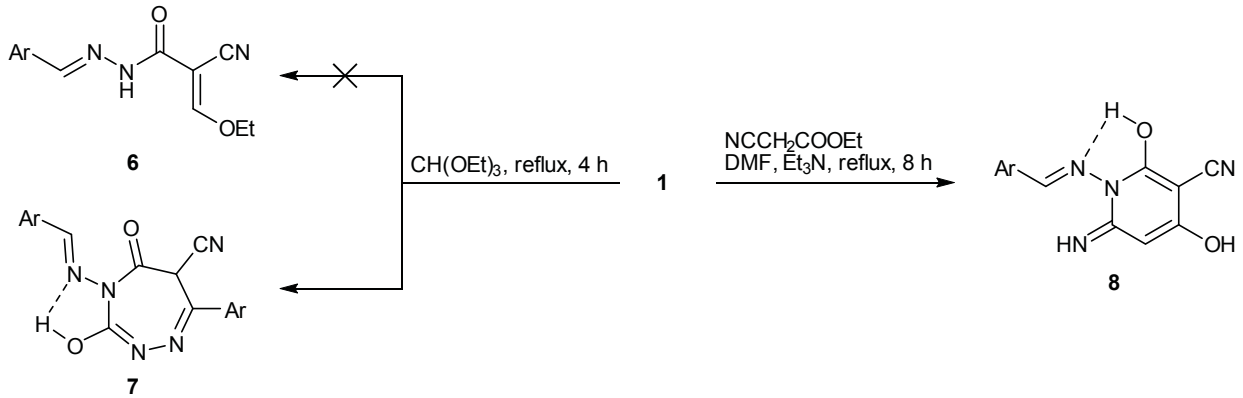


droxypyridine derivative **8** (Scheme 2). The IR spectrum of compound **8** lacked absorption bands assignable to C=O and NH_2 groups, and three D_2O-exchangeable one-proton singlets were observed in the ^1H NMR spectrum due to two OH protons and one NH proton. The formation of compound **8** could be explained by Scheme 4.

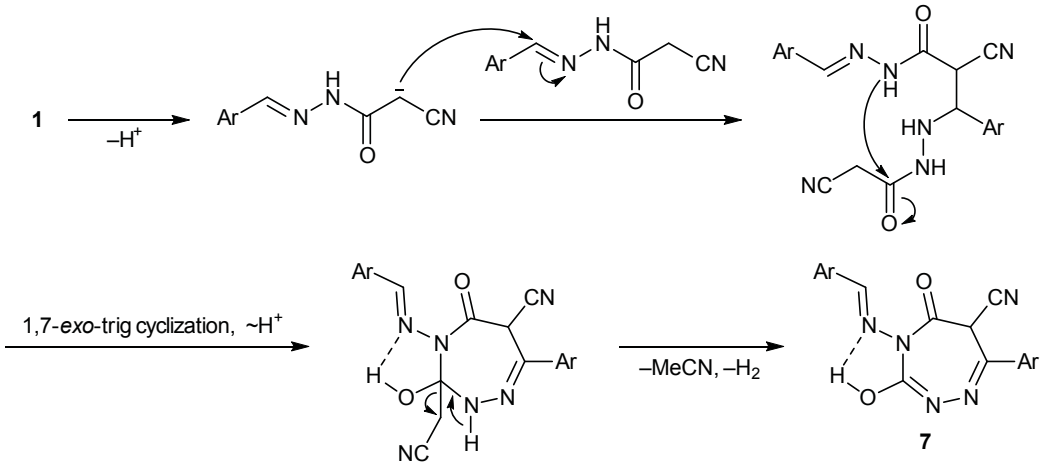
Treatment of **1** with acetyl chloride afforded pyrazolone **9** which was obtained previously by cyclization of **1** in ethanol under reflux in the presence of a few drops of piperidine [11] (Scheme 5). Treatment of **9** with phosphorus pentasulfide in refluxing toluene gave pyrazolethione derivative **10** (Scheme 5). The structure of compound **10** was determined from its analytical and spectral data. The IR spectrum displayed the absence of carbonyl absorption, but absorption bands for NH, C≡N, and C=S groups were present. Compound **10** was converted to *N*-chloroacetyl derivative **11** by treatment with chloroacetyl chloride in dioxane containing few drops of triethylamine at room temperature (Scheme 5). The IR spectrum of compound **11** showed C=O stretching band at 1694 cm^{-1}, whose increased frequency may be attributed to field effect of the chlorine atom.

In the reaction of hydrazone **1** with thiosemicarbazide we isolated thiosemicarbazone **13** instead of the expected cyclization product, aminothiadiazole **12** (Scheme 6). The structure of **13** was supported by spectral data, as well as by direct comparison with

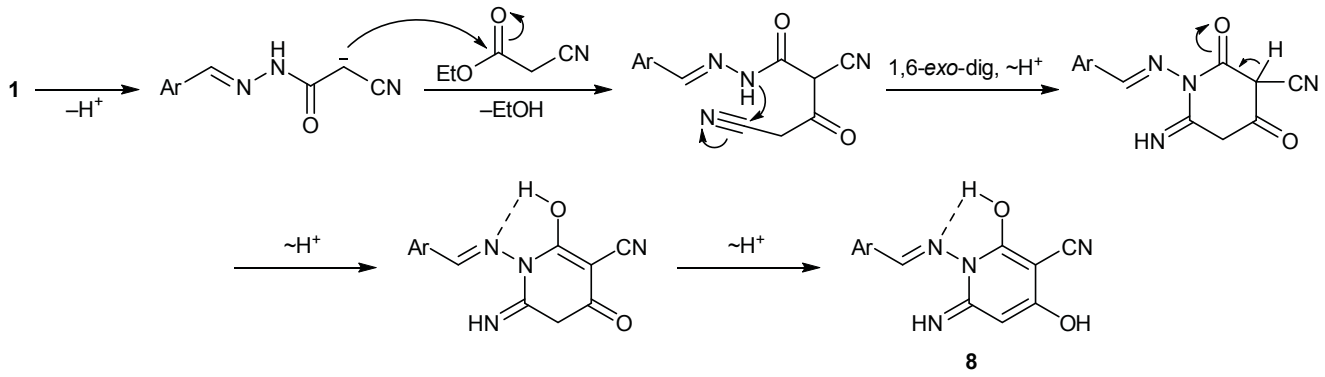
Scheme 2.



Scheme 3.



Scheme 4.



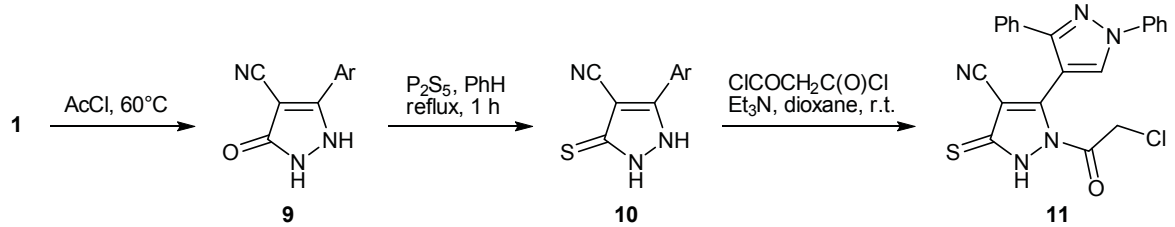
an authentic sample prepared by the condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with thiosemicarbazide in refluxing dioxane [1]. Presumably, compound **13** is formed via nucleophilic attack of the free NH_2 group of thiosemicarbazide on the CH=N carbon atom of **1**, followed by elimination of 2-cyanoacetohydrazide.

In summary, we have synthesized and characterized some nitrogen-containing heterocycles of the thiazolidine, chromenone, pyranoquinoline, and pyridine series with potential biological activity using 2-cyano-*N*′-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]acetohydrazide as the key building block.

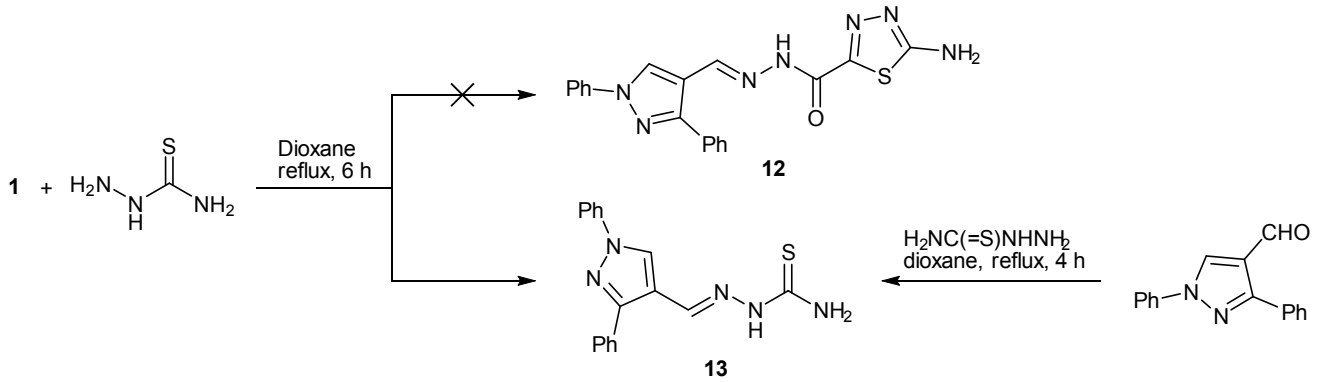
EXPERIMENTAL

All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra were recorded using KBr disks on a Thermo Electron Nicolet iS10 spectrometer (USA) at the Chemistry Department Laboratory, Faculty of Science, Ain Shams University. The ^{1}H NMR spectra were run at 400 MHz on a Bruker spectrometer (USA) using tetramethylsilane as internal standard and DMSO-d_6 as solvent at the Faculty of Pharmacy, Ain Shams University. Elemental analyses were carried out at the microanalytical unit, Cairo University, Giza,

Scheme 5.



Scheme 6.



Egypt. The reactions were monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} analytical sheets (Fluka).

***N*′-[(1,3-Diphenyl-1*H*-pyrazol-4-yl)methylidene]-4-imino-3-phenyl-2-sulfanylidene-5-carbohydrazide (2).** Phenyl isothiocyanate (2 mmol) and elemental sulfur (2 mmol) were added to a solution of hydrazide **1** (2 mmol) in *N*,*N*-dimethylformamide (10 mL) containing triethylamine (0.5 mL). The mixture was heated at 60°C for 5 h with continuous stirring. After cooling, the mixture was acidified with cold 10% aqueous HCl, and the separated solid was collected by filtration, washed several times with water, dried, and recrystallized from petroleum ether (bp 60–80°C)–benzene (1:1). Yield 63%, yellow crystals, mp 200–202°C. IR spectrum, ν, cm^{-1}: 3445, 3209 (NH), 1686 (C=O), 1631 (C=N), 1245 (C=S). ^{1}H NMR spectrum, δ, ppm: 11.61 s (1H, =NH, exchangeable), 11.36 s (1H, NHCO, exchangeable), 9.02 s (1H, CH=N), 8.76 s (1H, 5′-H), 8.27–7.16 m (15H, Ph), 4.12 s (1H, CH). Found, %: C 62.64; H 3.89; N 16.95. $C_{26}H_{20}N_6OS_2$. Calculated, %: C 62.88; H 4.06; N 16.92.

2-Cyano-*N*′-[(1,3-diphenyl-1*H*-pyrazol-4-yl)-methylidene]-3-(3,4,5-trimethoxyphenyl)prop-2-enehydrazide (3). 3,4,5-Trimethoxybenzaldehyde (2 mmol) was added to a solution of **1** (2 mmol) in 10% ethanolic KOH (10 mL), and the mixture was refluxed for 1 h. After cooling, the precipitate was collected by filtration, washed with ethanol, dried, and recrystallized from dioxane. Yield 69%, beige crystals, mp >360°C. IR spectrum, ν, cm^{-1}: 3416 (NH), 2206 (C≡N), 1650 (C=O), 1617 (C=N). ^{1}H NMR spectrum, δ, ppm: 11.84 s (1H, NH, exchangeable), 9.12 s (1H, CH=N), 9.03 s (1H, 5′-H), 7.88–7.20 m (13H, H_{arom}, CH=). Found, %: C 68.42; H 4.79; N 13.78. $C_{29}H_{25}N_5O_4$. Calculated, %: C 68.63; H 4.97; N 13.80.

Compounds 4 and 5 (*general procedure*). A solution of **1** (2 mmol) and 4-hydroxy-1,1′-biphenyl-3-carbaldehyde or 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2 mmol) in dioxane (20 mL) containing 2 drops of piperidine was stirred at room temperature for 3 h. The solid product was filtered off and recrystallized from an appropriate solvent.

***N*′-[(1,3-Diphenyl-1*H*-pyrazol-4-yl)methylidene]-2-imino-6-phenyl-2*H*-chromene-3-carbohydrazide (4).** Yield 67%, orange crystals, mp 238–240°C (from benzene). IR spectrum, ν, cm^{-1}: 3442 (NH, H-bonded), 1682 (C=O), 1628 (C=N). ^{1}H NMR spectrum, δ, ppm: 11.33 s (1H, =NH, exchangeable), 11.21 s (1H, NHCO, exchangeable), 9.16 s (1H, CH=N), 9.10 s (1H, 5′-H), 8.97 s (1H, 4-H), 8.81 s (1H, 5-H), 8.02–6.84 m (17H, H_{arom}). Found, %: C 75.30; H 4.41; N 13.79. $C_{32}H_{23}N_5O_2$. Calculated, %: C 75.43; H 4.55; N 13.74.

***N*′-[(1,3-Diphenyl-1*H*-pyrazol-4-yl)methylidene]-2-imino-2*H*-pyrano[2,3-*b*]quinoline-3-carbohydrazide (5).** Yield 57%, yellow crystals, mp 275–277°C (from EtOH–dioxane, 1:1). IR spectrum, ν, cm^{-1}: 3419 (NH, H-bonded), 1650 (C=O), 1616 (C=N). ^{1}H NMR spectrum, δ, ppm: 11.34 s (1H, =NH, exchangeable), 11.23 s (1H, NHCO, exchangeable), 9.17 s (1H, CH=N), 9.13 s (1H, 5′-H), 8.95 s (1H, 4-H), 8.84 s (1H, 5-H), 8.00–7.02 m (14H, H_{arom}). Found, %: C 71.61; H 3.89; N 17.30. $C_{29}H_{20}N_6O_2$. Calculated, %: C 71.89; H 4.16; N 17.35.

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-{[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]amino}-3-hydroxy-5-oxo-5,6-dihydro-4*H*-1,2,4-triazepine-6-carbonitrile (7). A suspension of **1** (2 mmol) in triethyl orthoformate (5 mL) was refluxed for 3 h. Excess solvent was evaporated under rediced pressure, the residue was triturated with light petroleum, and the

precipitate was filtered off and recrystallized from ethanol–dioxane (1:1). Yield 76%, yellow crystals, mp 306–308°C. IR spectrum, ν, cm^{-1}: 3422 (OH), 2207 (C≡N), 1679 (C=O), 1614 (C=N). ^{1}H NMR spectrum: 11.75 s (1H, OH, exchangeable), 9.28 s (1H, CH=N), 8.98 s (1H, 5′-H), 8.77 s (1H, 5″-H), 8.14–7.30 m (20H, H_{arom}), 3.59 s (1H, CH). Found, %: C 69.97; H 3.87; N 20.42. $C_{36}H_{25}N_9O_2$. Calculated, %: C 70.23; H 4.09; N 20.48.

1-{[(1,3-Diphenyl-1*H*-pyrazol-4-yl)methylidene]-amino}-2,4-dihydroxy-6-imino-1,6-dihydropyridine-3-carbonitrile (8). Ethyl cyanoacetate (2 mmol) was added to a solution of **1** (2 mmol) in DMF (10 mL) containing 2 drops of triethylamine, and the mixture was refluxed for 8 h. After cooling, the mixture was acidified with cold 10% aqueous HCl, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 55%, yellow crystals, mp 250–252°C. IR spectrum, ν, cm^{-1}: 3335 br (OH, NH), 2217 (C≡N), 1628 (C=N). ^{1}H NMR spectrum, δ, ppm: 11.87 s (1H, NH, exchangeable), 10.71 br.s (2H, OH, exchangeable), 9.09 s (1H, CH=N), 9.01 s (1H, 5′-H), 7.85–7.14 m (11H, H_{arom}, 5-H). Found, %: C 66.42; H 3.81; N 21.18. $C_{22}H_{16}N_6O_2$. Calculated, %: C 66.66; H 4.07; N 21.20.

Cyclization of compound 1. A solution of hydrazone **1** (2 mmol) in acetyl chloride (5 mL) was heated at 60°C for 2 h. Excess acetyl chloride was evaporated, the residue was triturated with light petroleum, and the precipitate was recrystallized from dioxane. The product was identified as 5-oxo-1′,3′-diphenyl-2,5-dihydro-1*H*,1′*H*-[3,4′-bipyrazole]-4-carbonitrile (**9**); yellow crystals, mp 250–252°C; published data [11]: mp 247–248°C.

1′,3′-Diphenyl-5-sulfanylidene-2,5-dihydro-1*H*,1′*H*-[3,4′-bipyrazole]-4-carbonitrile (10). A mixture of **9** (2 mmol) and phosphorus pentasulfide (1 mmol) in anhydrous toluene (10 mL) was refluxed for 1 h. The precipitate was filtered off from the hot mixture and recrystallized from toluene. Yield 71%, yellow crystals, mp 240–242°C. IR spectrum, ν, cm^{-1}: 3417 (NH), 2209 (C≡N), 1623 (C=N), 1235 (C=S). ^{1}H NMR spectrum, δ, ppm: 11.82 s (1H, NHCS, exchangeable), 8.01 s (1H, NH, exchangeable), 9.11 s (1H, 5′-H), 7.95–7.15 m (10H, H_{arom}). Found, %: C 66.27; H 3.65; N 20.35. $C_{19}H_{13}N_5S$. Calculated, %: C 66.45; H 3.82; N 20.39.

2-(2-Chloroacetyl)-1′,3′-diphenyl-5-sulfanylidene-2,5-dihydro-1*H*,1′*H*-[3,4′-bipyrazole]-4-carbonitrile (11). Chloroacetyl chloride (2.1 mmol) was added dropwise with stirring at room temperature to a solution of **10** (2 mmol) in dioxane (10 mL) containing 2 drops of triethylamine. The mixture was stirred for 2 h, and the solid product was collected by filtration and recrystallized from ethanol–dioxane (2:1). Yield 64%, yellow crystals, mp 272–274°C. IR spectrum, ν, cm^{-1}: 3442 (NH), 2220 (C≡N), 1694 (C=O), 1619 (C=N), 1233 (C=S). ^{1}H NMR spectrum, δ, ppm: 11.80 s (1H, NHCS, exchangeable), 9.01 s (1H, 5′-H), 7.94–7.11 m (10H, H_{arom}), 4.02 s (2H, CH_2). Found, %: C 59.82; H 3.17; N 16.71. $C_{21}H_{14}ClN_5OS$. Calculated, %: C 60.07; H 3.36; N 16.68.

Reaction of compound 1 with thiosemicarbazide. A solution of **1** (2 mmol) and thiosemicarbazide (2 mmol) in dioxane (10 mL) was refluxed for 2 h. After cooling, the obtained solid was filtered off and recrystallized from ethanol–dioxane (1:1). The product was identified as 2-[(1,3-diphenyl-1*H*-pyrazol-4-yl)-methylidene]hydrazine-1-carbothioamide (**13**), yellow crystals, mp 232–234°C. It was identical in IR spectrum, melting point, mixed melting point, and TLC data with an authentic sample prepared by the condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with thiosemicarbazide in refluxing dioxane [1].

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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