Heteroatom Chemistry
Volume 16, Number 1, 2005

Reactions of 2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene and 2-Amino-3-cyano-4,7-diphenyl-5-methyl-4*H*-pyrano[2,3-*c*] pyrazole with Phenylisocyanate, Carbon Disulfide, and Thiourea

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Received 17 December 2003; revised 7 April 2004

ABSTRACT: *2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene* **1a** *or 2-amino-3-cyano-4,7-diphenyl-5-methyl-4H-pyrano[2,3-c]pyrazole* **2a** *reacted with phenylisocyanate in dry pyridine to give 2-(3-phenylureido)-3-cyanobenzo[b]thiophene* **1b** *or 2-disubstituted amino-3-cyanopyranopyrazole* **2b** *derivative. However, when* **1a** *and* **2a** *were refluxed with carbon disulfide in 10% ethanolic sodium hydroxide solution, they afforded the thieno[2,3-d]pyrimidin-2,4-dithione derivative* **5** *in the former case, 2,4-dicyano-1,3-bis(dithio carboxamino)cyclobuta-1,3-diene* **6** *and pyrazolopyranopyrido[2,3-d]pyrimidin-2,4-dithione derivative* **7** *in the latter one. Treatment of* **2a** *with thiourea in refluxing ethanol in the presence of potassium carbonate gave 2,2′-dithiobispyrimidine derivative* **9** *(major) in addition to pyranopyrazole derivative* **10** *and 2,2′-dithiobis ethoxypyrimidine derivative* **11** *in minor amounts. The structures of all products were evidenced by microanalytical and spectral data.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:6–11, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20070

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INTRODUCTION

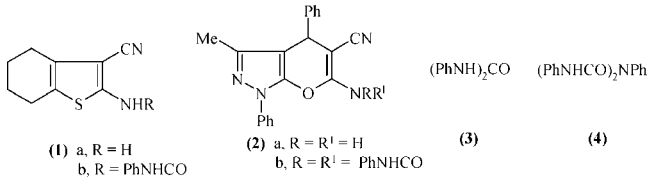
It has been reported [1] that 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene **1a** reacted with phenylisocyanate in DMF and carbon disulfide in pyridine to give dithienopyrimidopyrimidinone and thienopyrimidinedithione beside dithienopyrimidopyrimidinethione, respectively. However, Sukumaran and Rajasekharass [2] reported the formation of thienothiazine upon treating **1a** with carbon disulfide in pyridine.

In the present investigation, we are intended to study the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene **1a** and 2-amino-3-cyano-4,7-diphenyl-5-methyl-4*H*-pyrano[2,3-*c*]pyrazole **2a** with phenylisocyanate, carbon disulfide, and thiourea under different conditions. It is observed that the obtained results are different from those reported in the literature.

RESULTS AND DISCUSSION

Refluxing equimolar amounts of **1a** and **2a** with phenylisocyanate in dry pyridine gave 2-(3-phenylureido)-3-cyanobenzothiophene **1b** and 2-disubstituted amino-3-cyanopyranopyrazole **2b** derivatives, respectively, in addition to 1,3-diphenylurea **3** and 1,3,5-triphenylbiuret **4** as the major product in both cases. However, treating **2a** with phenylisocyanate in

refluxing dioxane yielded **3** and **4** as the only isolated products, whereas **2a** was recovered unchanged.

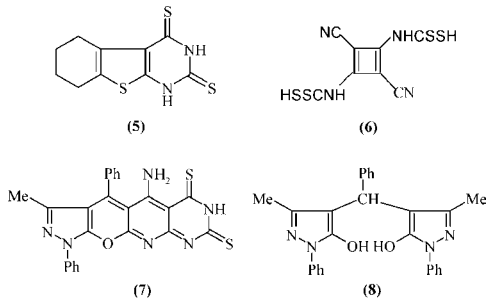


Structures of compounds **1b** and **2b** were deduced from their microanalytical and spectral data, whereas compounds **3** and **4** were rigidly confirmed by mp comparison with authentic samples. The infrared spectra of compounds **1b** and **2b** show absorptions corresponding to NH, CN, and CO groups. Moreover, the ^{1}H-NMR spectra of compounds **1b** and **2b** are in accord with the proposed structures. The EI-MS spectrum of compound **1b** showed a correct molecular ion peak. However, the EI-MS spectrum of compound **2b** did not show the molecular ion peak but it showed a peak at *m/e* 404 which corresponds to [$M^{+\cdot}$-PhNCO and HNCO].

The formation of compounds **1b** and **2b** could be interpreted on the basis of a nucleophilic attack of the amino group in compounds **1a** and **2a** at the isocyanato group of phenylisocyanate. On the other hand, the formation of compounds **3** and **4** could be explained through easy conversion of phenylisocyanate; by a trace amount of water present in the used solvent, into the unstable carbamic acid to give aniline that then attacks either the phenylisocyanate monomer to give **3** or its dimer to give **4** (Scheme 1)

Compounds **3** and **4** were the only isolated products upon treating **2a** with phenylisocyanate in refluxing dioxane or upon refluxing phenylisocyanate in pyridine or dioxane alone that reflects the important role of pyridine in the enhancement of the nucleophilicity of amino group.

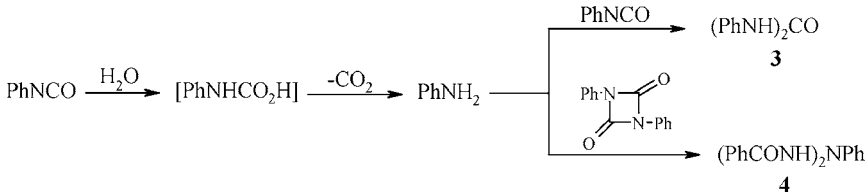
Treatment of compounds **1a** or **2a** with carbon disulfide in 10% ethanolic sodium hydroxide solution afforded the thieno[2,3-*d*]pyrimidin-2,4-dithione **5** or 2,4-dicyano-1,3-bis(dithiocarboxamino)-cyclobuta-1,3-diene **6** and pyrazolo[4′,3′:5,6]pyrano-[3′,2′:5,6]pyrido[2,3-*d*]pyrimidin-2,4-dithione derivative **7** as well as 4,4′-(phenylmethylene) bis (3-methyl- 1-phenyl-1*H*-pyrazol-5-ol) **8**.



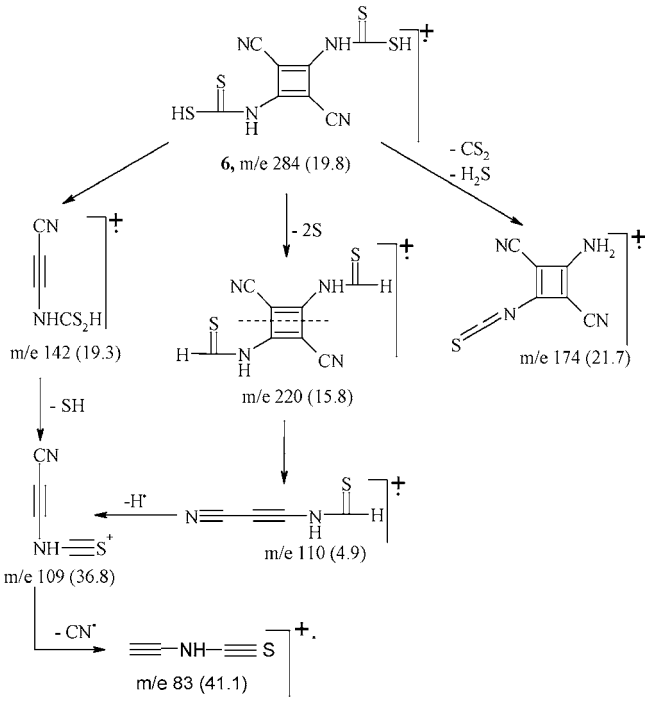
The structures of compounds **5** and **8** were substantiated from their spectral data and they were rigidly confirmed by mp comparison with that reported [1,3]. However, the structures of compounds **6** and **7** were deduced spectroscopically as well as chemically in the former one. Thus, the infrared spectra of compounds **6** and **7** showed absorption corresponding to NH and C═S groups besides additional absorptions correlated with SH and C≡N groups for compound **6** which are in accord with the proposed structures.

The ^{1}H-NMR spectra of compounds **6** and **7** were consistent with their suggested structures. Moreover, the structures of compounds **6** and **7** get a further support from their EI-MS spectra where they showed correct molecular ion peaks beside some of the abundant peaks. The fragmentation pathway of compound **6** is shown in Scheme 2. Some stable cyclobutadiene derivatives are reported [4,5].

The formation of compounds **6, 7**, and **8** could be interpreted through a base catalyzed ring opening of the pyrano ring of **2a** to give the benzylidenepyrazolone (**A**) and cyanoacetamide (**B**). Benzylidenepyrazolone (**A**) undergoes benzylidene elimination [6] to give benzaldehyde and pyrazolinone that attacks another molecule of (**A**) to give **8**. On the other hand, cyanoacetamide (**B**) adds to carbon disulfide to give the intermediate (**C**) (not isolated) that either dimerizes to give **6** or attacks another molecule of **2a** to afford **7** as outlined (Scheme 3). The conversion of the thiazinethione derivative (**D**) into the pyrimidine dithione derivative (**E**) is well established in the



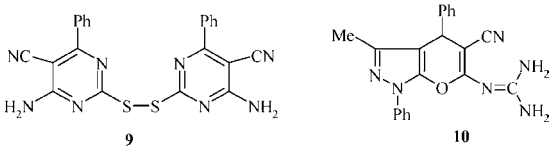
SCHEME 1



SCHEME 2 Fragmentation pathway of compounds **6**.

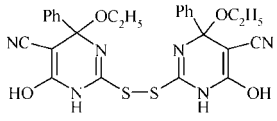
presence of a base [2,7]. Compound **6** was proved chemically by comparison with an authentic sample prepared from cyanoacetamide and carbon disulfide under similar conditions.

Thiourea reacted with 2-amino-3-cyanopyrano-[2,3-*c*]pyrazole derivative **2a** in refluxing ethanol in the presence of potassium carbonate to give 2,2′ dithiobis-pyrimidine derivative **9** (major) in addition to pyranopyrazole derivative **10** and 2,2′-dithiobis-ethoxypyrimidine derivative **11** in minor amounts.



9

10



11

The structures of compounds **9–11** were deduced from their microanalytical and spectral data. Thus, their infrared spectra showed absorptions characteristic for NH and CN groups. The absorption signals in the ^{1}H-NMR spectra of compounds **9** and **11** reflected their molecular symmetry. On the other hand, the spectra were devoid of any signals corresponding to methyl and methine protons that revealed the absence of the pyranopyrazole moiety, but exhibited absorptions characteristic for aromatic and acidic protons as well as ethyl absorptions for compound **11**. A further evidence for structure **10** was gained from its ^{13}C-NMR spectrum (cf. Experimental). The EI-MS spectra of compounds **9** and **11** showed molecular ion peaks whereas compound **10** did not.

The formation of compounds **9–11** (Scheme 4) could be rationalized on the basis of a base catalyzed attack of the amino group of the pyranopyrazole derivative **2a** at the thiocarbonyl group of thiourea followed by an elimination of hydrogen sulfide to give compound **10** (route a). A base catalyzed pyrano ring opening (route b) gave (**D**) and the benzylidenepyrazolone (**A**). (**A**) undergoes benzylidene elimination [6] to give **8** that was detected by TLC in the reaction mixture. Compound (**D**) condenses with benzaldehyde to give (**E**) which either oxidizes to give compound **9** or hydrolyzes followed by oxidation and addition of 2 moles of ethanol to give compound **11**.

The suggested mechanism was proved chemically by reacting equimolar amounts of cyanoacetamide, thiourea, and benzaldehyde under similar conditions where compound **9** was isolated and compound **11** was detected by TLC in the reaction mixture. Compound **9** was identified by comparison with an authentic sample (mp, mixed mp, and TLC).

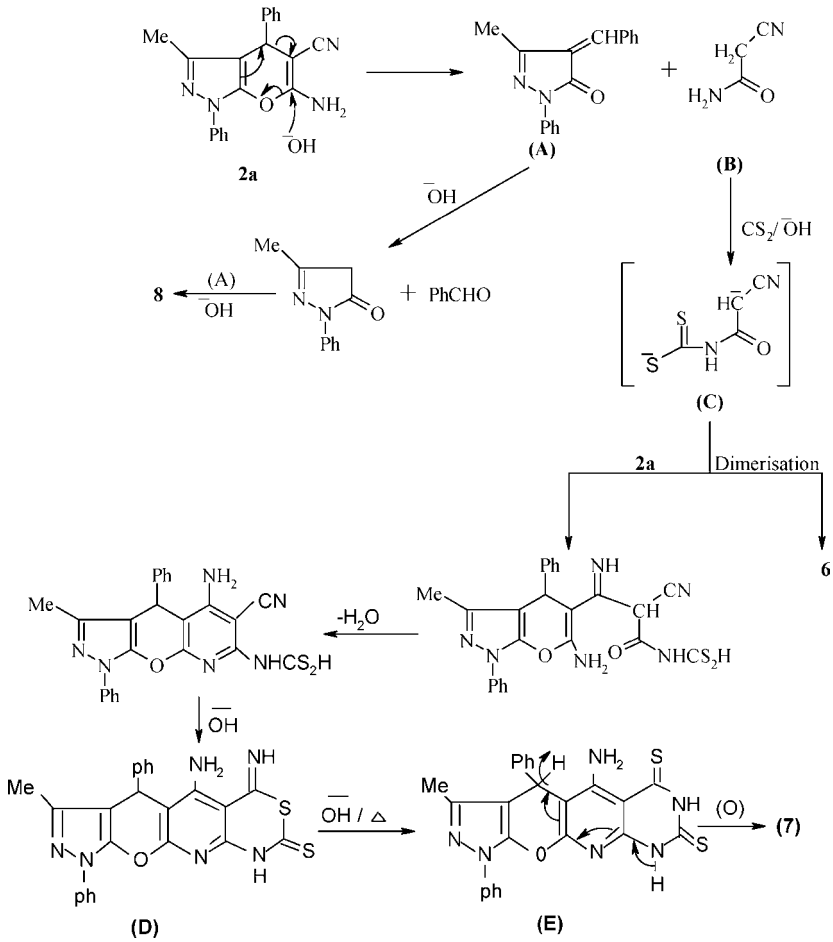
EXPERIMENTAL

All melting points were not corrected. Infrared spectra were measured on a Unicam SP 1200 spectrometer as KBr disks. ^{1}H- and ^{13}C-NMR spectra were measured in DMSO-d_6 or $CDCl_3$ on a Varian Gemini instrument at 200 and 50 MHz, respectively; in both cases, chemical shifts were given in ppm downfield from internal TMS. Mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument operating at 70 eV. TLC was performed on Merk Kieselgel 60 F_{254} aluminum backed plates.

2-Amino-3-cyano-4,5,6,7-tetrahydro-benzo[*b*]-thiophene **1a** [8] and 2-amino-3-cyano-4,7-diphenyl-5-methyl-4*H*-pyrano[2,3-*c*]pyrazole **2a** [9] were prepared according to the literature methods.

Reactions of **1a** *and* **2a** *with Phenylisocyanate*

General Procedure. ***In Dry Pyridine***. A mixture of **1a** (0.01 mole) or **2a** (0.01 mole) and phenylisocyanate (0.01 mole) in dry pyridine (20 mL) was refluxed for 10 h. The reaction mixture was cooled



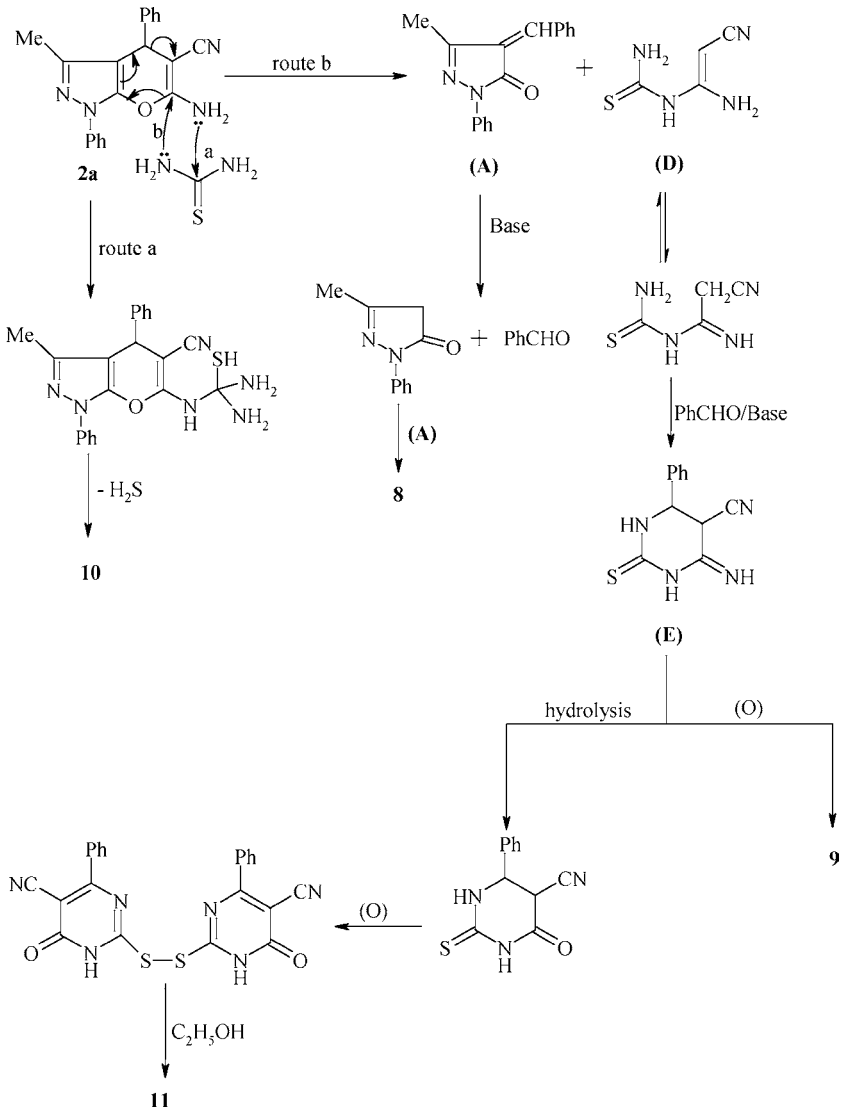
SCHEME 3

and poured into ice cold HCl. The precipitated solid was filtered off and recrystallized to give *1,3-diphenylurea* **3**, (40% yield), colorless crystals, mp 232–234°C (benzene/ethanol), lit. [10] mp 241–242°C; identical with an authentic sample (mp, mixed mp, and TLC) prepared from aniline hydrochloride and urea [10]. The mother liquor was left to evaporate at room temperature to give a semisolid. Trituration with methanol (2 mL) gave a solid which was fractionally recrystallized to give *1,3,5-triphenylbiuret* **4**, (30% yield), bright yellow needles, mp 142–144°C (methanol), lit. [11] mp 143–145°C; identical with authentic sample (mp, mixed mp, and TLC) prepared by fusion of 1,3-diphenylurea **3** with phenylurea. The insoluble part in boiling methanol was recrystallized from dioxane to give **1b** in the case of **1a** and **2b** on using **2a**.

2-(3-Phenylureido)-2-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene **1b**: (20% yield), colorless crystals, mp 200–202°C (dioxane). IR ν_{max} 3325 (NH), 3027 (aryl-H), 2933 (alkyl-H), 2212 (C≡N), 1711 (CO), 1648, 1596, 1553 (C=C), 752 and 696 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H-NMR (DMSO-d_6) δ 1.76 (br.s, 4, $(CH_2)_2$), 2.49 (br.s, 2, CH_2), 2.51 (br.s, 2, CH_2), 6.97–7.49 (m, 5, ArH), 8.67 and 9.20 (each br.s, 1, NH, exchangeable). EIMS *m/z* (%) 299 ($M^{+\cdot}$ + 2, 1), 297 ($M^{+\cdot}$,9), 204 ($M^{+\cdot}$ -$PhNH_2$, 25), 180 (4), 178 ($M^{+\cdot}$ -PhNCO,72), 152 (7), 151 (10), 150 (base). Anal. Calcd for $C_{16}H_{15}N_3OS$ (297.386): C, 64.62; H, 5.08; N, 14.13; S, 10.78. Found: C, 64.39; H, 4.95; N, 13.87; S, 10.65%.

3-Cyano-4,7-diphenyl-2-(diphenylformamido)-amino-5-methyl-4H-pyrano [2,3-c] pyrazole **2b**: (5% yield), gray crystals, mp 140–142°C (dioxane). IR ν_{max} 3450, 3320 (NH), 3060 (aryl-H), 2930 (alkyl-H), 2230 (C=N), 1745, 1715 (CO), 1590 (C=C), 750 and 690 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H-NMR ($CDCl_3$) δ 1.99 (s, 3, CH_3), 3.71 (s, 1, methine H), 7.12–7.89 (m, 20, ArH), 8.95 (br.s, 2NH, exchangeable). EIMS *m/z* (%) 404 ($M^{+\cdot}$-PhNCO and HNCO, 1), 328 (32), 327 (37), 105 (23), 77 (base), 51 (31). Anal. Calcd for $C_{34}H_{26}N_6O_3$ (566.60): C, 72.07, H, 4.62; N, 14.83. Found: C, 71.88; H, 4.51; N, 14.69%.

In Dry Dioxane. A mixture of **2a** (0.01 mole) and phenylisocyanate (0.01 mole) in dioxane (20 mL) was



SCHEME 4

refluxed for 20 h. The reaction mixture was concentrated and left at room temperature to give a precipitate that was recrystallized from ethanol to afford **2a** (85% yield). The mother liquor was left to stand at room temperature for 3 h to give 1,3-diphenylurea 3, (50% yield), mp 232–234°C (benzene/ethanol), identical in all respect with an authentic sample (mp, mixed mp, and TLC). However, evaporation of the mother liquor at room temperature and trituration with methanol gave 1,3,5-triphenylbiuret 4, (30% yield), mp 142–144°C (methanol), identical with an authentic sample (mp, mixed mp, and TLC).

Reactions of **1a** *and* **2a** *with Carbon Disulfide*

General Procedure. To a solution of **1a** (0.01 mole) or **2a** (0.01 mole) in 10% alcoholic sodium hydroxide (3 g NaOH/30 mL ethanol), carbon disulfide (10 mL) was added whereby the reaction mixture becomes brown in color. The reaction mixture was refluxed for 2 h.

In case of **1a**, the reaction mixture was cooled to room temperature, poured into ice cold water and acidified with acetic acid to give 5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-2,4-dithione **5**, golden (20% yield), yellow crystals, mp 265–266°C (ethanol/benzene), lit. [1] mp 260–262°C.

In case of **2a**, a yellow solid was precipitated after 5 min which was filtered off while hot, dissolved in water and acidified with acetic acid to give *2,4-dicyano-1,3-bis(dithiocarboxamino)cyclobuta-1,3-diene* **6**, (20% yield), yellow crystals, mp 200–202°C (ethanol). IR ν_{max} 3320, 3180 (NH), 2480 (SH), 2250 (C≡N), 1640 (C=C), 1115 cm^{-1} (C=S).

^{1}H-NMR (DMSO-d_6) δ 9.62 (br.s, SH, exchangeable), 10.42 (br.s, NH, exchangeable). EIMS *m/z* (%) 286 ($M^{+\cdot}$ + 2, 4), 284 ($M^{+\cdot}$, 20), 220 ($M^{+\cdot}$-2S, 16), 174 ($M^{+\cdot}$ -CS_2 and H_2S, 22), 142 (19), 109 (37), 83 (41), 82 (21), 76 (20), 66 (19), 64 (18), 60 (base). Anal. Calcd for $C_8H_4N_4S_4$ (284.408): C, 33.78; H, 1.42; N, 19.70; S, 45.09. Found: C, 33.53; H, 1.34; N, 19.61; S, 44.85%. The reaction mixture was refluxed for further 2 h, cooled, poured into ice cold water and acidified with acetic acid to afford *5-amino-6,9-diphenyl-7-methylpyrazolo[4′,3′: 5,6]pyrano [3′,2′: 5,6]pyrido[2,3-d]pyrimidin-2,4-dithione* **7**, (20% yield), orange crystals, mp 300–302°C (ethanol). IR ν_{max} 3430 (NH), 3071 (aryl-H), 2916, 2851 (alkyl-H), 1638, 1586 (C=N and/or C=C), 1183, 1109 (C=S), 747, 680 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H-NMR (DMSO-d $_6$) δ 2.13 (s, 3, CH_3), 5.36 (br.s, NH_2, exchangeable), 6.79 (br.s, NH, exchangeable), 7.21–7.35 (m, 10, ArH). EIMS *m/z* (%) 468 ($M^{+\cdot}$, 1), 465 (19), 464 (19), 217 (16), 215 (54), 91 (base), 83 (33), 67 (16), 64 (34), 51 (26). Anal. Calcd for $C_{24}H_{16}N_6OS_2$ (468.548): C, 61.50; H, 3.44; N, 17.94; S, 13.69. Found: C, 61.38; H, 3.37; N, 17.59; S, 13.41%. On leaving the mother liquor to stand at room temperature, it gave *4,4′-(phenylmethylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)* **8**, (≈5% yield), colorless crystals, mp 162–164°C (ethanol), lit. [3] mp 162–164°C, identical with an authentic sample (mp, mixed mp, and TLC behavior) prepared by refluxing 1-phenyl-3-methylpyrazolin-5-one and benzaldehyde in benzene.

Reactions of **2a** *with Thiourea*

General Procedure. An equimolar amounts of **2a** (0.01 mole), thiourea (0.01 mole), and potassium carbonate (0.01 mole) were refluxed in ethanol (40 mL) for 6 h. The reaction mixture was cooled, poured into ice cold water to give *2,2′-dithiobis-(5-cyano-4-ethoxy-6-hydroxy-4-phenyl-1,4-dihydro pyrimidine)* **11**, (5% yield), green crystals, mp 210–212°C (ethanol). IR ν_{max} 3446, 3425 (OH), 3323, 3218 (NH), 3080 (aryl-H), 2979, 2926 (alkyl-H), 2224, 2201 (C≡N), 1625, 1586, 1550 (C=N and/or C=C), 768, 699 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H-NMR (DMSO-d_6) δ 1.36 (t, 3, $C\underline{H_3}$—CH_2, J = 7.0 Hz), 4.46 (q, 2, $CH_3C\underline{H_2}$, J = 7.0 Hz), 7.51–7.61 (m, 5, Ar-H), 7.97 (br.s, 2, OH and NH exchangeable). EIMS *m/z* (%) 548 ($M^{+\cdot}$,1), 265 (19), 264 (88), 263 (35), 237 (19), 236 (base), 235 (25), 209 (28), 208 (27), 180 (14), 154 (12). Anal. Calcd for $C_{26}H_{24}N_6O_4S_2$ (548.628): C, 56.92; H, 4.41; N, 15.32. Found: C, 56.73; H, 4.30; N, 15.18%. The aqueous solution was cooled and acidified with concentrated hydrochloric acid to give a yellow solid which was fractionally crystallized from ethanol to give *3-cyano-2-diaminomethyleneamino-4,7-diphenyl-5-methyl-4H-pyrano[2,3-c]pyrazole* **10**, (10% yield), yellow crystals, mp 203–205°C (ethanol). IR ν_{max} 3430, 3360, and 3280 (NH_2), 3069 (aryl-H), 2920 (alkyl-H), 2213 (C≡N), 1639, 1600 (C=N and/or C=C), 750, 690 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3, CH_3), 4.81 (s, 1, CH), 7.11–7.67 (m, 14, 10 ArH + $2NH_2$ exchangeable). ^{13}C-NMR (DMSO-d_6) δ 10.73 (CH_3), 32.31 (C-4), 105.37 (C-3), 122.36 (CN), 126.53, 127.16, 127.63, 128.53, 129.37, 134.82 (phenylcarbons), 140.96 (C-5), 146.12 (C-2), 158.25 (methylene carbon). EIMS *m/z* (%) 263 [$M^{+\cdot}$ + 1 —NC—C≡C—N=C$(NH_2)_2$, 42], 262 [$M^{+\cdot}$ —NC—C≡C—N=C$(NH_2)_2$, 50], 185 (68), 174 (28), 91 (48). Anal. Calcd for $C_{21}H_{18}N_6O$ (370.42): C, 68.09; H, 4.89; N, 22.69. Found: C, 68.20; H, 4.78; N, 22.58%.

The insoluble part in ethanol gave *2,2′-dithiobis-(6-amino-5-cyano-4-phenylpyrimidine)* **9**, (25% yield), yellow crystals, mp >300°C (dioxane). IR ν_{max} 3373, 3307, 3263, 3216 (NH), 3093 (aryl-H), 2218, 2188 (C≡N), 1643, 1563 (C=N and/or C=C), 747, 700 cm^{-1} ($\delta_{5\text{-H}}$). ^{1} H-NMR (DMSO-d_6) δ 3.68 (br.s, 2, NH_2, exchangeable), 7.35–7.55 (m, 5, ArH). EIMS *m/z* (%) 456 ($M^{+\cdot}$ + 2, <1), 454 ($M^{+\cdot}$,3), 228 (5), 227 (19), 169 (34), 161 ($M^{+\cdot}$-PhNH_2, 11), 153 (26), 151 (base). Anal. Calcd for $C_{22}H_{14}N_8S_2$ (454.53): C, 58.13; H, 3.11, N, 24.65; S, 14.11. Found: C, 57.76; H, 2.98; N, 24.47; S, 13.85%.

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