Synthesis of Some New Pyrimidothienopyridazines and Related Heterocycles

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5-Amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carbonitrile **2a** was reacted with propylene diamine to give tetrahydropyrimidinyl derivative **3**. The latter compound (**3**) underwent certain cyclocondensation reactions to produce pyrimidothienopyridazines **4-6**. Also, the reactions of 5-amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carboxamide with heterocyclic aldehydes and/or cycloalkanones were carried out and their products were identified. Moreover, some novel pyridazinothienopyrimidobenzimidazoles **14-17** were synthesized.

Keywords: Thienopyridazines; Pyrimidothienopyridazines; Benzimidazoles; Pyrimidines; Spiro compounds.

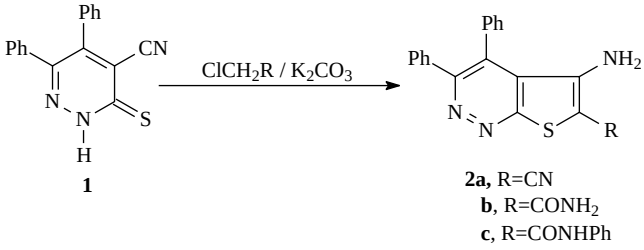
INTRODUCTION

It is interesting to note that many pyridazine derivatives have antihypertensive[1] and cardiotonic activity.[2] Also other pyridazine derivatives serve as insecticides, miticides and nematocides.[3] In view of the above benefits and in continuation of our work on the synthesis and reactivity of pyridazines,[4-7] we aimed, in this work, to prepare some new heterocycles containing thieno[2,3-c]pyridazine moiety condensed with other heterocyclic ones hoping that some of them will have biological activities.

INVESTIGATIONS, RESULTS AND DISCUSSION

The starting compounds, 6-functionalized 5-amino-3,4-diphenylthieno[2,3-c]pyridazines **2a-c** were prepared by reaction of 4-cyano-4,5-diphenylpyridazine-3(2*H*)-thione (**1**) with the respective halocompounds.

Scheme I



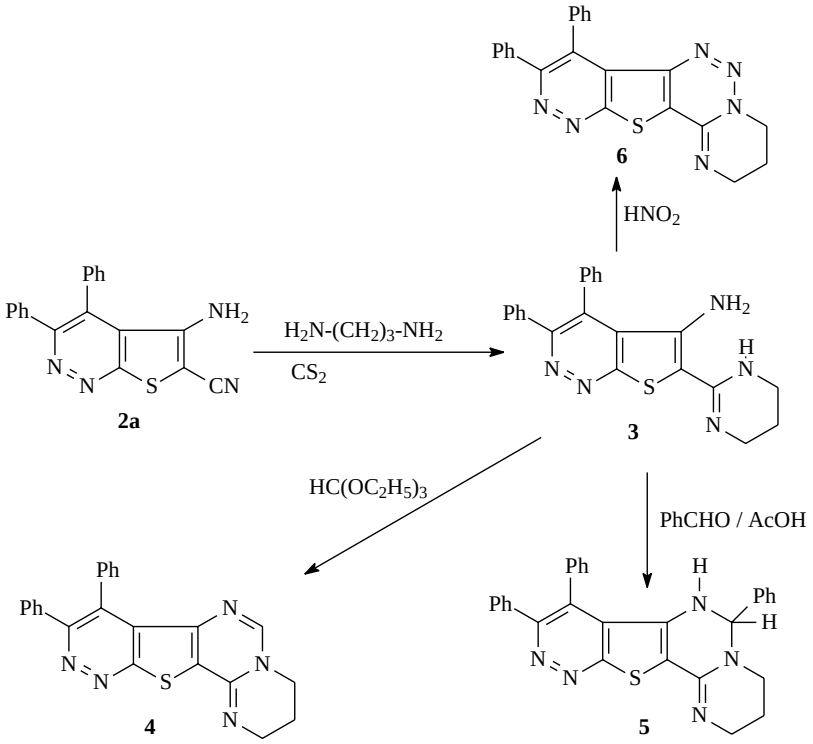
1

2a, R=CN
b, R=$CONH_2$
c, R=CONHPh

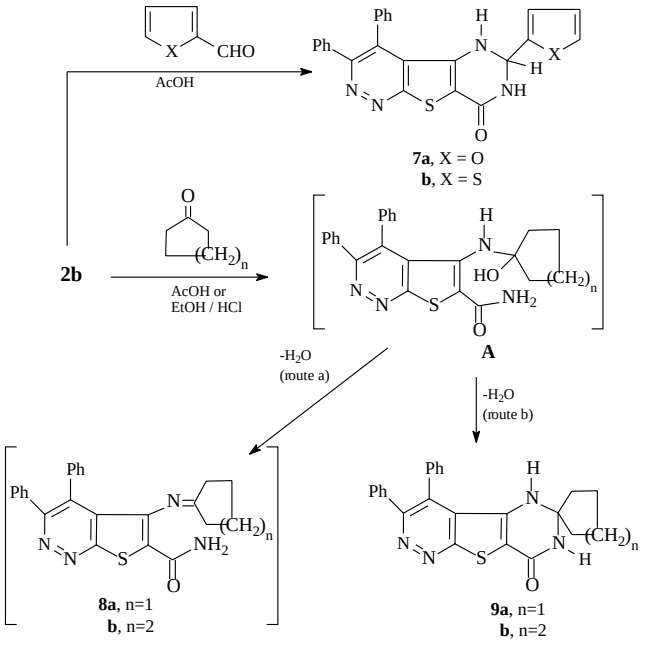
Reaction of 6-cyano-5-amino-3,4-diphenylthieno[2,3-c]pyridaine (**2a**) with propylene diamine in the presence of carbon disulfide gave the tetrahydropyrimidinyl derivative **3**.[8] The latter compound upon reaction with triethyl orthformate or benzaldehyde, in refluxing acetic acid,[9] gave the corresponding tetrahydropyrimido[1″,2″:1′,6′]pyrimido-[4′,5′;4,5]thieno[2,3-c]pyridazines **4** and **5**, respectively. On the other hand, treatment of compound **3** in a mixture of acetic acid and hydrochloric acid with sodium nitrite solution at low temperature led to the formation of 8,9-diphenyl-2,3,4-trihydropyrimido[1″,2″-f]pyridazino[3′,4′:4,5]thieno[2,3-d]triazine (**6**) (Scheme II).

When 5-amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carboxamide (**2b**) was allowed to react with heterocyclic aldehydes in boiling acetic acid, a cyclocondensation reaction occurred and tetrahydropyrimidothienopyridazines **7a,b** were obtained (Scheme III). The carboxamide **2b** was also reacted with cyclopentanone or cyclohexanone upon refluxing in glacial acetic acid or in ethanol containing a few drops of HCl. In view of an earlier report[10] and the spectral data, the products of this reaction were identified as spiro compounds **9a,b** rather than Schiff bases **8a,b**. Thus, the IR spectra of the products showed two absorption bands at 3400, 3200 cm^{-1} characteristic for (2NH) and an absorption band at 1650 cm^{-1} for (C=O). The IR spectra revealed also the absence of any bands corresponding to a NH_2 group. The ^1H NMR spectra in DMSO-d_6 showed no signal equivalent to a $CONH_2$ group but showed two singlets at δ 4.4 equivalent to (NH) and at δ 6.5 to (NH). The proposed pathway of this reaction is depicted in

Scheme II



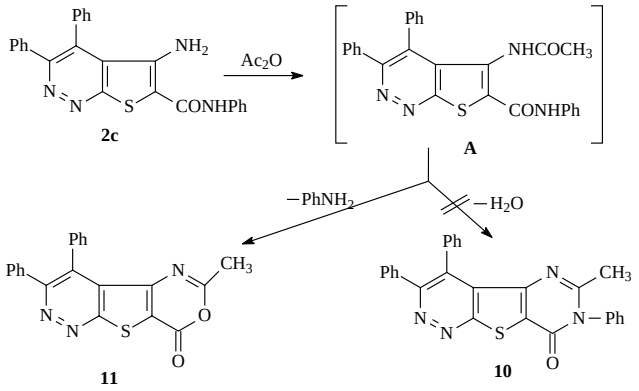
Scheme III



Scheme III. Thus, this reaction involves the formation of addition product **A** which may undergo spontaneous dehydration to give the expected products **8a,b** or **9a,b** *via* two probable routes (a and b) (Scheme III).

Refluxing of 5-amino-3,4-diphenyl-6-(*N*-phenyl)carbamoylthieno[2,3-c]pyridazine (**2c**) with acetic anhydride for 6 hours led to the formation of oxazinone derivative **11** rather the pyrimidinone **10**.[11] The pathway of this reaction is given in Scheme IV.

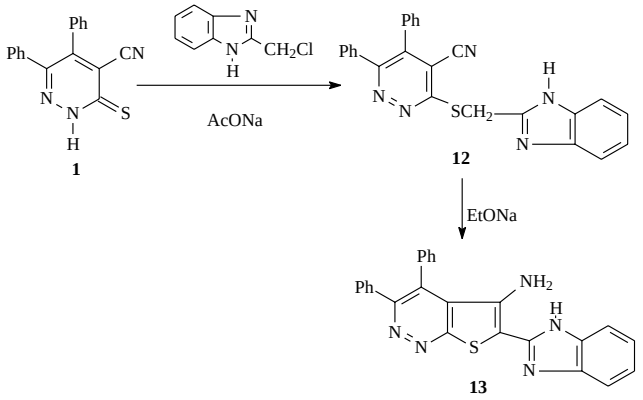
Scheme IV



The pyridazinethione **1** reacts also with 2-chloromethyl-1*H*-benzimidazole in refluxing ethanol containing sodium acetate to afford the intermediate **12** which underwent intramolecular *Thorpe-Ziegler* cyclization[12] upon heating with sodium ethoxide in ethanol to give 5-amino-6-(1*H*-benzimi-

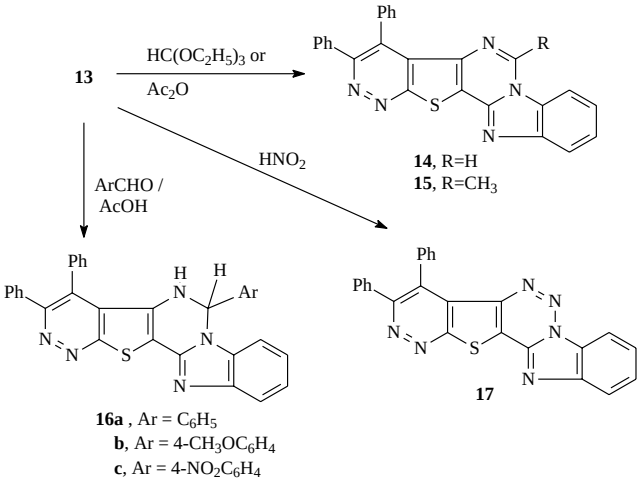
dazol-2-yl)-3,4-diphenylthieno[2,3-c]pyridazine derivative **13** (Scheme V).

Scheme V



The latter compound (**13**) was used as a versatile compound for the building of other new heterocyclic systems. Thus, its reactions with triethyl orthoformate, acetic anhydride and/or aromatic aldehydes, gave pyridazino-[3″,4″:4′,5′]thieno[2′,3′:4,5]pyrimido[1,6-a]benzimidazole derivatives **14**, **15** and **16**, respectively. Also, treatment of compound **13** in acetic acid and hydrochloric acid mixture with sodium nitrite solution produced pyridazino[3″,4″;4′,5′]-thieno[2′,3′;4,5]triazino[1,6-a]benzimidazole derivative (**17**) (Scheme VI).

Scheme VI



The structural formulas of all newly synthesized compounds were confirmed by elemental and spectroscopic analyses (*cf.* experimental section).

EXPERIMENTAL

All melting points are uncorrected and measured on a Gallan-Kamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; υ_{max} in cm^{-1}). ^{1}H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard (δ in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on an Elementar Analyses system GmbH VARIOEL $V_{2.3}$ July 1998 CHNS Mode.

6-Functionalized 5-amino-3,4-diphenylthieno[2,3-c]pyridaines 2a-c

These compounds were prepared according to our previous method.[13-15]

5-Amino-3,4-diphenyl-6-(1,4,5,6-tetrahydropyrimidin-2-yl)thieno[2,3-c]pyridazine (3)

To a mixture of compound **2a** (3.28 g, 0.01 mol) and propylene diamine (6 mL), 1 mL of carbon disulfide was added dropwise. The resulting mixture was heated on a water bath for 6 h. After cooling, the separated product was filtered off, washed with water and recrystallized (ethanol) to give **3** (80%), m.p. 213-215 °C. IR: 3450-3350 cm^{-1} (NH_2, NH) and 1600 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): 2.1-2.2 (m, 2H, pyrimidine ring), 2.6-2.7 (2H, m, pyrimidine ring), 3.5-3.6 (m, 2H, pyrimidine ring), 6.5 (s, 2H, NH_2), 6.7 (s, 1H, NH) and 7.3-7.5 (m, 10H, ArH). Anal. calcd. for $C_{22}H_{19}N_5S$ (385.46): C, 68.54; H, 4.96; N, 18.16; S, 8.31. Found: C, 68.32; H, 4.91; N, 17.96; S, 8.05.

3,4-Diphenyl-8,9,10-trihydropyrimido[1″,2″:1′,6′]pyrimido-[4′,5′:4,5]thieno[2,3-c]pyridazine (4)

Compound **3** (0.78 g, 0.002 mol) and triethyl orthformate (8 mL) were heated under reflux for 2 h. The precipitate that formed on cooling was collected and recrystallized (acetic acid) to give **4** (83%), m.p. 296-298 °C. IR: 1620 cm^{-1} (C=N). ^{1}H NMR (CF_3CO_2D): 2.4-2.5 (m, 2H, pyrimidine), 2.7-2.8 (m, 2H, pyrimidine), 3.7-3.8 (m, 2H, pyrimidine), 7.2-7.6 (m, 10H, ArH) and 8.3 (s, 1H, pyrimidine). Anal. calcd. for $C_{23}H_{17}N_5S$ (395.45): C, 69.85; H, 4.33; N, 17.69; S, 8.10. Found: C, 69.58; H, 4.23; N, 17.49; S, 7.93.

3,4,6-Triphenyl-5,6,8,9,10-pentahydropyrimido[1″,2″:1′,6′]-pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (5)

A mixture of **3** (0.78 g, 0.002 mol) and benzaldehyde (0.22 g, 0.002 mol) in glacical acetic acid (10 mL) was

refluxed for 4 h. The solid product that formed was collected and recrystallized (acetic acid) to afford **5** (76%); m.p. 302-304 °C. IR: 3450 cm^{-1} (NH) and 1620 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): 2.1-2.2 (m, 2H, pyrimidine), 2.4-2.5 (m, 2H, pyrimidine), 3.6-3.7 (m, 2H, pyrimidine), 6.2 (s, 1H, CH) and 7.2-7.6 (m, 15H, ArH). Anal. calcd. For $C_{29}H_{23}N_5S$ (475.57): C, 73.23; H, 5.30; N, 14.72; S, 6.74. Found: C, 72.97; H, 5.12; N, 14.53; S, 6.56.

3,4-Diphenyl-8,9,10-trihydropyrimido[1″,2″-f]pyridazino-[3′,4′;4,5]thieno[2,3-e]triazine (6)

To compound **3** (0.78 g, 0.002 mol) in a mixture of acetic acid (9 mL) and hydrochloric acid (3 mL) was added with stirring a solution of sodium nitrite (0.2 g in 5 mL H_2O). After addition, stirring was continued for 5 h. The formed product was filtered off and recrystallized (acetic acid) to afford **6** (72%); m.p. 203-205 °C. IR: 1620 cm^{-1} (C=N). Anal. Calcd. for $C_{22}H_{16}N_6S$ (396.44): C, 66.64; H, 4.06; N, 21.19; S, 8.08. Found: C, 66.32; H, 3.89; N, 20.97; S, 7.88.

Reaction of thieno[2,3-c]pyridazine 2b with heterocyclic aldehydes or cycloalkanones; formation of tetrahydropyrimido[4′,5′;4,5]thieno[2,3-c]pyridazine derivatives (7a,b) and (9a,b)

General procedure

A mixture of **2b** (0.002 mol) and hetrocyclic aldehydehyde or cycloalkanones (0.002 mol) in acetic acid (10 mL) was refluxed for 4 h. After cooling, the solid product separated was filtered off and recrystallized from the proper solvent to give compounds **7a,b** or **9a,b** respectively.

Compound 7a

It was obtained from **2b** and thiophene-2-carboxaldehyde in 73% yield; m.p. 271-273 °C (acetic acid). IR: 3350-3250 cm^{-1} (NH) and 1650 cm^{-1} (C=O). ^1H NMR (CF_3CO_2D): 6.6 (s, 1H, CH) and 7.2-7.7 (m, 13H, ArH and thiophene protons). Anal. calcd. for $C_{24}H_{16}N_4OS_2$ (440.51): C, 65.43; H, 3.66; N, 12.71; S, 14.55. Found: C, 65.11; H, 3.48; N, 12.54; S, 14.33.

Compound 7b

It was obtained from **2b** and furfural in 76% yield; m.p. 262-264 °C (ethanol-chloroform). IR: 3350-3250 cm^{-1} (NH) and 1650 cm^{-1} (C=O). ^1H NMR (CF_3CO_2D): 5.9-6.0 (m, 2H, furan), 6.3-6.3 (m, 1H, furan), 6.5 (s, 1H, CH) and 7.3-7.7 (m, 10H, ArH). Anal. calcd. for $C_{24}H_{16}N_4O_2S$ (424.45): C, 67.90; H, 3.79; N, 13.19; S, 7.55. Found: C, 67.58; H, 3.71; N, 12.92; S, 7.43.

Compound 9a

It was obtained from **2b** and cyclopentanone in 69% yield; m.p. 331-333 °C (ethanol), IR: 3400, 3200 cm^{-1} (2NH) and 1650 cm^{-1} (C=O). ^1H NMR (DMSO-d_6); 1.6-1.8 (m, 4H, cyclopentane), 2.0-2.2 (m, 4H, cyclopentane) and 7.2-7.6 (m, 10H, ArH), 4.4 (s, 1H, NH), 6.5 (s, 1H, NH). Anal. calcd. for $C_{24}H_{20}N_4OS$ (412.48): C, 69.87; H, 4.88; N, 13.59; S, 7.77. Found: C, 69.64; H, 4.66; N, 13.23; S, 7.54.

Compound 9b

It was obtained from **2b** and cyclohexanone in 71% yield; m.p. 323-325 °C (ethanol). IR: 3400, 3200 cm^{-1} (2NH) and 1650 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): 1.6-1.8 (m, 6H, cyclohexane), 2.0-2.2 (m, 4H, cyclohexane) and 7.5-7.7 (m, 10H, ArH), 4.4 (s, 1H, NH), 6.5 (s, 1H, NH). Anal. calcd. for $C_{25}H_{22}N_4OS$ (426.50): C, 70.39; H, 5.19; N, 13.13; S, 7.15. Found: C, 70.01; H, 4.92; N, 12.80; S, 6.91.

Reaction of thieno[2,3-c]pyridazine 2c with acetic anhydride; formation of oxazino[4′,5′:4,5]thieno[2,3-c]pyridazine derivative (11)

Compound **2c** (0.84 g, 0.002 mol) and acetic anhydride (15 mL) were heated under reflux for 5 h. Upon cooling, the precipitate formed was collected and recrystallized (ethanol) to give **11** (72%), m.p. 260-262 °C. IR: 1740 cm^{-1} (C=O) and 1600 cm^{-1} (C=N). ^1H NMR ($CDCl_3$); 2.6 (s, 3H, CH_3) and 7.3-7.7 (m, 10H, ArH). Anal. calcd. for $C_{21}H_{13}N_3O_2S$ (371.39): C, 67.90; H, 3.52; N, 11.31; S, 8.63. Found: C, 67.62; H, 3.43; N, 11.02; S, 8.42.

Reaction of pyridazinethione 1 with 2-chloromethyl-1*H*-benzimidazole; formation of benzimidazolylthieno[2,3-c]-pyridazine derivative 12

A mixture of compound **1** (2.89 g, 0.01 mol), 2-chloromethyl-1*H*-benzimidazole (1.66 g, 0.01 mol) and sodium acetate trihydrate (3.0 g) in ethanol (30 mL) was heated under reflux for 2 h. The product which separated on cooling was collected and recrystallized (ethanol) to give **12** (83%), m.p. 322-324 °C. IR: 3250 cm^{-1} (NH), 2200 cm^{-1} (C≡N). ^1H NMR (CF_3CO_2D): 5.2 (s, 2H, CH_2) and 7.2-7.8 (m, 14H, ArH). Anal. calcd. for $C_{25}H_{17}N_5S$ (419.47): C, 71.57; H, 4.08; N, 16.69; S, 7.64. Found: C, 71.16; H, 3.97; N, 16.49; S, 7.51.

3.4-Diphenyl-5-amino-6-(benzimidazol-2-yl)-thieno[2,3-c]-pyridazine (13)

A suspension of **12** (2.1 g, 0.005 mol) in sodium ethoxide solution (0.5 g sodium in 50 mL ethanol) was heated under reflux for 15 min. The solid product separating upon

treatment with acetic acid was collected and recrystallized (acetic acid) to afford **13** (63%), m.p. > 360 °C. IR: 3400, 3300, 3150 cm^{-1} (NH) and 1600 cm^{-1} (C=O). ^1H NMR (CF_3CO_2D): 7.3-7.7 (m, 14H, ArH). Anal. calcd. for $C_{25}H_{17}N_5S$ (419.47): C, 71.57; H, 4.08; N, 16.69; S, 7.64. Found: C, 71.23; H, 4.92; N, 16.39; S, 7.49.

3,4-Diphenylpyridazino[3″,4″:4′,5′]thieno[2′,3′:4,5]pyrimido[1,6-a]benzimidazole (14)

Compound **13** (0.82 g, 0.002 mol) and triethyl orthformate (8 mL) were heated under reflux for 2 h. After cooling, the precipitate formed was filtered off, washed with petroleum ether and recrystallized (acetic acid) to give **14** (87%), m.p. > 360 °C. IR: 1610 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D); 7.3-7.9 (m, 14H, ArH) and 8.2 (s, 1H, pyrimidine). Anal. calcd. for $C_{26}H_{15}N_5S$ (429.47): C, 72.70; H, 3.52; N, 16.30; S, 7.46. Found: C, 72.57; H, 3.45; N, 16.02; S, 7.13.

3,4-Diphenyl-6-methylpyridazino[3″,4″:4′,5′]thieno-[2′,3′:4,5]pyrimido[1,6-a]benzimidazole (15)

Compound **13** (0.42 g, 0.001 mol) and acetic anhydride (15 mL) were heated under reflux for 5 h. Upon cooling, the precipitate that formed was collected and recrystallized (acetic acid) to afford **15** (64%), m.p. > 360 °C. IR: 1620 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D); 3.3 (s, 3H, CH_3) and 7.3-7.9 (m, 14H, ArH). Anal. calcd. for $C_{27}H_{17}N_5S$ (443.49): C, 73.11; H, 3.86; N, 15.79; S, 7.22. Found: C, 72.84; H, 3.66; N, 15.56; S, 6.95.

Reaction of compound 13 with aromatic aldehydes; formation of pyridazino[3″,4″:4′,5′]thieno[2′,3′;4,5]pyrimido-[1,6-a]benzimidazoles 16a-c

A mixture of **13** (0.002 mol) and the appropriate aromatic aldehydes (0.002 mol) in glacical acetic acid (15 mL) was heated under reflux for 4 h. Upon cooling, the precipitate formed was collected and recrystallized from the proper solvent to afford **16a-c**.

Compound 16a

It was obtained in 78% yield (acetic acid), m.p. 281-283 °C. IR: 3400 cm^{-1} (NH) and 1600 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): 5.6 (s, 1H, CH) and 7.3-7.6 (m, 19H, ArH). Anal. calcd. for $C_{32}H_{21}N_5S$ (507.57): C, 75.71; H, 4.17; N, 13.79; S, 6.31. Found: C, 75.54; H, 4.02; N, 13.59; S, 6.11.

Compound 16b

It was obtained in 72% yield (ethanol-chloroform), m.p. 268-270 °C. IR: 3440 cm^{-1} (NH) and 1600 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): 3.9 (s, 3H, CH_3), 5.7 (s, 1H, CH) and 7.3-7.8 (m, 18H, ArH). Anal. calcd. for $C_{33}H_{23}N_5OS$ (537.60): C, 73.72; H, 4.31; N, 13.02; S, 5.96. Found: C, 73.51; H, 4.03; N, 12.88; S, 5.62.

Compound 16c

It was in 79% yield, m.p. 325-327 °C (acetic acid). IR: 3445 cm^{-1} (NH) and 1600 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): 5.8 (s, 1H, CH) and 7.2-7.8 (m, 18H, ArH). Anal. Calcd. for $C_{32}H_{20}N_6O_2S$ (552.57): C, 69.55; H, 3.64; N, 15.20; S, 5.80. Found: C, 69.23; H, 3.52; N, 15.01; S, 5.72.

3,4-Diphenylpyridazino[3″,4″:4′,5′]thieno[2′,3′:4,5]triazino[1,6-a]benzimidazole (17)

To compound **13** (0.82 g, 0.002 mol) in a mixture of acetic acid (9 mL) and hydrochloric acid (3 mL) was added with stirring a solution of sodium nitrite (0.2 g in 5 mL H_2O). After addition, stirring was continued for 5 h. The product that formed was filtered off and recrystallized (acetic acid) to afford **17** (62%), m.p. 240-242 °C. IR: 1620 cm^{-1} (C=N). Anal. calcd. for $C_{25}H_{14}N_6S$ (430.46): C, 69.75; H, 3.27; N, 19.52; S, 7.44. Found: C, 69.55; H, 3.12; N, 19.33; S, 7.23.

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