

## 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.

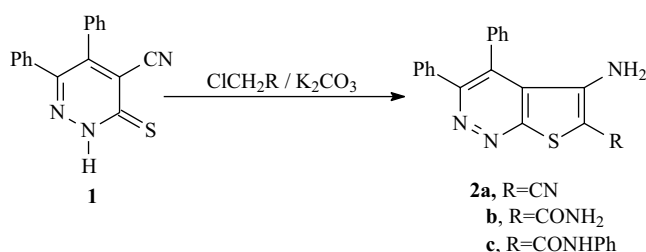
### INTRODUCTION

It is interesting to note that many pyridazine derivatives have antihypertensive<sup>1</sup> and cardiotonic activity.<sup>2</sup> Also other pyridazine derivatives serve as insecticides, miticides and nematocides.<sup>3</sup> In view of the above benefits and in continuation of our work on the synthesis and reactivity of pyridazines,<sup>4-7</sup> 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.

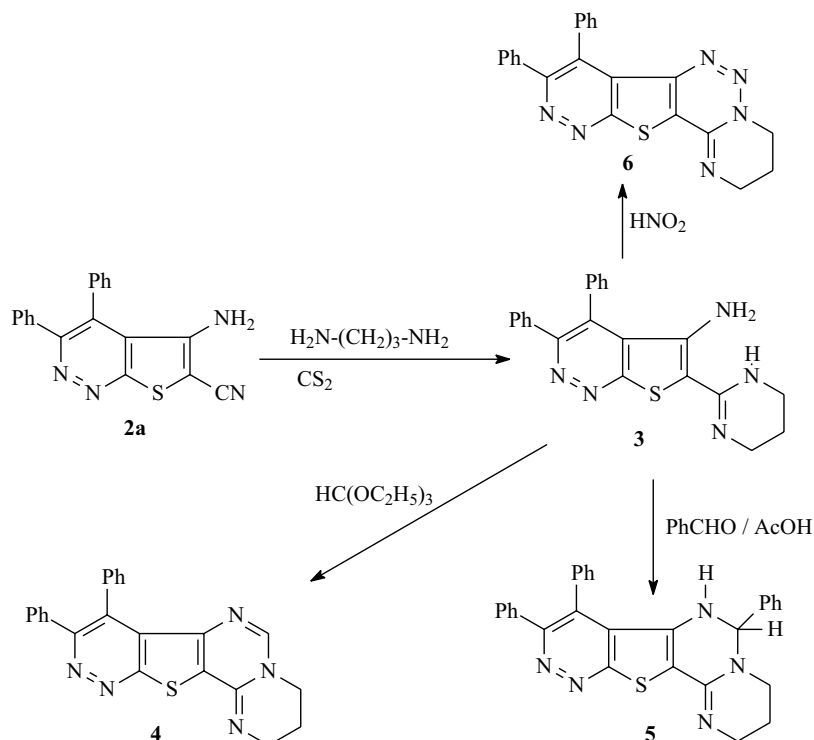
Scheme I



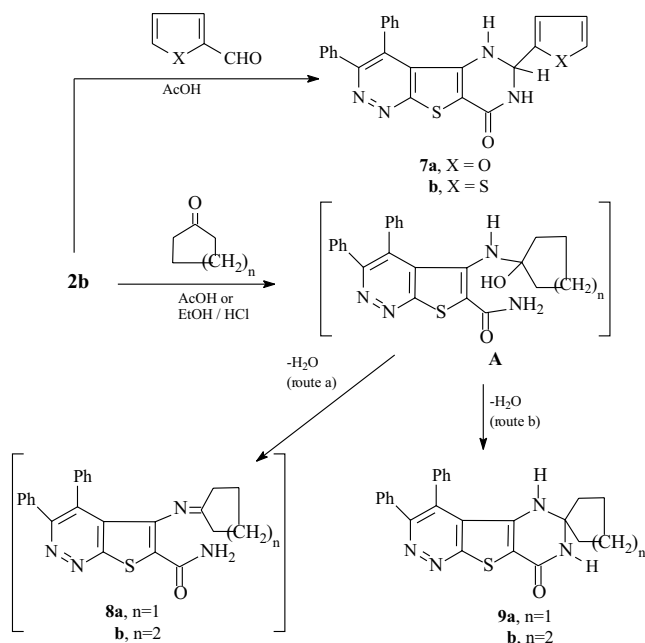
Reaction of 6-cyano-5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine (**2a**) with propylene diamine in the presence of carbon disulfide gave the tetrahydropyrimidinyl derivative **3**.<sup>8</sup> The latter compound upon reaction with triethyl orthoformate or benzaldehyde, in refluxing acetic acid,<sup>9</sup> 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<sup>10</sup> 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  $\text{cm}^{-1}$  characteristic for (2NH) and an absorption band at 1650  $\text{cm}^{-1}$  for (C=O). The IR spectra revealed also the absence of any bands corresponding to a NH<sub>2</sub> group. The <sup>1</sup>H NMR spectra in DMSO-*d*<sub>6</sub> showed no signal equivalent to a CONH<sub>2</sub> group but showed two singlets at  $\delta$  4.4 equivalent to (NH) and at  $\delta$  6.5 to (NH). The proposed pathway of this reaction is depicted in

Scheme II



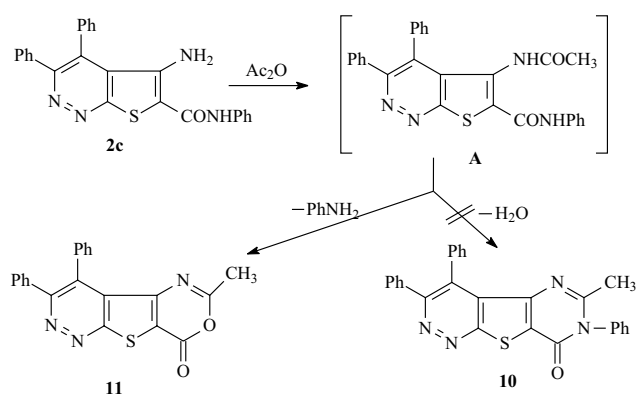
Scheme III



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 than the pyrimidinone **10**.<sup>11</sup> The pathway of this reaction is given in Scheme IV.

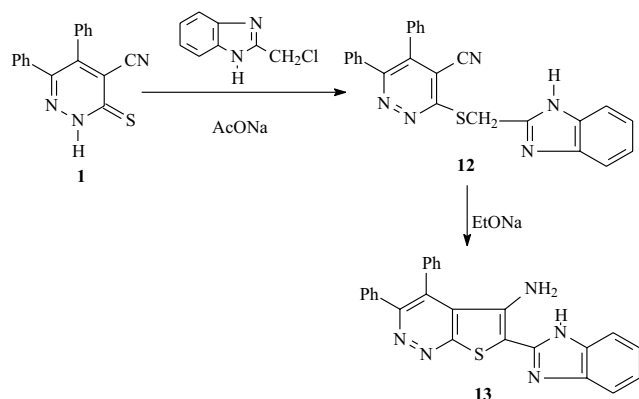
Scheme IV



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<sup>12</sup> upon heating with sodium ethoxide in ethanol to give 5-amino-6-(1*H*-benzimi-

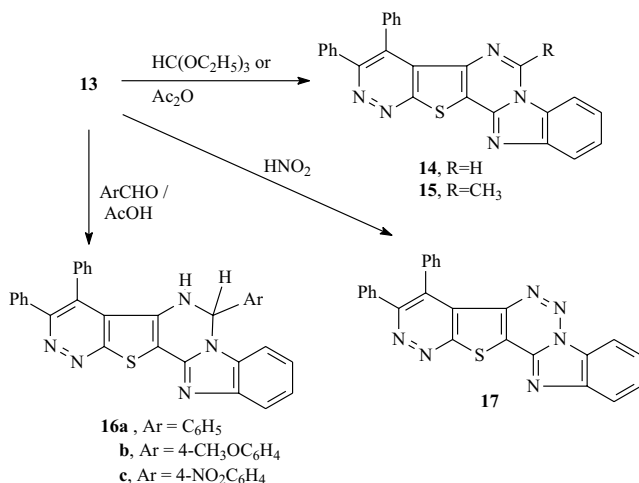
dazol-2-yl)-3,4-diphenylthieno[2,3-*c*]pyridazine derivative **13** (Scheme V).

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;  $\nu_{\max}$  in cm<sup>-1</sup>). <sup>1</sup>H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard ( $\delta$  in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on an Elemental Analyses system GmbH VARIOEL V<sub>2.3</sub> July 1998 CHNS Mode.

### 6-Functionalized 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazines **2a-c**

These compounds were prepared according to our previous method.<sup>13-15</sup>

### 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<sup>-1</sup> (NH<sub>2</sub>, NH) and 1600 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 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<sub>2</sub>), 6.7 (s, 1H, NH) and 7.3-7.5 (m, 10H, ArH). Anal. calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>5</sub>S (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 orthoformate (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<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 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<sub>23</sub>H<sub>17</sub>N<sub>5</sub>S (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 glacial 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  $\text{cm}^{-1}$  (NH) and 1620  $\text{cm}^{-1}$  (C=N).  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ): 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  $\text{C}_{29}\text{H}_{23}\text{N}_5\text{S}$  (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  $\text{H}_2\text{O}$ ). 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  $\text{cm}^{-1}$  (C=N). Anal. Calcd. for  $\text{C}_{22}\text{H}_{16}\text{N}_6\text{S}$  (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 heterocyclic aldehyde 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  $\text{cm}^{-1}$  (NH) and 1650  $\text{cm}^{-1}$  (C=O).  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ): 6.6 (s, 1H, CH) and 7.2–7.7 (m, 13H, ArH and thiophene protons). Anal. calcd. for  $\text{C}_{24}\text{H}_{16}\text{N}_4\text{OS}_2$  (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  $\text{cm}^{-1}$  (NH) and 1650  $\text{cm}^{-1}$  (C=O).  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ): 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  $\text{C}_{24}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$  (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  $\text{cm}^{-1}$  (2NH) and 1650  $\text{cm}^{-1}$  (C=O).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 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  $\text{C}_{24}\text{H}_{20}\text{N}_4\text{OS}$  (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  $\text{cm}^{-1}$  (2NH) and 1650  $\text{cm}^{-1}$  (C=O).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 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  $\text{C}_{25}\text{H}_{22}\text{N}_4\text{OS}$  (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  $\text{cm}^{-1}$  (C=O) and 1600  $\text{cm}^{-1}$  (C=N).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.6 (s, 3H,  $\text{CH}_3$ ) and 7.3–7.7 (m, 10H, ArH). Anal. calcd. for  $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$  (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-1H-benzimidazole; formation of benzimidazolylthieno[2,3-c]pyridazine derivative **12**

A mixture of compound **1** (2.89 g, 0.01 mol), 2-chloromethyl-1H-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  $\text{cm}^{-1}$  (NH), 2200  $\text{cm}^{-1}$  (C $\equiv$ N).  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ): 5.2 (s, 2H,  $\text{CH}_2$ ) and 7.2–7.8 (m, 14H, ArH). Anal. calcd. for  $\text{C}_{25}\text{H}_{17}\text{N}_5\text{S}$  (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<sup>-1</sup> (NH) and 1600 cm<sup>-1</sup> (C=O). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 7.3-7.7 (m, 14H, ArH). Anal. calcd. for C<sub>25</sub>H<sub>17</sub>N<sub>5</sub>S (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<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 7.3-7.9 (m, 14H, ArH) and 8.2 (s, 1H, pyrimidine). Anal. calcd. for C<sub>26</sub>H<sub>15</sub>N<sub>5</sub>S (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<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 3.3 (s, 3H, CH<sub>3</sub>) and 7.3-7.9 (m, 14H, ArH). Anal. calcd. for C<sub>27</sub>H<sub>17</sub>N<sub>5</sub>S (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 glacial 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<sup>-1</sup> (NH) and 1600 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 5.6 (s, 1H, CH) and 7.3-7.6 (m, 19H, ArH). Anal. calcd. for C<sub>32</sub>H<sub>21</sub>N<sub>5</sub>S (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<sup>-1</sup> (NH) and 1600 cm<sup>-1</sup> (C=N).

<sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 3.9 (s, 3H, CH<sub>3</sub>), 5.7 (s, 1H, CH) and 7.3-7.8 (m, 18H, ArH). Anal. calcd. for C<sub>33</sub>H<sub>23</sub>N<sub>5</sub>OS (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<sup>-1</sup> (NH) and 1600 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CF<sub>3</sub>CO<sub>2</sub>D): 5.8 (s, 1H, CH) and 7.2-7.8 (m, 18H, ArH). Anal. Calcd. for C<sub>32</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S (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<sub>2</sub>O). 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<sup>-1</sup> (C=N). Anal. calcd. for C<sub>25</sub>H<sub>14</sub>N<sub>6</sub>S (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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