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### Pyridazine Derivatives and Related Compounds, Part 20:<sup>1</sup> Synthesis of Different Heterocycles from 5-Aminothieno[2,3-c]pyridazine-6-carbohydrazide

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## Pyridazine Derivatives and Related Compounds, Part 20:<sup>1</sup> Synthesis of Different Heterocycles from 5-Aminothieno[2,3-*c*]pyridazine-6-carbohydrazide

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*7-substituted 3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines were synthesized starting from 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbohydrazide (1). Reaction of carbohydrazide 1 with phthalic anhydride afforded 12,13-diphenyl-6H-pyridazino-[3'',4'': 5',4']thieno[3',2':4,5]pyrimido-[2,1-*a*]phthalazine-5,6-dione, (6) which underwent further transformation to the related compounds.*

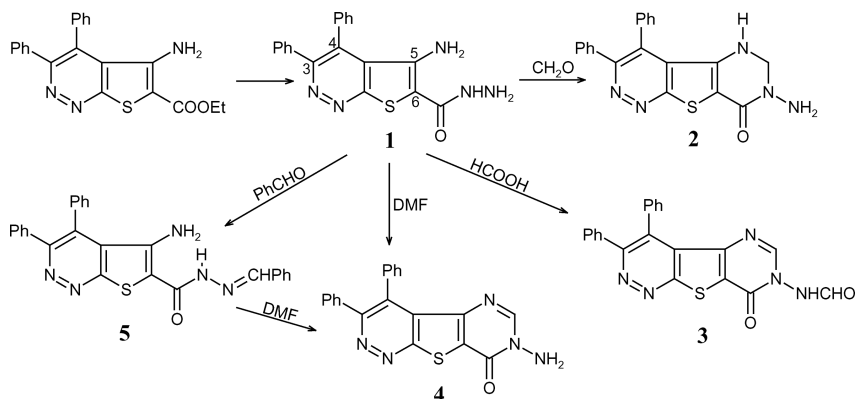
Derivatives of the thienopyridazine ring systems are known to possess potent biological and pharmacological properties.<sup>2</sup> As a part of our continuing study on the synthesis of fused pyridazine,<sup>3</sup> we became interested in the synthesis of new heterocyclic systems derived from thienopyridazine. In this context, we now wish to report the conversion of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbohydrazide (1) into derivatives of the new heterocyclic system in incorporating the thieno-pyridazine moiety.

Compound 1 was used as the starting material because it has suitable substituents for building on other heterocyclic rings and could be obtained from refluxing a solution of ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate and hydrazine hydrate in ethanol.<sup>4</sup> The pyrimidine rings were attached to the thiophene ring with different cyclization conditions. When carbohydrazide 1 was cyclized via refluxing with formaldehyde in presence of methanol, 7-amino-3,4-diphenyl-5,6-dihydropyrimido [4',5':4,5] thieno[2,3-*c*]pyridazin-8(7*H*)-one (2) was obtained in good yield (Scheme 1). Compound 2 was characterized by microanalyses and spectroscopic data. The mass spectra of 2 showed the expected molecular ion peak, and the IR spectra exhibited the characteristic bands of the amide group. Moreover, compound 2

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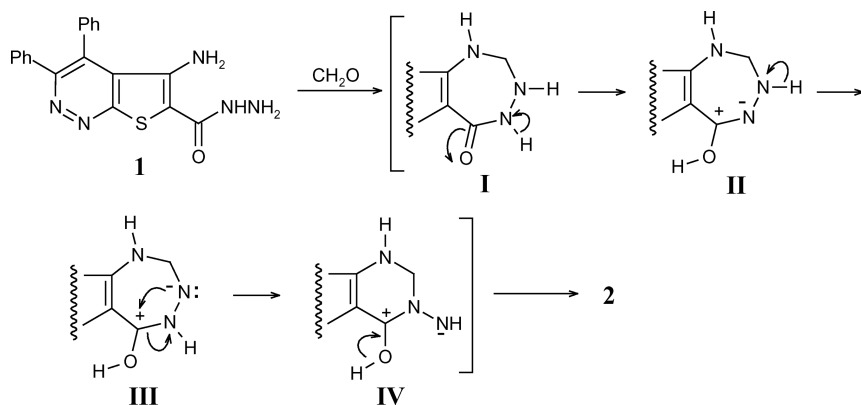
showed a characteristic peak between  $\delta$  5.73 and  $\delta$  6.55 for the 2 H-6 protons in the  $^1\text{H}$ -NMR spectra and two signals  $\delta$  4.08–5.16 and  $\delta$  6.03 exchangeable with deuterium, which can be attributed to the N-bound proton at position 5 and the  $\text{NH}_2$  at position 7, respectively.



**SCHEME 1**

Mechanistically, the formation of the tricyclic compound **2** from **1** and formaldehyde involves the initial condensation with two hydrogen atoms of the amino and hydrazido primary groups, forming 1,2,4-triazepine derivative **I**. The latter involves transfer of the hydrogen atom from an NH group to the oxygen atom to form a hybrid **II** (Scheme 2). The hybrid, following a translocation of the hydrogen atom from the nitrogen atom at position 7, changes into a transient structure **III**. The strongly electronegative nitrogen atom, in an internuclear nucleophilic rearrangement, forms a link with the carbonyl carbon atom and displaces the C–N bond. Structure **IV**, formed as a result of that rearrangement, is not stable and, after translocation of the hydrogen atom from the carbonyl oxygen atom, is transformed into compound **2**.

Similarly, the expected formylamino derivative **3** (Scheme 1) was obtained in high yield by refluxing 5-amino-6-carbohydrazide **1** with formic acid. Structural elucidation of compound **3** was accomplished from its analytical and spectral data. The mass spectrum showed the expected molecular ion peak and the IR spectra of compound **3** exhibited strong absorption bands at  $3310\text{--}3360\text{ cm}^{-1}$  due to an NH group at  $1670$  and  $1690\text{ cm}^{-1}$  due to the carbonyl groups. The  $^1\text{H}$ -NMR spectrum exhibited two singlet signals at  $\delta$  8.70 and  $\delta$  11.30 due to the NH and CHO groups, respectively; in addition, the 2Ph and H-6 protons resonated as a multiplet at  $\delta$  7.20–7.60, confirming the proposed structure.



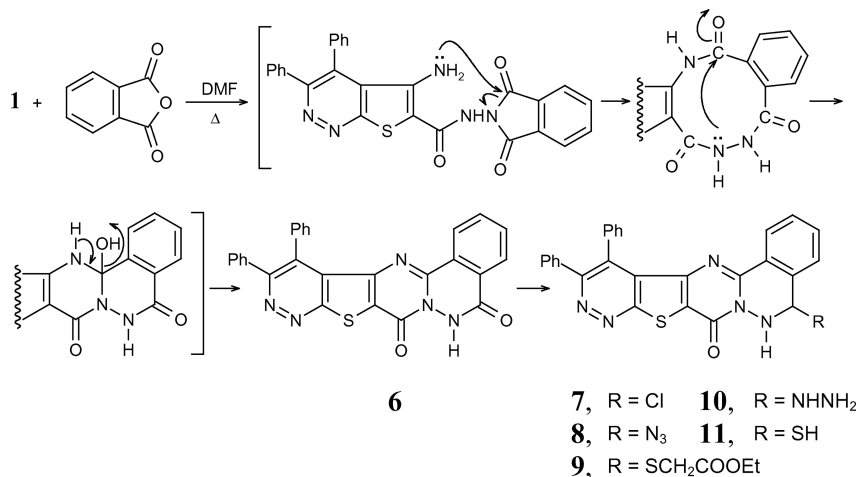
SCHEME 2

The cyclocondensation of 5-amino-6-carbohydrazide **1** in presence of dimethylformamide at refluxing temperature afforded a single product in a 60% yield. The isolated product was proven to be 7-amino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-*c*]pyridazin-8(7*H*)-one (**4**) (Scheme 1).

Alternatively, compound **4** was obtained upon heating with dimethyl-formamide and benzlidenecarbohydrazone **5**,<sup>4</sup> which underwent formylation and cyclization, followed by hydrolysis, to furnish **4**. The molecular structure of **4** was supported by spectral data and elemental analysis.

On the other hand the condensation of phthalic anhydride with the carbohydrazide **1** in dimethylformamide gave the 12,13-diphenyl-6*H*-pyridazino [3'',4'':5',4']thieno[3',2':4,5]pyrimido[2,1-*a*] phthalazine-5,8-dione (**6**) (Scheme 3). Structural elucidation of compound **6** was accomplished from its analytical and spectral data. The mass spectrum showed the expected molecular ion peak, and the IR spectrum exhibited strong absorption bands at 3310–3350 cm<sup>-1</sup> due to an NH group and at 1690 cm<sup>-1</sup> and 1665 cm<sup>-1</sup> due to the carbonyl groups. Mechanistically, the formation of the pentacyclic **6** involved the initial formation of a cyclic isoindole derivative, which underwent immediate intramolecular nucleophilic attack by the thiophene amino group on the isoindole carbonyl group with the elimination of a water molecule.

The reaction of compound **6** with phosphoryl chloride gave the corresponding 5-chloro derivative **7**, which has served as a facile point of departure into the desired molecules. The chloride atom of **7** showed the expected reactivity towards nucleophilic reagents such as azide and



### SCHEME 3

ethyl thioglycolate anions, giving the phthalazines **8** and **9**, respectively, while with hydrazine hydrate, hydrazinophthalazine **10** formed. Alternatively, the thionation of **7** with thiourea, followed by basic hydrolysis, resulted in the 5-mercaptophthalazine derivative **11** (Scheme 3). On the other hand, reacting **11** with ethyl chloroacetate in boiling acetone in presence of potassium carbonate afforded a single product. The isolated product proved to be identical in every respect with 5-carbethoxymercapto **9**. The structure of these compounds was assigned by elemental analyses as well as IR, mass, and NMR spectral data and are summarized under the Experimental section.

### EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and were uncorrected. The IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1310 as potassium bromide pellets, and frequencies are reported in cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectra were observed on a Perkin-Elmer R12B spectrometer, and chemical shifts (δ) are in δ (ppm) relative to internal TMS. Mass spectra were obtained at 70 eV by using a AEI MS 30 mass spectrometer. All reactions were monitored by thin layer chromatography and carried out on 0.2 mm silica gel 60F-254 (Merck) plates using UV light (254 nm and 366 nm).

**7-Amino-3,4-Diphenyl-5,6-Dihydropyrimido[4',5':4,5]thieno[2,3-c]-Pyridazin-8(7H)-One (2)**

To a solution of compound **1** (0.5 g, 1.38 mmol) in methanol (20 mL), was added formaldehyde (5 mL), and the reaction mixture was refluxed for 2 h. The solvent was evaporated under reduced pressure, and the residue was treated with water. The precipitate was filtered off, dried, and recrystallized from ethanol to give **2** (0.46 g, 90%), m.p. 195–196°C. IR: 3302, 3180 (NH, NH<sub>2</sub>), 1671 (C=O), 1613 (C=C) cm<sup>-1</sup>; MS *m/z* (%): 371 (M<sup>+</sup>, 3.9), 343 (M<sup>+</sup>-CO, 10.3, ion A) 299 (ion A-CH<sub>2</sub>=N-NH<sub>2</sub>, 4.3); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 6.8–7.1 (m, 10H, 2Ph), 6.55 (s, 2H, 2H-6), 6.03 (s, 2H, NH<sub>2</sub> exchangeable with deuterium), 5.16–4.98 (brs, 1H, NH, exchangeable with deuterium). Anal. Calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>5</sub>OS: C, 64.32; H, 4.04; N, 18.75. Found: C, 64.10; H, 3.90; N, 18.50.

**7-Formylamino-3,4-Diphenylpyrimido[4',5':4,5]thieno[2,3-c]-pyridazin-8(7H)-One (3)**

A mixture of compound **1** (0.5 g, 1.38 mmol) and formic acid (10 mL) was refluxed for 2 h. The reaction mixture was poured into water (50 mL), and the precipitate was filtered off, dried, and recrystallized from *n*-butanol to give **3** (0.3 g, 76.7%), m.p. 260–261°C. IR: 3360–310 (NH), 1690 (C=O formyl), 1670 (C=O cyclic) cm<sup>-1</sup>; MS, *m/z* (%): 400 (M<sup>+</sup> + 1, 2.1); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 1.3 (s, 1H, CHO), 8.7 (s, 1H, NH), 7.6–7.2 (m, 11H, 2Ph + H-6). Anal. Calcd. for C<sub>21</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>S: C, 63.14; H, 3.28; N, 17.53. Found: C, 63.00; H, 3.10; N, 17.40.

**7-Amino-3,4-Diphenylpyrimido[4',5':4,5]thieno[2,3-c]-pyridazin-8(7H)-One (4)****Method A**

A mixture of compound **1** (0.5 g, 1.38 mmol) and dimethylformamide (5 mL) was refluxed for 12 h; the cooled reaction mixture was poured into water (50 mL), and the precipitate was filtered off, dried, and recrystallized (ethanol) to give **4** (0.3 g, 60%), m.p. 177–178°C. IR: 3388, 3177 (NH<sub>2</sub>), 1735 (C=O), 1692 (C=N), 1610 (C=C) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 8.2 (s, 1H, H-6), 7.4–7.1 (m, 10H, 2Ph), 3.4 (s, 2H, NH<sub>2</sub>). Anal. Calcd. for C<sub>20</sub>H<sub>13</sub>N<sub>5</sub>OS: C, 64.67; H, 3.52; N, 18.85. Found: C, 64.50; H, 3.40; N, 18.70.

**Method B**

A mixture of compound **5**<sup>4</sup> (0.5 g, 1.11 mmol) and dimethylformamide (10 mL) was refluxed for 16 h. The cooled reaction mixture

was poured into water (50 mL), and the precipitate was filtered off, dried, and recrystallized (ethanol) to give **4** (0.29 g, 72.6%). It was identical with that prepared by Method A.

### **12,13-Diphenyl-6H-Pyridazino[3'',4'':5',4']thieno[3',2':4,5]-pyrido-[2,1-a]phthalazine-5,8-Dione (6)**

To a solution of compound **1** (0.5 g, 1.38 mmol) in dimethyl-formamide (5 mL), was added phthalic anhydride (0.2 g, 1.38 mmol). The reaction mixture was refluxed for 4 h, was cooled, and poured into water (50 mL). The precipitate was filtered off, washed with ethanol, dried, and recrystallized from *n*-butanol to give **6** (0.4 g, 58.8%), m.p. 182–183°C. IR: 3350, 3310 (NH), 1690 and 1665 for carbonyl groups, 1651 (C=N), 1610 (C=C)  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  9.8 (s, 1H, NH), 7.9–7.7 (m, 4H, aromatic), 7.4–7.1 (m, 10H, 2Ph). Anal. Calcd. for  $\text{C}_{27}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ : C, 68.48; H, 3.19; N, 14.79. Found: C, 68.30; H, 3.00; N, 14.60.

### **5-Chloro-12,13-Diphenylpyridazino[3'',4'':5,4]thieno-[3',2':4,5]-pyrido-[2,1-a]phthalazin-8-One (7)**

A mixture of compound **6** (0.5 g, 1.05 mmol) and phosphoryl chloride (5 mL) was refluxed for 4 h. The reaction mixture was poured into water (30 mL), and the precipitate was filtered off, dried, and recrystallized (ethanol) to give **7** (0.46 g, 89.2%), m.p. 280–281°C. IR: 3100 (CH aromatic), 1740 (C=O), 1623 (C=N), 1599 (C=C)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.8–7.2 (m, 14H, aromatic protons). Anal. Calcd for  $\text{C}_{27}\text{H}_{14}\text{ClN}_5\text{OS}$ : C, 65.91; H, 2.86; N, 14.23. Found: C, 65.80; H, 2.80; N, 14.10.

### **5-Azido-12,13-Diphenylpyridazino[3'',4'':5',4']thieno-[3',2':4,5]pyrido-[2,1-a]phthalazin-8-One (8)**

To a solution of compound **7** (0.5 g, 1.01 mmol) in ethanol (10 mL), was added sodium azide (0.19 g, 3.03 mmol). The reaction mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was treated with water. The precipitate was filtered off, dried, and recrystallized from ethanol to give **8** (0.4 g, 80%), m.p. 220–221°C. IR: 2200 ( $\text{N}_3$ ), 1716 (C=O), 1640 (C=N), 1603 (C=C)  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{27}\text{H}_{14}\text{N}_8\text{OS}$ : C, 65.04; H, 2.83; N, 22.47. Found: C, 64.90; H, 2.70; N, 22.20.

### **5-Carbethoxymethylmercapto-12,13-Diphenylpyridazino-[3'',4'':5',4']-Thieno[3',2':4,5] pyrido[2,1-a]phthalazin-8-One (9)**

To a solution of compound **7** (0.5 g, 1.01 mmol) in dry acetone (20 mL), were added ethyl 2-mercaptoacetate (0.12 g, 1.01 mmol) and unhydrous

potassium carbonate (0.11 g, 1.01 mmol). The reaction mixture was refluxed for 10 h. The insoluble solid was removed by filtration and washed with acetone. The combined filtrate was evaporated under reduced pressure, and the residue was washed with water, filtered off, dried, and recrystallized (ethanol) to give **9** (0.3 g, 51.7%), m.p. 190–191°C. IR: 1738 (C=O ester), 1659 (C=O cyclic), 1625 (C=N)  $\text{cm}^{-1}$ ; MS,  $m/z$  (%): 575 ( $\text{M}^+$ , 1.4), 502 ( $\text{M}^+ - \text{CO}_2\text{Et}$  3.8), 456 ( $\text{M}^+ - \text{SCH}_2\text{CO}_2\text{Et}$ , 2.2). Anal. Calcd. for  $\text{C}_{31}\text{H}_{21}\text{N}_5\text{O}_3\text{S}_2$ : C, 64.67; H, 3.67; N, 12.16. Found: C, 64.40; H, 3.50; N, 12.00.

### 5-Hydrazino-12,13-Diphenylpyridazino[3'',4'':5',4']thieno-[3',2':4,5]-Pyrido[2,1-a]Phthalazin-8-One (**10**)

To a solution of compound **7** (0.5 g, 1.01 mmol) in ethanol (10 mL) was added hydrazine hydrate 85% (0.5 g, 1.01 mmol). The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure, and the residue was treated with water. The precipitate was filtered off, dried and recrystallized (ethanol) to give **10** (0.3 g, 61.2%), m.p. 180–181°C. IR: 3173, 3075 (NH,  $\text{NH}_2$ ), 1655 (C=O), 1600 (C=N), 1595 (C=C)  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{27}\text{H}_{17}\text{N}_7\text{O}$ S: C, 66.51; H, 3.51; N, 20.11. Found: C, 66.30; H, 3.20; N, 19.90.

### 5-Mercapto-12,13-Diphenylpyridazino[3'',4'':5',4']thieno-[3',2':4,5]-Pyrido[2,1-a]phthalazin-8-One (**11**)

To a solution of compound **7** (0.5 g, 1.01 mmol) in ethanol (10 mL) was added thiourea (0.07 g, 1.01 mmol). The mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue treated with 2.5 *N* sodium hydroxide (15 mL). The mixture was refluxed for 2 h. The reaction mixture was filtered hot, and the cooled filtrate was neutralized with 3 *N* hydrochloric acid (pH = 6). The precipitate was filtered off, washed with water, dried, and recrystallized (ethanol) to give **11** (0.3 g, 61.2%), m.p. 250–251°C. IR: 2400 (SH), 1640 (C=O), 1620 (C=N)  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{27}\text{H}_{15}\text{N}_5\text{OS}_2$ : C, 66.23; H, 3.08; N, 14.30. Found: C, 66.00; H, 2.90; N, 14.10.

### Reaction of Compound **11** With Ethyl Chloroacetate

To a solution of compound **11** (0.5 g, 1.02 mmol) in dry acetone (10 mL), were added ethyl chloroacetate (0.12 g, 1.02 mmol) and anhydrous potassium carbonate (0.14 g, 1.02 mmol). The reaction mixture was refluxed for 4 h and filtered hot. The filtrate was evaporated under reduced pressure. The solid residue was washed with water, dried, and

recrystallized (ethanol) to give **9** (0.35 g, 60.3%). It was identical with that prepared by previous method.

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