Synthesis and Some Reactions of New Thieno[2,3-c]pyridazine Derivatives

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Received June 11, 2002

Treatment of ethyl 5-hydroxy-3,4-diphenylthieno[2,3-c]pyridazine-6-carboxylate (**1a**) with hydrazine hydrate in ethanol gave the carbohydrazide **2**. Some derivatives of the latter compound have been synthesized. Also, 6-acetyl-3,4-diphenyl-5-hydroxythieno[2,3-c]pyridazine (**1b**) was subjected to some reactions to produce other new thienopyridazine derivatives.

Key Words : Thienopyridazines, Pyranothienopyridazines, Pyrazoline, Oxadiazole

Introduction

Pyridazines and condensed pyridazine derivatives are reported to have good biological activities and consequently, 4-phenylfuro[2,3-d]pyridazin-7-one used as intermediate for cardiovascular agents.[1] Some thieno[3,4-d]pyridazines were used as modules of protein tyrosine phosphatases (PTpases).[2] Also, some imidazo[1,2-b]pyridazine derivatives are reported to possess antiasthmatic[3] and analgesic activity.[4] In view of the aforementioned facts and as a continuation of our previous work on the chemistry of pyridazine compounds,[5-9] we report herein the synthesis of some heterocyclic systems containing thieno[2,3-c]pyridazine moiety, as new compounds in this field, of anticipated biological activities.

Results and Discussion

In our previous work,[10] we proved that compounds **1a**, **b** exist predominantly in the enol form rather than keto form. Thus, compound **1a** reacts smoothly with hydrazine hydrate to give the corresponding carbohydrazide derivative **2** (Scheme 1).

Treatment of the carbohydrazide **2** with sodium nitrite in glacial acetic acid at room temperature produced the carboazide derivative **3** which underwent *Curtius* rearrangement followed by intramolecular cyclization upon refluxing in dry toluene to furnish oxazolo[5',4':4,5]thieno[2,3-c]pyridazine **5** *via* the isocyanate intermediate **4**. Compound **2** also reacts with triethyl orthoformate, benzaldehyde, acetic acid and / or phenyl isothiocyanate to afford compounds **6**, **7**, **8** and **9** respectively. Moroever, heating of the thiourea derivative **9** with ethanolic sodium hydroxide solution afforded the triazolinethione derivative **10** (Scheme 2).

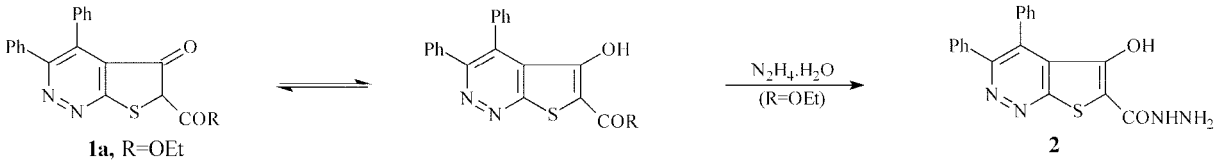
Furtheremore, refluxing of compound **6** in glacial acetic acid resulted in the formation of the oxadiazolyl derivative **11**, instead of the tricyclic compound **12** *via* elimination of ethanol (Scheme 3).

Thieno[2,3-c]pyridazine derivative **1b** reacts with hydrazine hydrate, benzaldehyde and/or ethyl cyanoacetate in the presence of ammonium acetate to afford the expected compounds **13**, **14** and **15**, respectively. Upon heating of the styryl derivative **14** in a mixture of acetic acid and orthophosphoric acid, it readily cyclized into pyrano[2',3':4,5]thieno[2,3-c]pyridazine derivative **16**. The cyclocondensation reaction of **14** with hydrazine hydrate in refluxing ethanol gave the pyrazolinyl compound **17** (Scheme 4).

Experimental Section

All melting points are uncorrected and measured on a Fisher-John apparatus. IR spectra were recorded on 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 an internal standard (δ in ppm). MS were recorded on a Jeol JMS-600 mass spectrometer. Elemental analysis were carried out on Elementar Analysensystem GmbH VARIOEL V2.3 July 1998 CHNS Mode; their results were in good agreement with the calculated values.

5-Hydroxy-3,4-diphenylthieno[2,3-c]pyridazine-6-carbohydrazide (2): A mixture of compound **1a** (3.6 g, 0.01 mol) and hydrazine hydrate 85% (5 mL) in ethanol (30 mL) was heated under reflux for 5 hours. Upon cooling, the solid



1a, R=OEt
1b, R=CH_3

2

Scheme 1

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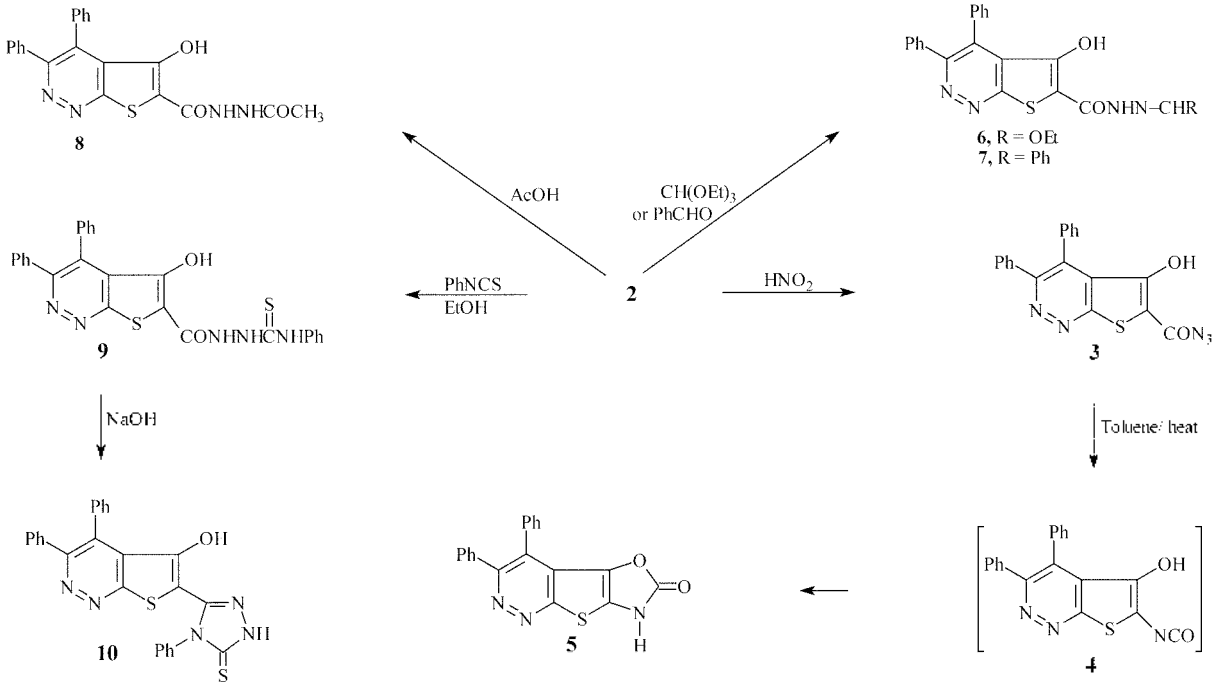
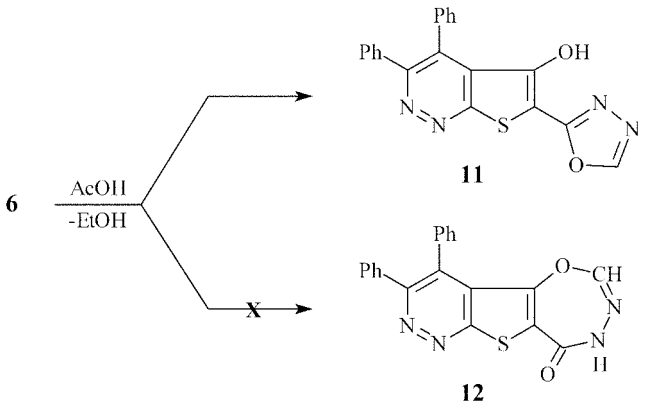


Scheme 2



Scheme 3

product so formed was filtered off and recrystallized (ethanol) to give **2** (73%), m.p.: 267-69 °C. IR: 3300, 3200, 3150 cm^{-1} (OH, $NHNH_2$) and 1640 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 4.1 (s, 2H, NH_2), δ 7.2-7.4 (m, 10H, ArH), δ 8.2 (s, 1H, NH) and 10.5 (s, 1H, OH). Anal. Calcd. for $C_{19}H_{14}N_4O_2S$ (362.38): C, 62.96; H, 3.89; N, 15.46; S, 8.8%. Found: C, 63.17; H, 3.87; N, 15.60; S, 9.11%.

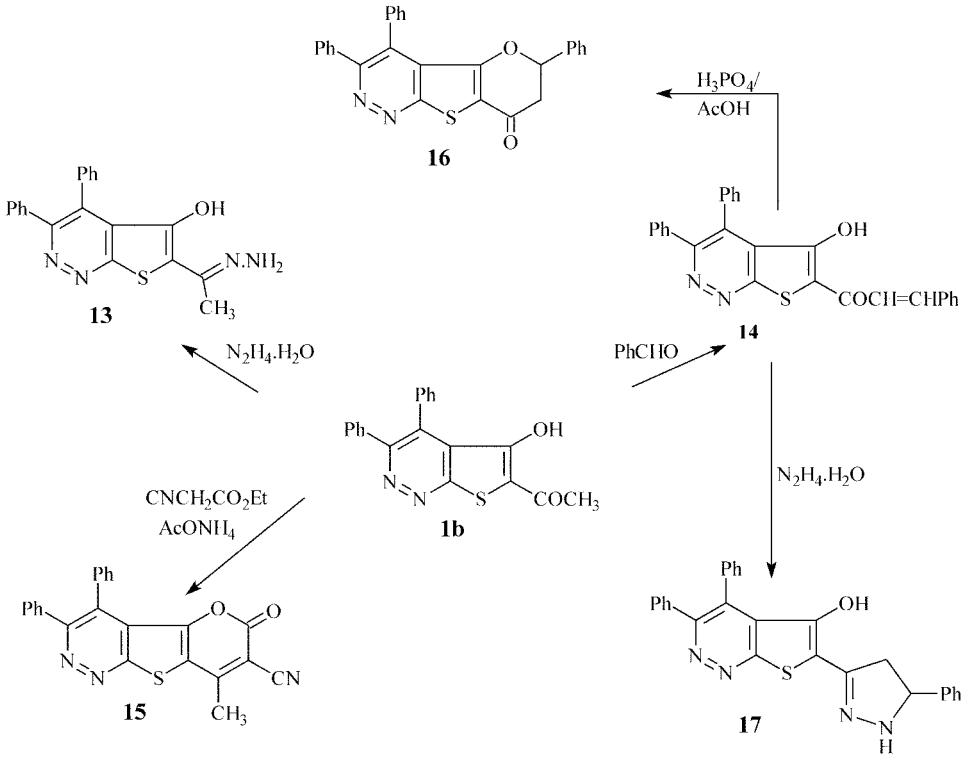
3,4-Diphenyl-5-hydroxythieno[2,3-c]pyridazine-6-carboazide (3): To a well stirred solution of **2** (0.5 g) in glacial acetic acid (15 mL) was added at room temperature a solution of sodium nitrite (0.3 g in 5 mL water) and stirring was continued for three hours. The solid that formed was filtered off, air dried and used in the next step without crystallization (65%), m.p.:160 °C (dec.). IR: 3400-3100 cm^{-1} (br., OH), 2120 cm^{-1} (N_3) and 1730 cm^{-1} (C=O). Anal. Cacd. for $C_{19}H_{11}N_5O_2S$ (373.36): C, 61.11; H, 2.96; N, 18.75; S, 8.58%. Found: C, 61.34; H, 3.11; N, 18.80; S, 8.70%.

3,4-Diphenyloxazolo[5',4':4,5]thieno[2,3-c]pyridazine-8(7*H*)-one (5): A solution of **3** (0.5 g) in dry toluene (10 mL) was refluxed for two hours and then allow to cool. The formed product was filtered off and recrysallized (acetic acid) to give **5** (64%), m.p. : 276-278 °C. IR: 3400 cm^{-1} (NH) and 1700 cm^{-1} (C=O). Anal. Cacd. for $C_{19}H_{11}N_3O_2S$ (345.34): C, 66.07; H, 3.21; N, 12.16; S, 9.28%. Found: C, 66.13; H, 3.29; N, 12.35; S, 9.12%.

Reaction of 2 with triethyl orthoformate; Formation of the methanimidate derivative 6: A mixture of **2** (1 g) and triethyl orthoformate (10 mL) was gently refluxed for 5 hours. The product precipitated after cooling was filtered off, washed with ethanol and recrystallized (ethanol/benzene) mixture to afford **6** (73%), m.p.: 247 °C. IR: 3150 cm^{-1} (NH) and 1620 cm^{-1} (C=O). ^1H NMR (TFA): δ 1.1-1.3 (t, 3H, CH_3), 4.1-4.3 (q, 2H, OCH_3), 7.2-7.5 (m, 10H, ArH), 8.1 (s, 1H, N=CH) and 11.0 (s, 1H, OH). Anal. Cacd. for $C_{22}H_{18}N_4O_3S$ (418.44): C, 63.13; H, 4.33; N, 13.38; S, 7.66%. Found: C, 62.98; H, 4.21; N, 13.44; S, 7.69%.

N^1-Benzylidene-3,4-diphenyl-5-hydroxythieno[2,3-c]pyridazine-6-carbohydrazide (7): A mixture of **2** (0.72 g, 0.002 mol) and benzaldehyde (0.12 mL, 0.002 mol) in ethanol (10 mL) was heated under reflux for two hours. The product formed after cooling was filtered off and recrystallized (acetic acid) to give 7 (83%), m.p.: 300 °C. IR 3100 cm^{-1} (NH) and 1625 cm^{-1} (C=O). ^1H NMR (TFA): δ 7.3-7.6 (m, 15H, ArH), 8.1 (s, 1H, N=CH) and 11.0 (s, 1H, OH). Anal. Cacd. for $C_{26}H_{18}N_4O_2S$ (450.48): C, 69.31; H, 4.02; N, 12.43; S, 7.11%. Found: C, 69.67; H, 4.10; N, 12.32; S, 7.20%.

Reaction of 2 with acetic acid; Formation of the monoacetyl derivative 8: Compound **2** (1 g) in glacial acetic acid (15 mL) was refluxed for 6 hours. Upon cooling,



Scheme 4

the separated product was filtered off and recrystallized (ethanol) to give **8** (67%), m.p.: 227-229 °C. IR 3300, 3200 cm^{-1} (OH, NH) and 1680, 1620 cm^{-1} (2C=O). MS: *m/z* = 404 (M+). Anal. Calcd. for $C_{21}H_{16}N_4O_3S$ (404.42): C, 62.36; H, 3.98; N, 13.85; S, 7.92%. Found:C, 62.50; H, 4.11; N, 13.78; S, 8.17%.

1-(3,4-Diphenylthieno[2,3-c]pyridazin-6-yl)-4-phenylthiosemicarbazide (9): A mixture of **2** (1.1 g, 0.002 mol) and phenyl isothiocyante (0.42 g, 0.003 mol) in ethanol (20 mL) was refluxed for 2 hours. After cooling, the precipitate that formed was filtered off, washed with ethanol and recrystallized (acetic acid) to give **9** (81%), m.p.: 236-238 °C. IR: 3300, 3200 cm^{-1} (OH, NH) and 1630 cm^{-1} (CO). Anal. Calcd. for $C_{26}H_{19}N_5O_2S_2$ (497.56): C, 62.75; H, 3.84; N, 14.07; S, 12.88%. Found: C, 62.90; H, 3.79; N, 14.11; S, 12.95%.

3,4-Diphenyl-5-hydroxy-6-(4-phenyl-3-thioxo-*s*-triazolin-5-yl)-thieno[2,3-c] pyridazine (10): A suspension of **9** (0.5 g, 0.001 mol) and NaOH (5 mL, 2N) was heated on a water bath for 5 hours. After cooling the reaction mixture was acidified with dilute HCl. The solid that formed was filtered off and recrystallized (ethanol) to give **10** (73%); m.p.: >300 °C. IR: 3450 cm^{-1} (NH), 3300 cm^{-1} (OH) and 1620 cm^{-1} (C=N). Anal. Calcd. for $C_{29}H_{17}N_5OS_2$ (479.54): C, 65.11; H, 3.57; N, 14.60; S, 13.37%. Found: C, 65.10; H, 3.47; N, 14.82; S, 13.60%.

3,4-Diphenyl-5-hydroxy-6-(1,3,4-oxdiazol-5-yl)-thieno-[2,3-c]pyridazine (11): Compound **6** (0.5 g) in glacial acetic acid (10 mL) was heated under reflux for 3 hours. After cooling, the product which separated was filtered off, and recrystallized (acetic acid) to give **11** (69%); m.p.: >300 °C. IR 3450-3200 cm^{-1} (br, OH). ^{1}H NMR (TFA): δ 7.2-7.4 (m, 10H, ArH), 9.2 (s, 1H, CH oxadiazole ring) and 11.5 (s, 1H, OH). Anal. Calcd. for $C_{20}H_{12}N_7O_2S$ (372.37): C, 64.50; H, 3.21; N, 15.04; S, 8.60%. Found: C, 64.60; H, 3.23; N, 15.16; S, 8.67%.

3,4-Diphenyl-5-hydroxythieno[2,3-c]pyridazine-6-acetylhydrazone (13): A mixture of **1b** (0.5 g) and hydrazine hydrate 85% (0.1 mL) in ethanol (10 mL) was refluxed for two hours. Upon cooling, the precipitate that formed was filtered off and recrystallized (acetic acid) to give **13** (82%), m.p.: >300 °C. IR: 3400, 3200 cm^{-1} (OH, NH) and 1640 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): δ 3.3 (s, 3H, CH_3), 4.8 (s, 2H, NH_2), 7.3-7.6 (m, 10H, ArH) and at 10.5 (s, 1H, OH). MS: *m/z* = 360 (M^+). Anal. Calcd. for $C_{20}H_{16}N_4OS$ (360.41): C, 66.64; H, 4.47; N, 15.54; S, 8.89%. Found: C, 66.80; H, 4.42; N, 15.54; S, 8.89%.

Reaction of 1b with benzaldehyde; Formation of the styryl derivative 14: To a mixture of **1b** (3.83 g, 0.01 mol) and benzaldehyde (1.5 mL, 0.015 mol) in absolute ethanol (30 mL), few drops of piperidine were added. The reaction mixture was heated under reflux for 5 hours. After cooling, the product so formed was filtered off and recrystallized (acetic acid) to give **14** (76%); m.p.: 240 °C. IR 3400-3250 cm^{-1} (br, OH) and 1660 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ 7.2-7.5 (m, 17H, ArH and CH=CH) and at 10.5 (s, 1H, OH). MS: *m/z* = 434 (M^-). Anal. Calcd. for $C_{27}H_{18}N_2O_2S$ (434.48): C, 74.63; H, 4.17; N, 6.44; S, 7.37%. Found: C, 74.41; H, 4.19; N, 6.62; S, 7.52%.

7-Cyano-3,4-diphenyl-8-methylpyrano[2',3':4,5]thieno-[2,3-c]pyridazine-6-one (15): A mixture of **1b** (1.7 g, 0.005 mol), ethyl cyanoacetate (1.1 g, 0.01 mol) and ammonium

acetate (2 g) was gently refluxed for 4 hours. Upon cooling, the product that formed was filtered off, washed with water and recrystallized (acetic acid) to give **15** (63%); m.p.: >300 °C. IR: 2200 cm^{-1} (CN) and 1770 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 3.3 (s, 3H, CH_3) and 7.2-73 (m, 10H, ArH). MS: m/z = 395 (M^+). Anal. Calcd. for $C_{23}H_{13}N_3O_2S$ (395.43): C, 69.86; H, 3.31; N, 10.63; S, 8.11%. Found: C, 69.70; H, 3.34; N, 10.71; S, 8.00%.

8-Oxo-6,7,8-trihydro-3,4,6-triphenylpyrano[2',3':4,5]-thieno[2,3-c]pyridazine (16): A sample of **14** (0.5 g) in glacial acetic acid (10 mL) and orthophosphoric acid (4 mL) was heated at 100 °C for 3 hours. The cooled reaction mixture was diluted with water and neutralized with ammonia solution. The product that separated was filtered off, washed with water and recrystallized (ethanol-chloroform) mixture to give **16** (60%); m.p.: 263-265 °C. IR 1700 cm^{-1} (C=O, pyranone). ^1H NMR (DMSO-d_6): δ 2.7 (d, 2H, CH_2), δ 4.7 (t, 1H, CH) and d 7.3-7.6 (m, 15H, ArH). Anal. Calcd. for $C_{27}H_{18}N_2O_2S$ (434.48): C, 74.63; H, 4.17; N, 6.44; S, 7.37%. Found: C, 74.72; H, 4.16; N, 6.73; S, 7.56%.

3,4-Diphenyl-5-hydroxy-(5-phenyl-D^2-pyrazolin-3-yl)-thieno[2,3-c]pyridazine (17): A mixture **14** (1 g) and hydrazine hydrate 85% (0.4 mL) in ethanol (10 mL) was refluxed for 3 hours. The solid product which formed on cooling was filtered off and recrystallized (ethanol) to give **17** (75%); m.p.: 282-284 °C. IR: 3300, 3050 cm^{-1} (NH, OH). ^1H NMR (DMSO-d_6): δ 3.0 (s, 1H, NH pyrazoline), 3.3 (d, 2H, CH_2 pyrazoline); 4.6 (t, 1H, CH pyrazoline), 7.2-7.6 (m, 15H, ArH) and at 10.5 (s, 1H, OH). Anal. Calcd. for $C_{27}H_{20}N_4OS$ (448.51): C, 72.29; H, 4.49; N, 12.49; S, 7.14%. Found: C, 72.63; H, 4.34; N, 12.60; S, 7.37%.

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