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A Simple and Efficient Synthesis of New Substituted Benzothienopyridazine Spiro- Derivatives of Pyrazolone, Pyrimidinone and Diazepinone

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ABSTRACT

*Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **1** was used as a starting material to synthesize **2a-c** via coupling with acetyl acetone, ethylcyanoacetate or malononitrile, respectively. Heating under reflux in sodium ethoxide solution **2a-c** gave **3a-c**. When compounds **3a-c** were heated under reflux in ethanol with hydrazine hydrate, thiourea or 1,2-diaminoethane and a catalytic amount of piperidine to produce the spiro compounds **4a-c**, **5a-c** and **6**, respectively.*

Keywords: spiro, benzothiophene, benzothienopyridazine, benzothienopyrida-zinepyrazolone, benzothienopyridazinepyrimidinone and benzothienopyridazine-diazepinone.

INTRODUCTION

Many spiro-compounds are known for their biological activities. For example, spirohydantoins and spiro-thioxanthene have been reported as glycogen and phosphorylase inhibitors, herbicides and anti-inflammatory agents [1,2], spiro-isoxazolines, spiro-dioxazoles and spirotetrazines exhibit antitumor and anti-HIV activities [3-7], spiro- pyrazole thieno, pyrimidine thieno and benzodiazepine thieno pyridazine derivatives used as antimicrobial activity [8]. In spite of the immense biological activities of many spiro heterocyclic compounds, no report is yet available on the synthesis of benzothienopyridazine spiro derivatives. Prompted by this observation, and in continuation of our earlier interest on chemical synthesis of biodynamic heterocyclic compounds [8,9] as a part of a program directed to the synthesis of different heterocyclic compounds containing the rigid conformations of spiro cyclic skeletons showing a wide range of biological and pharmacological properties [10-12], attempts have been made to synthesize novel tetracyclic derivatives bearing benzothienopyridazine moiety spiro-linked with pyrazole,

pyrimidine and diazepine nuclei, it is well known that diazepines have a wide range of biological and pharmacological activities[13,14].

EXPERIMENTAL SECTION

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus. Microanalyses were carried out at the Microanalytical units, National Research Center and Faculty of Science, Cairo University. IR spectra were recorded on a FT/IR-300 E Jasco using KBr discs. ^{1}H-NMR spectra were measured in DMSO or $CDCl_3$, using JEOL-JNM-Ex270 NMR spectrometer. Signals were measured with reference to TMS as an internal standard. The Mass spectra were recorded on Finnigan SSQ 7000 spectrometer. Microbiological analyses were carried out by the Micro-analytical Center, Faculty of Science, Cairo University, Giza, Egypt. All solid compounds were recrystallized to produce constant melting points.

Table 1: Physical data for the products 2a – 6

Comp. No.	m.p. ^{o}C	Yield %	M.F. (M.wt.)	Elemental analyses (calcd./ found)			
				%C	%H	%N	%S
2a	130-134	80	$C_{16}H_{20}N_2O_4S$ 336.38	57.13 57.18	5.98 5.86	8.32 8.30	9.53 9.47
2b	120-122	75	$C_{16}H_{19}N_3O_4S$ 349.38	55.00 55.12	5.47 5.40	12.02 12.10	9.17 8.89
2c	173-176	60	$C_{14}H_{14}N_4O_2S$ 302.33	55.61 55.57	4.66 4.62	18.53 18.32	10.60 10.91
3a	123-125	80	$C_{14}H_{14}N_2O_3S$ 290.32	57.91 57.87	4.85 4.81	9.64 9.60	11.04 10.79
3b	180-182	75	$C_{14}H_{13}N_3O_3S$ 303.32	55.43 55.41	4.31 4.27	13.85 13.38	10.57 10.72
3c	194-198	65	$C_{12}H_8N_4OS$ 256.27	56.24 56.36	3.14 3.13	21.86 21.14	12.51 11.98
4a	190-192	73	$C_{14}H_{14}N_4OS$ 286.34	58.72 58.50	4.92 4.71	19.56 19.90	11.19 10.86
4b	200-204	70	$C_{12}H_{11}N_5O_2S$ 289.30	49.82 49.65	3.82 3.78	24.20 23.77	11.08 10.89
4c	231-236	65	$C_{12}H_{12}N_6OS$ 288.31	49.99 49.61	4.19 4.35	29.14 28.75	7.99 7.76
5a	195-197	75	$C_{15}H_{14}N_4OS_2$ 330.41	54.52 54.10	4.26 3.99	16.95 16.54	19.40 19.32
5b	205-207	65	$C_{13}H_{11}N_5O_2S_2$ 333.37	46.83 46.42	3.32 3.01	21.00 20.97	19.23 19.00
5c	185-187	75	$C_{13}H_{12}N_6OS_2$ 332.39	46.97 46.62	3.63 3.85	25.28 25.26	19.29 19.14
6	143-147	48	$C_{16}H_{18}N_4OS$ 314.38	61.12 61.32	5.76 5.55	17.81 17.04	10.19 10.31

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (1):
Compound **1** was prepared according to the Karl Gewald method [15].

General method for preparation 2a-c:

To an ice-cold solution of the appropriate amine **1** (0.01 mole) glacial acetic acid (30 ml) and phosphoric acid (10 ml), was added dropwise a solution of sodium nitrite (1.03g, 0.01 mole) dissolved in the minimum amount of water, in an ice bath at -5^{o}C. This previously prepared diazonium salt was added dropwise to a mixture of active methylene acetylacetone,

malononitrile or ethylcyanoacetate respectively (0.01 mol) and anhydrous sodium acetate in ethanol. The reaction mixture was allowed to stand overnight at room temperature, then it was poured into water. The formed solid was filtered off, washed with water, dried and recrystallized from the appropriate solvent to produce **2a-c**.

3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazoacetyl acetone (2a):
Compound **2a** was obtained by the reaction mixture of **1** (2.25 g, 0.01 mole) and acetyl acetone (1.00 g, 0.01 mol). The compound was recrystallized from ethanol to produce **2a** as deep orange crystals; IR spectrum (KBr) cm^{-1}: 3400-2600 (br,OH), 1695 and 1676 (2CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.34 (t, 3H, CH_3), 1.73 (m, 4H, 2CH), 1.87 (s, 6H,2CH_3), 2.61 (t, 4H, 2CH_2), 4.36 (q, 2H, CH_2) and 14.90 (br, 1H, OH, D_2O exchangeable); ^{13}C-NMR (75 MHz, $CDCl_3$): δ211(s,2C) ppm, 164 (s), 140 (s), 134 (s), 132 (s), 129 (s), 64 (t), 36 (q, 2C), 24 (t), 22 (t, 2C), 20 (t), 16 (q) and 11 (d)). MS (m/z): 336 (M^+) 100%.

3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazoethyl cyanoacetate (2b):
Compound **2b** was obtained by the reaction mixture of **1** (2.25 g, 0.01 mol) and ethylcyanoacetate (1.13 g, 0.01 mol). The compound was recrystallized from ethanol to produce 2b as yellow crystals; IR spectrum (KBr) cm^{-1}: 2223 (CN) and 1712, 1676 (2CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.33 (t, 6H, 2CH_3), 1.71 (m, 4H, 2CH_2), 2.33 (s, 1H, CH), 2.58 (t, 4H, 2CH_2), 4.28 (q, 2H, CH_2) and 4.35 (q, 2H, CH_2); MS (m/z): 349 (M^+) 78%.

3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazomalononitrile (2c):
Compound **2c** was obtained by the reaction mixture of **1** (2.25 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol). The compound was recrystallized from ethanol to produce 2c as orange crystals; IR spectrum (KBr) cm^{-1}: 2225 (2CN), 1672 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.36 (t, 3H, CH_3), 1.66 (m, 4H, 2CH_2), 2.48 (s, 1H, CH), 2.57 (t, 4H, 2CH_2) and 4.31 (q, 2H, CH_2); MS(m/z): 302 (M^+) 100%.

General method for preparation 3a-c:

Compound **2a-c** (0.01 mol) was refluxed in sodium ethoxide solution (prepared by dissolving sodium metal (0.23 g, 0.01 mol) in absolute ethanol (30 ml) was heated under reflux for three hours. The reaction mixture was allowed to cool to room temperature, poured into water and neutralized by dilute acetic acid solution. The solid product precipitated was filtered off, dried and recrystallized from the proper solvent to produce **3a-c**.

3,3-Diacetyl-3H,4H-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-c]pyridazin-4-one (3a):
Compound **3a** was obtained by refluxing of **2a** (3.36 g, 0.01 mol) in sodium ethoxide solution. The solid product was recrystallized from dioxane to produce **3a** as deep orange crystals; IR spectrum (KBr) cm^{-1}: 1708 (2CO) and 1678(CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.78 (m, 4H, 2CH_2), 1.93 (s, 6H, 2CH_3) and 2.76 (t, 4H, 2CH_2); MS (m/z): 290 (M^+) 55.37%.

Ethyl 3-cyano-4-oxo-3H,4H-5,6,7,8-tetra hydro benzo[b]thieno[2,3-c]pyridazine-3-carboxylate (3b):
Compound **3b** was obtained by refluxing of **2b** (3.49 g, 0.01 mol) in sodium ethoxide solution. The solid product was recrystallized from dioxane to produce **3b** as orange crystals; IR spectrum (KBr) cm^{-1}: 2225 (CN) and 1709, 1680 (2CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.32 (t, 3H, CH_3), 1.76 (m, 4H, 2CH_2), 2.61 (t, 4H, 2CH_2) and 4.32 (q, 2H, CH_2); MS (m/z): 303 (M^+) 100%.

4-Oxo-4H-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-c]pyridazine-3,3-dicarbonitrile (3c):
Compound **3c** was obtained by refluxing of **2c** (3.02 g, 0.01 mol) in sodium ethoxide solution. The solid product was recrystallized from dil. dimethylformamide to produce **3c** as yellow

crystals; IR spectrum (KBr) cm^{-1}: 2223 (CN) and, 1680 (CO); 1H-NMR (DMSO-d_6) δ ppm: 1.73 (m, 4H, $2CH_2$) and 2.57 (t, 4H, $2CH_2$); MS (m/z): 256 (M^+) 34%.

General method for preparation 4a-c:

A mixture of **3a-c** (0.01 mol) and hydrazine hydrate (99-100%) (7 ml, 0.03 mol) was refluxed in ethanol (30mol) containing a catalytic amount of piperidine for 5h. The reaction mixture was cooled and filtered off and recrystallized from the proper solvent to produce **4a-c**.

3,5-Dimethyl-5\',6\',7\',8\'-tetrahydro-4\'H-spiropyrazole[4,3\']benzo[b]thieno[2,3-c]pyridazin-4-one (4a):

Compound 4a was obtained by refluxing of **3a** (2.90g, 0.01 mol) and hydrazine hydrate in ethanol containing a catalytic amount of piperidine. The solid product recrystallized from dioxane to produce **4a** as deep yellow crystals; IR spectrum (KBr) cm^{-1}: 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.72 (m, 4H, 2 CH_2), 1.86 (s, 6H, 2 CH_3) and 2.34 (t, 4H, 2 CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 190 (s) ppm, 160 (s, 2C), 146 (s), 138 (s), 133 (s), 129 (s), 75 (s), 25 (t), 22 (t, 3C) and 15 (q, 2C); MS (m/z): 286 (M^+) 71%.

5-Amino-3-hydroxy-5\',6\',7\',8\'-tetrahydro-4\'H-spiropyrazole[4,3\']benzo[b]thieno[2,3-c] pyridazin-4-one (4b):

Compound **4b** was obtained by refluxing of **3b** (3.03g, 0.01 mol) and hydrazine hydrate in ethanol containing a catalytic amount of piperidine. The solid product recrystallized from ethanol to produce **4b** as orange crystals; IR spectrum (KBr) cm^{-1}: 3400-2600 (br, OH&NH_2) and 1668 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.68 (m, 4H, $2CH_2$), 1.95 (br, 2H, NH_2, D_2O exchangeable), 2.23 (br, OH, D_2O exchangeable) and 2.46 (t, 4H, 2 CH_2); MS (m/z): 289 (M^+) 35%.

3,5-Diamino-5\',6\',7\',8\'-tetrahydro-4\'H-spiropyrazole[4,3\']benzo[b]thieno[2,3-c] pyridazin-4-one (4c):

Compound **4c** was obtained by refluxing of **3c** (2.56g, 0.01 mol) and hydrazine hydrate in ethanol containing a catalytic amount of piperidine. The solid product recrystallized from ethanol to produce **4c** as deep yellow crystals; IR spectrum (KBr) cm^{-1}: 3310, 3180 (NH_2) and 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.68 (m, 4H, $2CH_2$), 1.95 (br, 2H, NH_2, D_2O exchangeable) and 2.46 (t, 4H, 2 CH_2); MS (m/z): 288 (M^+) 65%.

General method for preparation 5a-c:

A mixture of **3a-c** (0.01 mol) and thiourea (0.01, mol) was refluxed in ethanol containing a catalytic amount of piperidine for 3h, The reaction mixture was cooled and poured into water. The solid product so precipitated was filtered off, dried and recrystallized from the proper solvent to produce **5a-c**.

4,6-Dimethyl-2-thioxo-5\',6\',7\',8\'-tetrahydro-2H,4\'H-spiro pyrimidine[5,3\']benzo[b] thieno[2,3-c]pyridazin-4-one (5a):

Compound **5a** was obtained by refluxing of **3a** (2.90 g, 0.01 mol) and thiourea (0.76 g, 0.015 mol). The solid product recrystallized from dioxane to produce **5a** as yellow crystals; IR spectrum (KBr) cm^{-1}: 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.32 (s, 6H, $2CH_3$), 1.62 (m, 4H, $2CH_2$) and 2.34 (t, 4H, $2CH_2$); MS (m/z): 330 (M^+) 32%.

4-Amino-6-hydroxy-2-thioxo-5\',6\',7\',8\'-tetrahydro-2H,4\'H-spiropyrimidine[5,3\']benzo[b] thieno[2,3-c]pyridazin-4-one (5b):

Compound **5b** was obtained by refluxing of **3b** (3.03g, 0.01 mol) and thiourea (0.76 g, 0.015 mol). The solid product recrystallized from dioxane to produce **5b** as a deep yellow powder; IR

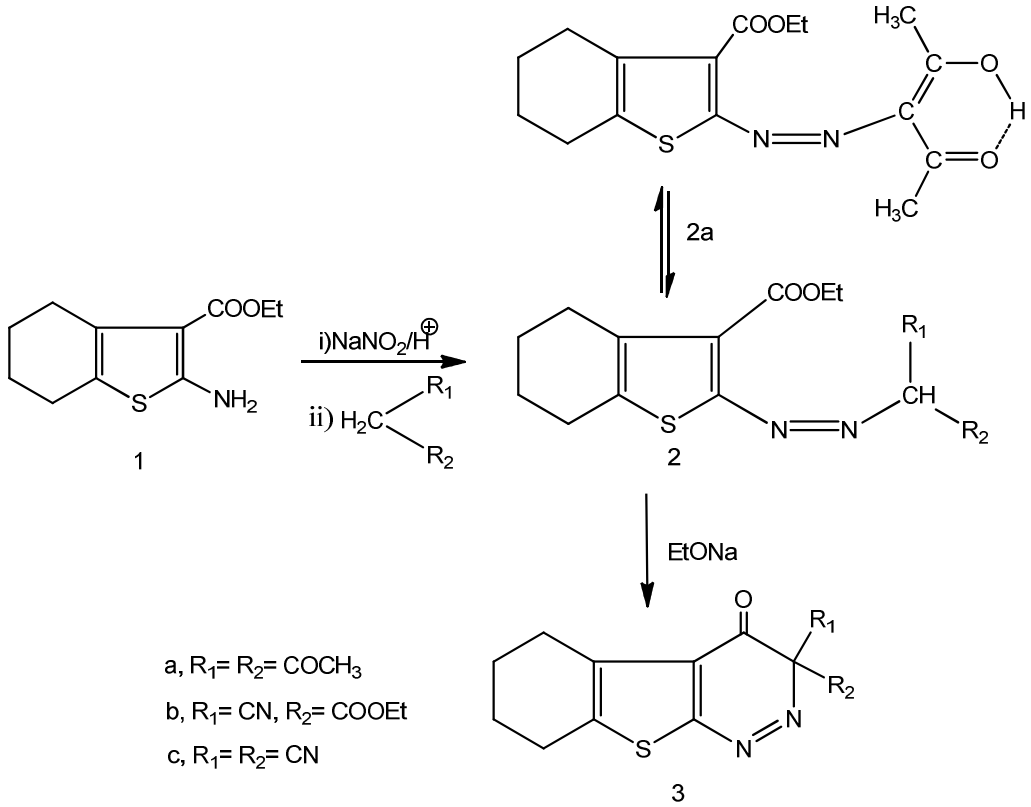
spectrum (KBr) cm^{-1}: 3300-2800 (br, OH&NH_2) and 1676 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.68 (m, 4H, $2CH_2$), 1.95 (br, 2H, NH_2, D_2O exchangeable), 3.34 (br, OH, D_2O exchangeable) and 2.46 (t, 4H, 2 CH_2); MS (m/z): 333 (M^+) 54%.

4,6-Diamino-2-thioxo-5\',6\',7\',8\'-tetrahydro-2H,4\'H-spiro pyrimidine[5,3\']benzo[b]thieno [2,3-c] pyridazin-4-one (5c):

Compound **5c** was obtained by refluxing of **3c** (2.56g, 0.01 mol) and thiourea (0.76 g, 0.015 mol). The solid product recrystallized from ethanol to produce **5c** as orange crystals; IR spectrum (KBr) cm^{-1}: 3340, 3200 (NH_2) and 1658 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.21 (s, 3H, CH_3), 1.57 (m, 4H, $2CH_2$), 1.85 (s, 2H, NH_2, D_2O exchangeable,) and 2.44 (t, 4H, 2 CH_2); MS (m/z): 332 (M^+) 60%

5,7-Dimethyl-5\',6\',7\',8\'-tetrahydro-4\'H-spiro-1,4-diazepine[6,3\']benzo[b]thieno[2,3-c] pyridazin-4-one (6):

A mixture of **3a** (2.90g, 0.01 mol) and ethylenediamine (0.60g, 0.01 mol) was refluxed in boiling ethanol containing a catalytic amount of piperidine for 5 hrs. The reaction mixture was cooled. The formed solid was filtered off, dried and recrystallized from dioxane to produce **6 as** yellow crystals; IR spectrum (KBr) cm^{-1}: 1667 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.18 (s, 6H,$2CH_3$), 1.52 (t, 4H, $2CH_2$), 1.66 (m, 4H, $2CH_2$) and 2.73 (t,4H, $2CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ190 (s) ppm, 166 (s, 2C), 143 (s), 140 (s), 134 (s), 129 (s), 66 (s), 44 (t, 2C), 29 (t), 24 (t, 2C), 20 (t) and 15(q, 2C); MS (m/z): 314 (M^+) 15%.

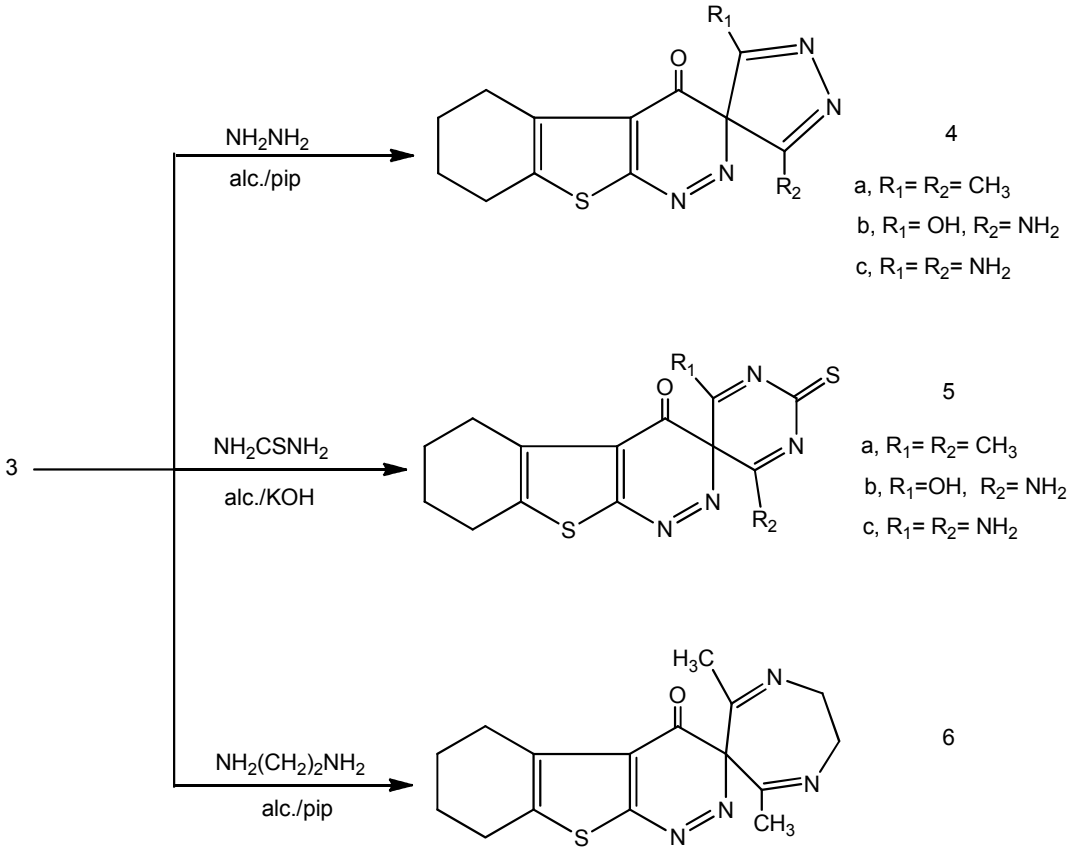


Scheme 1

RESULTS AND DISCUSSION

For synthesis of novel spiro derivatives, the first step was to prepare dinitrile or diacetyl derivatives by oxidative cyclization of diazotized aminobenzothieno derivatives. Thus, by

diazotizing, then coupling ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**1)** [15] with some active methylene group compounds, namely, acetylacetone, ethyl cyanoacetate or malononitrile, we obtained 3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazoacetyl acetone (**2a),** 3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazoethyl cyanoacetate (**2b)** and 3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl diazomalononitrile (**2c)** respectively**.** The IR spectrum of **2a**, as an example showed a broad absorption band around 3400-2600 cm^{-1}, most probably due to the intramolecular hydrogen bond as shown in Scheme 1. The H-bonded OH group is also shown in ^{1}H-NMR of **2a** that showed a signal at δ 14.90 (1H, OH, D_2O exchangeable).



Scheme 2

Heating **2a-c** under reflux with ethanolic sodium ethoxide solution for 3 hours yielded 3,3-disubstituted benzothienopyridazine derivatives **3a-c**. Compounds **3a-c** gave expected values in elemental analyses and spectral data, Experimental.

Compounds **3a-c** underwent oxidative cyclization upon heating under reflux in ethanol with hydrazine hydrate in the presence of a catalytic amount of piperidine to produce 3,5-disubstituted-5\,6\,7\,8\-tetrahydro-4\H-spiropyrazole[4,3\]benzo[b]thieno[2,3-c] pyridazin-4-one **4a-c** with a new ring system (Scheme 2). Compounds **4a-c** gave the expected elemental analyses as well as compatible spectral data, Experimental. IR and mass spectra are sufficient tools to infer structures **4a-c** as the reaction products. IR spectra of **4a, 4b** and **4c** revealed the appearance of only one carbonyl absorbance, the appearance of carbonyl and broad hydroxyl and

amino absorptions, as well as the appearance of carbonyl and broad amino absorptions, respectively. Respective mass spectra of **4a-b** give the molecular ions at m/z 286, 289 and 288.

In a similar manner, compounds **3a-c** reacted with thiourea in boiling ethanol containing catalytic amount of piperidine to produce the novel spiro-compounds 4,6-disubstituted-2-thioxo-5\',6\',7\',8\'-tetrahydro-2H,4\'H-spiropyrimidine[5,3\']benzo[b]thieno[2,3-c]pyridazin-4-one **5a-c** Scheme 2. Compounds **5a-c** showed expected spectral data and elemental analyses, Experimental.

Also, heating **3a** under reflux with ethylenediamine in boiling ethanol containing a catalytic amount of piperidine to produce 5,7-dimethyl-5\',6\',7\',8\'-tetrahydro-4\'H-spiro-1,4-diazepine[6,3\']benzo[b]thieno[2,3-c]pyridazin-4-one (**6),** Scheme 2. Besides the expected values of elemental analyses, the spectral data of **6** are in agreement with the assigned structure, Experimental.

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