SYNTHESIS OF A NOVEL HETEROCYCLIC RING SYSTEM: 4-SUBSTITUTED-1-THIOXO[1,2,4,5]TETRAAZINO[1,2-b]PHTALAZINE-6,11-DIONE

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Abstract : 1,4-dioxo-3,4-dihydro-2(1H)phtalazinecarbothiohydrazide **3** was initially synthesized by reaction of phtalic anhydride with thiocarbohydrazide. Compounds **4a-e** with the novel heterocyclic ring system of 4-substituted-1-thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2-b]phtalazine-6,11-dione were subsequently synthesized by cyclocondensation of **3** with trimethyl orthoformate, trimethyl orthoacetate, benzoic anhydride, cyanogen bromide and carbon disulfide, respectively.

Key words: thiocarbohydrazide, phtalazine, tetraazino phtalazine

Introduction

Pharmacological tests carried out on a variety of antitumor agents obtained from both natural origins and synthetic routes have shown that the common 2-phenyl naphthalene type fused ring system structural pattern is necessary for the pharmacological and biological activities of such agents (1). Such a system could be either carbocyclic or heterocyclic with nitrogen, oxygen or sulfur atoms located at suitable positions (1). Heterocyclic compounds derived from phtalazines have shown a broad spectrum of pharmacological activities, which include antihypertensional (2), antibacterial (3) and antifungal (4) activities.

Since our previous works have been on the synthesis of fused heterocycles with potential biological activities (5), we decided to synthesize a number of new compounds with the novel heterocyclic fused ring system of 4-substituted-1-thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2-b]phtalazine-6,11-dione. These compounds were prepared via the routes outlined in Scheme-1.

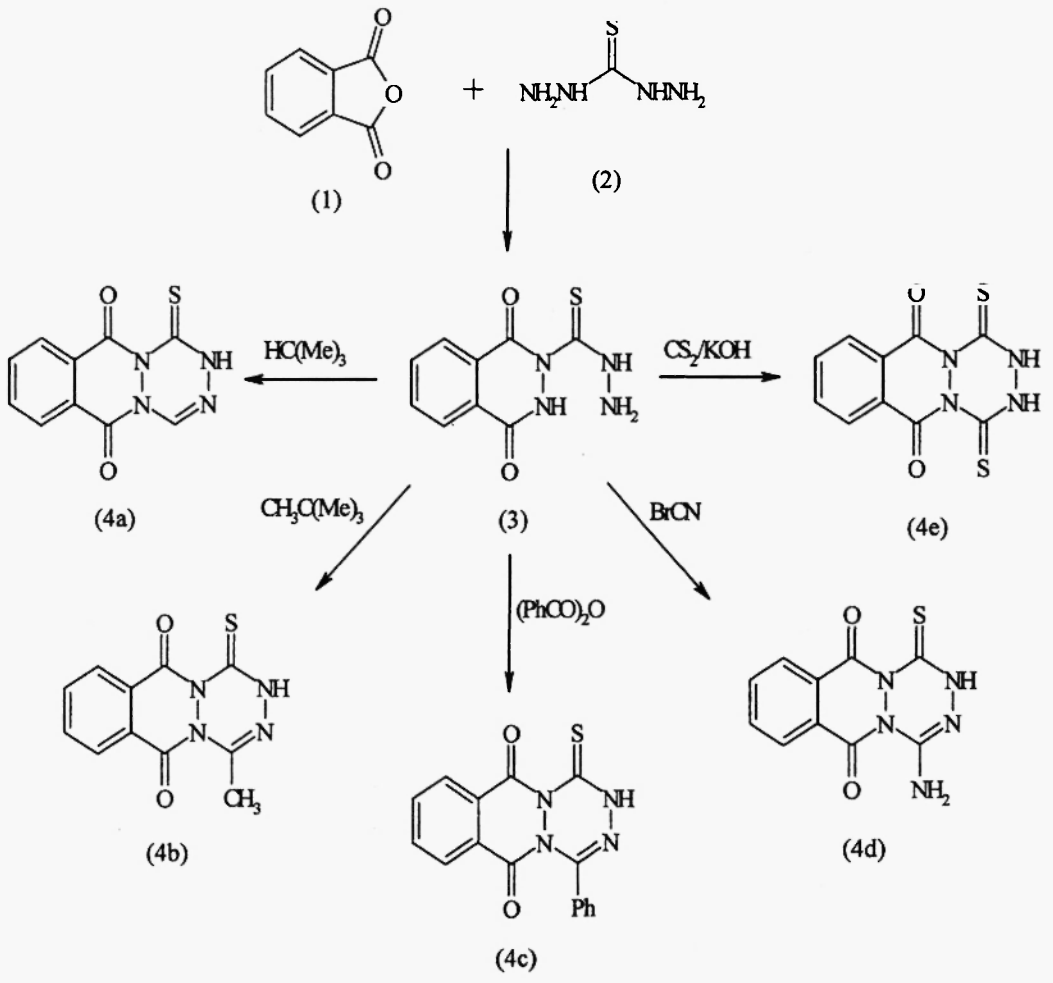
Phtalic anhydride **1** was first treated with thiocarbohydrazide **2** to afford 1,4-dioxo-3,4-dihydro-2(1H)-phtalazine carbothiohydrazide **3**. Their IR spectra showed a sharp band in the region 1754 Cm^{-1} characteristic of υC=O and a band at 3150-3350 Cm^{-1} for υN-H. The ^{1}H-NMR spectrum of compound **3** showed a multiplet for aromatic protons at 7.9-8 ppm, a singlet at 9.6 ppm (1H,N-H,phtalazine ring protons) and a broad signal for the N-H group at 4.5-6.7 ppm (3H,NH,NH_2); the last two signals were both removed on deuteration (Table 1).

Subsequent treatment of compound **3** with trimethyl orthoformate in refluxing ethanol afforded compound **4a**. The ^{1}H-NMR spectrum of this compound was devoid of the signals at 4.5-6.7 ppm for NH_2 group and at 9.6 ppm for the N-H phtalazine ring proton, and revealed two singlets at 9.4 ppm (1H,CH of tetraazine) and 11.6-13.4 ppm (1H,NH). Reaction of compound **3** with triethyl orthoacetate in refluxing ethanol in the presence of KOH afforded compound **4b**. When compound **3** was reacted with benzoic anhydride, compound **4c** was afforded. Reaction of compound **3** with cyanogen bromide afforded compound **4d**. Finally, when compound **3** was reacted with carbon disulfide in refluxing methanol in the presence of KOH, compound **4e** was isolated.

Compounds **3** and **4a-e** were characterized from their spectral data (Table-1).

Table-1: Physical and spectral data for compounds **3** and **4a-e**

Compound	MP °C	Yield %	Molecular formula	C Calcd. (Found)	H Calcd. (Found)	N Calcd. (Found)	S Calcd. (Found)	Spectral data
3	227-8	85	$C_9H_8N_4O_2S$	45.76 (44.83)	3.39 (3.27)	23.73 (23.90)	13.56 (13.65)	^{1}H-NMR: σ (d_6-DMSO), 4.5-6.7 (broad,3H,NH_2), 7.9-8.0 (m,4H,Ph), 9.6 (s,H,NH of phtalazine); IR: υ (KBr disc): 3350,3150,1810,1745 Cm^{-1}; m/z: 235 (M).
4a	251-2	70	$C_{10}H_8N_4O_2S$	48.78 (49.52)	2.44 (2.41)	22.76 (23.12)	13.01 (12.30)	^{1}H-NMR: σ (d_6-DMSO), 7.9-8.5 (m,4H,Ph), 9.4 (s,1H,H of tetraazine), 11.6-13.4 (broad,1H,NH); IR: υ (KBr disc): 3200,1780,1750 Cm^{-1}; m/z: 245 (M^+).
4b	362-3	50	$C_{11}H_8N_4O_2S$	50.77 (50.21)	3.07 (2.90)	21.54 (21.78)	12.31 (12.44)	^{1}H-NMR: σ (d_6-DMSO), 3.5 (s,3H,CH_3), 7.9-8.2 (m,4H,Ph), 14.3 (s,1H,NH); IR: υ (KBr disc): 3200,1790,1750 Cm^{-1}; m/z: 260 (M).
4c	196-7	60	$C_6H_{10}N_4O_2S$	59.62 (59.93)	3.10 (2.91)	17.74 (17.50)	9.94 (9.62)	^{1}H-NMR: σ (d_6-DMSO), 7.5-8.0 (m,9H ,2Ph), 10.6 (s,1H,NH); IR: υ (KBr disc): 3300,1800,1740 Cm^{-1}; m/z: 321 (M^+).
4d	350-1	45	$C_{10}H_7N_3O_2S$	45.98 (46.15)	2.68 (2.45)	26.82 (27.10)	12.26 (11.92)	^{1}H-NMR: σ (d_6-DMSO), 5.3 (s,2H,NH_2), 7.8-8.3 (m,4H,Ph) 14.2 (s,1H,NH); IR υ (KBr disc): 3300-3150,1770 1710 Cm^{-1}; m/z 261 (M).
4e	322-3	65	$C_{10}H_6N_4O_2S_2$	43.17 (42.76)	2.16 (2.31)	20.14 (20.35)	23.02 (22.70)	^{1}H-NMR: σ (d_6-DMSO), 7.8-8.4 (m,4H,Ph), 14.2-14.5 (s,2H,2NH); IR: υ (KBr disc): 3200,3100,1810,1760 Cm^{-1}; m/z: 277 (M^+).



Scheme-1

Experimental

Melting points were recorded on an electrothermal type 9100 melting point apparatus.

IR spectra were obtained on a 4300 Shimadzu spectrometer as KBr disc.

^{1}H-NMR spectra were recorded on a Brucker AC 100 instrument.

Mass spectra were obtained using a Varian CH-7 instrument at 70 eV.

Elemental analysis results were obtained using a Thermo Finnigan Flash EA microanalyser.

Synthesis of 1,4-dioxo-3,4-dihydro-2(1H)phtalazinecarbothiohydrazide 3

A mixture of phtalic anhydride (1.48 g, 0.01 mol) and thiocarbohydrazide (1.06 g, 0.01 mol) in water (10 mL) was heated under reflux for 5 hours. The solution was then cooled to room temperature to give a white crystalline solid (2.0 g, 85% yield, m.p. 227-8 °C).

Synthesis of 1-thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2-b]phtalazine-6,11-dione 4a

A mixture of compound **3** (0.236 g, 0.001 mol) and trimethyl orathoformate (0.2 mL, 0.212g, 0.002 mol) in ethanol (5 ml) was heated under reflux for 4 hours. The solution was then allowed to cool to room temperature to give a precipitate which was then filtered off, washed with water and recrystallized from ethanol to afford the title compound (0.17 g, 70% yield, m.p. 251-2 °C).

Synthesis of 4-methyl-1-thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2-b]phtalazine-6,11-dione 4b

A mixture of compound **3** (0.236 g, 0.001 mol), trimethyl orthoacetate (0.2mL, 0.240g, 0.002 mol) and potassium hydroxide (0.230 g, 0.004 mol) in ethanol (10 mL) was heated under reflux for 5 hours. The solution was then allowed to cool to room temperature and subsequently neutralized with dilute HCl to give a precipitate. The precipitate was then filtered off, washed with water and recrystallized from ethanol to afford the title compound (0.13 g, 50% yield, m.p. 362-3 °C).

Synthesis of 4-pheny1-1- thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2,-b]phtalazine-6,11-dione 4c

A mixture of compound **3** (0.236 g, 0.001 mol) and benzoic anhydride (0.226 g, 0.001 mol) in ethanol (10 mL) was heated under refluxed for 6 hours. The solution was then allowed to cool to room temperature to give a white crystalline solid which was then filtered off and recrystallized from ethanol to afford the title compound (0.2 g, 60% yield, m.p. 196-7 °C).

Synthesis of 4-amino-1-thioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2-b]phtalazine-6,11-dione 4d

A mixture of compound **3** (0.236 g, 0.001 mol) and cyanogen bromide (0.106g, 0.001 mol) in 75% aqueous ethanol (10 mL) was heated under reflux for 6 hours. The solvent was evaporated off under reduced pressure and water (2 mL) was added to the crude. The solid was filtered off and recrystallized from ethanol to afford the title compound (0.11 g, 45% yield, m.p. 350-1°C).

Synthesis of 1,4-dithioxo-1,2-dihydro[1,2,4,5]tetraazino[1,2,-b]phtalazine-6,11-dione 4e

A mixture of compound **3** (0.236 g, 0.001 mol), carbon disulfide (0.12 mL, 0.15 g, 0.002 mol) and a solution of potassium hydroxide (0.112 g, 0.002 mol) in methanol (10 mL) was heated under reflux for 8 hours. Water (5 mL) was added to the crude. The solid was filtered off and recrystallized from ethanol to afford the title compound (0.18g, 65% yield, m.p. 322-3 °C).

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