Articles

A Facile One-pot Synthesis of Fused 2-Thiouracils: Dipyrimidinopyridine, Pyrazolopyrimidine and Pyridazinopyrimidines

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A novel fused thiouracil containing a heterocyclic ring system, dipyrimidinopyridine (**3**), has been prepared through the cyclization of compound **2**. Compound **2** was formed by the formylation of 6-amino-2-thiouracil **1**, pyrazolopyrimidines **8-10** *via* the heating of 6-arylhydrazono-2-thiouracils **5-7**, compound **11**, using Vilsmeier reagent with compound **4**, pyrazolylpyrimidine **12**, indolodiazinopyrimidine **14** and pyridazinopyrimidine **15**. Pyridazino-pyrimidine **15** was formed by the condensation of compound **4** with acetylacetone, isatin and benzyl, respectively.

Key Words : Dipyrimidinopyridine, Pyrazolo[5,4-d]pyrimidines, Pyrazolylpyrimidine, Indolodiazinopyrimidine and pyridazino[6,5-d]pyrimidine

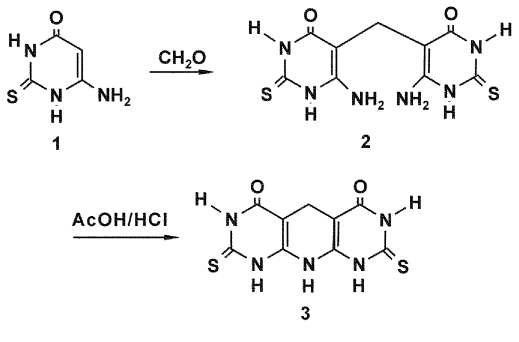
Introduction

The importance of fused pyrimidines, common sources for the development of new potential theraputic agents,[1,2] is well known. In 1943, Astwood discovered the high antithyroid activity and low toxicity of 2-thiouracil,[3] and many derivatives of this compound have been prepared and tested for physiological activity.[4-7] In general it has been found that the substitution on either the sulfur[4] or the nitrogen[5] of the molecule decreased or destroyed the antithyroid potency of the parent compound, while substitution of a small alkyl group in either the 5- or the 6-position enhanced such activity. From these points and extending to our work,[8] we look to prepare a new fused thiouracils, which might exhibit biological activities.

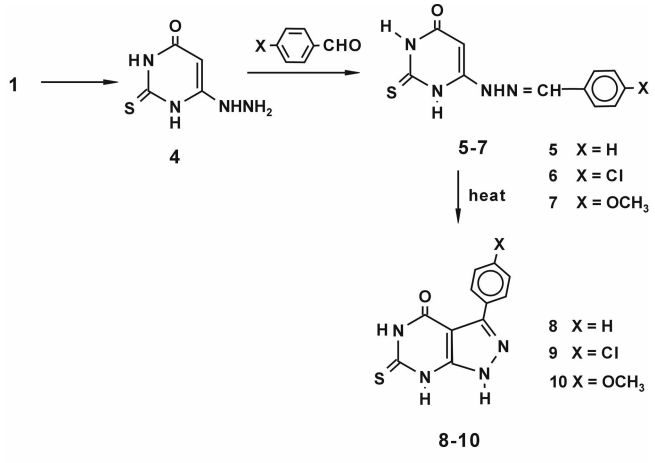
The requisite starting material 6-amino-2-thiouracil **1** was prepared by the condensation of thiourea with ethyl cyanoacetate in sodium ethoxide according to the known procedure.[9,10] In the present work, we describe new synthetic methods for the preparation of fused uracil derivatives, using electrophillic formylation, also condensation reactions of aldehydes and diketocompounds with 6-hydrazino-2-thiouracil **4**.

The formylation of compound **1** with formalin (40%) in ethanol led to the formation of methylene bis derivative **2**, which cyclized by heating under reflux using acetic acid in the presence of a few drops of hydrochloric acid to afford dipyrimidopyridine **3** in a good yield as in Scheme 1. ^{1}H NMR shows the disappearance of NH_2 group signal at δ 6.78 ppm in compound **2**.

On the other hand, 4-hydrazino-2-thiouracil (**4**) was synthesized according to a reported method[11] by the treatment of 4-amino-2-thiouracil (**1**) with a mixture of hydrazine hydrate and hydrazine sulfate in ethanol under nitrogen condition. The treatment of compound **4** with different aromatic aldehydes, such as benzaldehyde, 4-chloro-, and 4-methoxybenzaldehyde, in ethanol at room temperature led to



Scheme 1



Scheme 2

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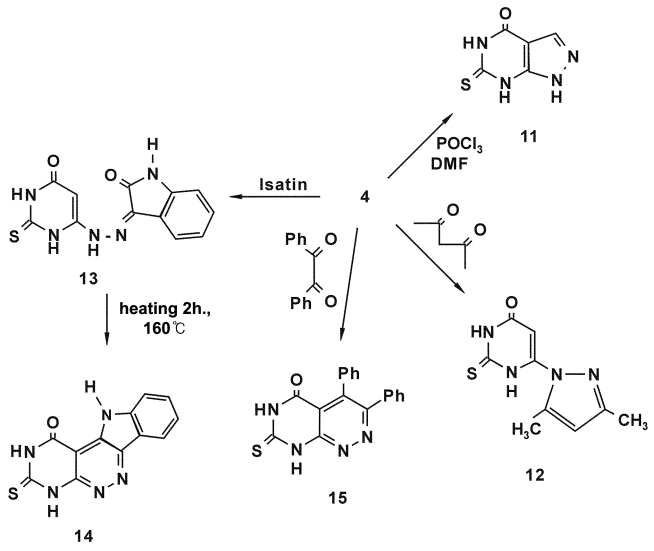

Scheme 3

the formation of Schiffs base analogues **5-7**, which were cyclized on heating at higher temperature than their melting points, affording compounds **8-10** as in Scheme 2.

The formation of pyrazolopyrimidine **11** takes place using Vilsmeier reagents on compound **4**. Thus, treatment of compound **4** with $POCl_3$ in DMF by heating afforded compound **11**, which confirms by analytical and spectral data. The reaction of compound **4** with β-diketones as acetyl acetone in absolute ethanol in the presence of TEA (triethylamine) afforded 4-pyrazolyluracil **12** *via* the cyclization into pyrazole ring by an intramolecular dehydration in the side chain. While, treatment of compound **4** with isatin under reflux in ethanol afforded compound **13**, which easily cyclized by heating with DMF in the presence of TEA at 160° for 2 h to give **14**. The structure of compounds **13** and **14** was inferred from ^{1}H-NMR, which shows a characterized peaks at δ 4.72 (C5) and δ 10.69 (NH(6)) in compound **13**, which disappears in compound **14**. ^{13}C-NMR shows 12 peaks in compound **13**.

On the other hand, the condensation of compound **4** with diketocompound, such as benzil, in absolute ethanol in the presence of TEA under reflux for 2 h gave pyridazinopyrimidine analogues **15** as in (Scheme 3, which was unequivocally confirmed by elemental analysis, ^{1}H-NMR and ^{13}C-NMR, which shows 14 peaks.

Experimental Section

All melting points were recorded on an electrothermal (Prolabo 9200) apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JUM-LA 400 MHz spectrometer, 100 MHz. Chemical shifts δ are on parts per million (ppm) with $(CD_3)_2SO$-d_6 as solvent and relative to tetramethylsilane (TMS) as the internal standard. Microanalyses were carried out in the microanalytical Center, Faculty of Science, Cairo University, Giza, Egypt.

6-Amino-2-thiouracil (1). This compound was prepared according to the reported method.[9,10] Ethyl cyanoacetate (22.6 g, 0.2 mol) was added to sodium methoxide solution (sodium (9.0 g, 0.4 mol) in methanol (200 ml.)). After 15 min., thiourea (15.2 g, 0.2 mol) in methanol (50 ml.) was added, the mixture was refluxed for 2 hrs. The formed white precipitate was collected by filtration then dissolved in diluted potassium hydroxide and reprecipitated with acetic acid to give 28.4 gm of 6-amino-2-thiouracil, which recrystallized from ethanol in 89% yield; m.p. >380 °C.[1] H NMR (DMSO-d_6): 11.56 (s, 2H, 2NH), 6.35 (s, 2H, NH_2), 4.70 (s, 1H, CH(5)). ^{13}C NMR (DMSO-d_6): 175.89 (C=S), 162.88 (C=O), 158.83, 78.55. MS (m/e): 143.4 (100), 115.0 (24), 85 (6), 73 (5), 68 (49), 42 (45), 40 (12). Analalysis Calcd. for $C_4H_5N_3OS$: C, 33.55; H, 3.52; N, 29.36. Found: C, 33.50; H, 3.57; N, 28.60.

5,5'-Methylene bis(6-amino-2-thiouracil) (2). A mixture of compound **1** (0.6 g, 4.60 mmol) and 40% formalin (0.07 g, 2.30 mmol) in absolute ethanol was heated under reflux for 4 h. The reaction mixture was concentrated, cooled, and the solid product was filtered, washed with water and recrystallized by dissolving in 1 N NaOH and reprecipitated by 1 N HCl to give **2** with m.p >360 °C; ^{1}H NMR (DMSO-d_6): 11.93 (s, 2H, NH), 11.69 (s, 2H, NH), 6.78 (s, 4H, NH_2), 3.10 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6): 172.72 (2C=S), 163.21 (2C=O), 152.85, 89.08, 15.75 (CH_2). MS (m/e): 298 (6), 279 (8), 208 (7), 195 (9), 156 (21), 155 (40), 143 (76), 115 (27), 59 (39), 53 (29), 44 (100). Analalysis Calcd. for $C_9H_{10}N_6O_2S_2$: C, 36.24; H, 3.38; N, 28.18. Found: C, 36.00; H, 3.23; N, 28.01.

2,7-Dithio-4,5-dioxo-1,2,6,8-tetraza-1,2,3,4,5,6,7,8,9,10-decahydroacridine (3). Compound **2** (0.67 g, 2.26 mmol) was heated under reflux in glacial acetic acid (15 ml.) for 3 h The reaction mixture was evaporated in vacuo and water was added after cooling. The solid product was filtered, washed with water and recrystallized by dissolving in 1 N NaOH and reprecipitated by 1 N HCl to afford compound **3** in 85% yield with m.p. >360 °C. ^{1}H NMR (DMSO-d_6): 11.93 (s, 2H, NH (1,9)) 11.68 (s, 2H, NH (3,7)), 6.78 (s, 2H, CH_2 (5)), 3.10 (s, 1H, NH (10)). ^{13}C NMR (DMSO-d_6): 15.74 (CH_2), 89.08, 152.85, 163.37 (2C=O), 172.72 (2C=S). Analalysis Calcd. for $C_9H_7N_5O_2S_2$: C, 38.44; H, 2.50; N, 24.92. Found: C, 38.31; H, 2.38; N, 24.69.

6-Hydrazino-2-thiouracil (4). Compound **4** was prepared as in a reported method.[11] A mixture of hydrazine sulfate (29.7 g, 0.23 mol), hydrazine hydrate 80% (17.5 g, 0.35 mol) and 4-amino-2-thiouracil (7.15 g, 0.05 mol) **1** was heated at 140-150 °C under the atmosphere of nitrogen. Fifty percent ethanol was added and the mixture was cool to room temperature, the formed precipitate was collected by filtration and recrystallized from water to give **4** in 78% yield with m.p. >380 °C; ^{1}H NMR (DMSO-d_6): 11.62 (s, 1H, NH), 11.55 (s, 1H, NH), 6.39 (s, 2H, NH_2), 4.72 (s, 1H, CH), 3.41 (s, 1H, NH (6)); ^{13}C NMR (DMSO-d_6): 174.46 (C=S), 161.61 (C=O), 154.28, 78.09. Analysis Calcd for $C_4H_6N_4OS$: C, 30.38; H, 3.82; N, 35.43. Found: C, 30.2; H, 3.81; N, 35.3.

6-Benzylidinehydrazino-2-thiouracil (5-7), General method. An equimolar amount of compound **4** (1.6 g, 0.01

mol) and appropriate aldehydes, namely benzaldehyde, 4-chlorobenzaldehyde and/or 4-anisaldehyde in ethanol (6.0 mL) wer stirred at room temperature for 3 h. The solid product was filtered and recrystallized from ethanol.

5) Yield 92%; m.p. 290 °C; ^{1}H-NMR (DMSO-d_6): 11.98 (s, 1H, NH (3)), 11.63 (s, 1H, NH (1)), 8.02 (s, 1H, CH), 7.19 (m, 5H), 5.33 (s, 1H, CH (5)), 3.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 172.18 (C=S), 164.11 (C=O), 162.33 (C=N), 152.14 (C-N), 135.28, 129.34, 125.89, 118.72, 88.14. Analalysis Calcd. for $C_{11}H_{10}N_4OS$: C, 53.65; H, 4.09; N, 22.75. Found: C, 53.43; H, 3.87; N, 21.99.

6) Yield 97%; m.p. 306-304 °C; ^{1}H-NMR (DMSO-d_6): 12.02 (s, 1H, NH (3)), 11.80 (s, 1H, NH (1)), 7.95 (s, 1H, CH), 7.23 (m, 4H), 5.36 (s, 1H, CH (5)), 2.89 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 172.73 (C=S), 162.92 (C=O), 162.21 (C=N), 153.36 (C-N), 137.86, 127.74, 126.38, 125.21, 90.18 (C5). Analalysis Calcd. for $C_{11}H_{9}ClN_4OS$: C, 47.07; H, 2.33; N, 19.96. Found: C, 46.98; H, 3.09; N, 19.65.

7) Yield 88%; m.p. 267 °C; 1H-NMR: 12.08 (s, 1H, NH (3)), 11.77 (s, 1H, NH (1)), 7.67 (s, 1H, CH), 7.03 (m, 2H), 7.78 (m, 2H), 5.34 (s, 1H, CH (5)), 3.82 (s, 3H, OCH_3), 2.70 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 174.22 (C=S), 165.28 (C=O), 163.38 (C=N), 155.78, 138.45, 129.21, 128.15, 126.88, 99.17, 53.14 (OCH_3). Analalysis Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.17; H, 3.37; N, 20.28. Found: C, 52.08; H, 3.22; N, 20.12.

3-Arylpyrazolo[5,4-d]pyrimidine-6-thio-2(5H,7H)-one (8-10), General method. Compound **5**, **6**, or **7** (0.1 mol) was heated above its melting point till completely melted, then the reaction mixture was boiled in ethanol (100 mL). The solid product was separated by filtration and dried to furnish compounds **8-10**.

8) Yield 65%; m.p. 195-97 °C; ^{1}H-NMR (DMSO-d_6): 13.71 (s, 1H, NH), 13.52 (s, 1H, NH), 10.92 (s, 1H, NH), 8.15 (m, 2H, aromatic), 7.50-7.52 (m, 3H, aromatic); ^{13}C NMR (DMSO-d_6): 173.88, 160.67, 158.32, 154.02, 134.34, 130.72, 128.66, 127.22, 78.23. Analalysis Calcd. for $C_{11}H_8N_4OS$: C, 54.10; H, 3.30; N, 22.94. Found: C, 53.06; H, 3.19; N, 22.48.

9) Yield 72%; m.p. 215-16 °C; ^{1}H NMR (DMSO-d_6): 13.70 (s, 1H, NH), 13.51 (s, 1H, NH), 10.88 (s, 1H, NH), 7.88 (m, 2H, aromatic), 7.51-7.54 (m, 2H, aromatic); ^{13}C NMR (DMSO-d_6): 174.91 (C=S), 161.47 (C=O), 159.66, 154.38, 136.02, 132.77, 129.89, 128.95, 78.41. Analalysis Calcd. for $C_{11}H_7ClN_4OS$: C, 47.41; H, 2.53; N, 20.10. Found: C, 47.27; H, 2.43; N, 19.52.

10) Yield 68%; m.p. 170-72 °C; ^{1}H NMR (DMSO-d_6): 13.68 (s, 1H, NH), 13.47 (s, 1H, NH), 10.53 (s, 1H, NH), 7.48 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), 4.03 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 174.98 (C=S), 161.22 (C=O), 159.43, 154.76, 136.42, 133.01, 130.33, 129.12, 78.76, 55.39 (OCH_3). Analalysis Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.67; N, 20.43. Found: C, 52.34; H, 3.61; N, 20.22.

Pyrazolo[5,4-d]pyrimidine-6-thio 4-(5H,7H)-one (11). Phosphorousoxychloride (1.0 g, 6.5 mmol) was added dropwise to a mixture of compound **4** (2.0 g, 12.6 mmol) and DMF (5 mL). The reaction mixture was heated under reflux for 30 min., the excess of $POCl_3$ was evaporated in vacuo and the mixture was poured over ice. The solid product was filtered, washed with ether and recrystallized from ethanol to give **11** in 85% yield with m.p. >340 °C. ^{1}H NMR (DMSO-d_6): δ 12.16 (s, 1H, NH), 11.89 (s, 1H, NH), 9.70 (s, 1H, CH), 8.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 171.09 (C=S), 168.48 (C=O), 164.99 (C=N), 133.32, 97.56. Analalysis Calcd. for $C_5H_4N_4OS$: C, 35.72; H, 2.39; N, 33.32. Found: C, 35.59; H, 2.37; N, 33.11.

6-(3,5-Dimethylpyrazol-1-yl)-2-thiouracil (12). A mixture of compound **4** (2.0 g, 12.60 mmol) and acetylacetone (1.5 g, 15 mmol) was heated under reflux in absolute ethanol (20 mL) in the presence of triethylamine (4 drops) for 4.5 h. The reaction mixture was evaporated *in vacuo*. The separated solid was filtered and recrystallized from DMF/ethanol to give **12** in 64% yield with m.p. 288-290 °C: ^{1}H NMR (DMSO-d_6): δ 12.83 (s, 1H, NH), 12.46 (s, 1H, NH), 7.01 (s, 1H, CH), 3.37 (s, 1H, CH), 2.62 (s, 3H, CH_3), 2.44 (s, 3H, CH_3). Analysis calcd for $C_9H_{10}N_4OS$: C, 48.64; H, 4.53; N, 25.21. Found: C, 48.49; H, 4.51; N, 24.98.

6-Hydrazino(indol-2-one-3-ylidene)-2-thiouracil (13). Isatin (1.85 g, 12.60 mmol) in ethanol (5 mL) was added to compound **4** (2.0 g, 12.60 mmol) in ethanol (20 mL). The mixture was refluxed for 4 hr. The reaction mixture was evaporated *in vacuo* and the separated solid was filtered, washed with water and recrystallized from ethanol to afford **13** in 75% yield with m.p. 298 °C: ^{1}H NMR (DMSO-d_6): δ 11.65 (s, 1H, NH), 11.55 (s, 1H, NH), 10.69 (s, 1H, NH), 7.36 (m, 1H, aromatic), 7.15 (m, 1H, aromatic), 6.98 (m, 1H, aromatic), 6.86 (m, 1H, aromatic), 6.39 (s, 1H, NH), 4.72 (s, 1H, CH (5)); ^{13}C NMR (DMSO-d_6): 174.51 (C=S), 162.70 (C=O), 156.13 (C=O), 151.23 (C=N), 138.57, 126.95, 126.19, 122.18, 121.26, 117.37, 109.87, 78.11. Analysis Calcd for $C_{12}H_9N_5O_2S$: C, 50.17; H, 3.15; N, 24.38. Found: C, 49.81; H, 3.01; N, 23.99.

Indolo[2',3':10,11]pyridazino[3,4-d]pyrimidine-7-thio-5-(6H,8H)-one (14). Compound **13** (1.10 g, 3.80 mmol) was heated under reflux in DMF (15 mL) in the presence of TEA (3 drops) for 2 h. After cooling, the solid product was filtered, washed with ethanol and recrystallized from aqueous acetic acid to give **14** in 83% yield with m.p. 325 °C; ^{1}H NMR (DMSO-d_6): δ 12.01 (s, 1H, NH), 11.88 (s, 1H, NH), 10.09 (s, 1H, NH), 7.42 (m, 1H, aromatic), 7.22 (m, 1H, aromatic), 7.04 (m, 1H, aromatic), 6.92 (m, 1H, aromatic). Analysis Calcd for $C_{12}H_7N_5OS$: C, 53.53; H, 2.62; N, 26.01. Found: C, 53.42; H, 2.59; N, 25.68.

3,4-Diphenylpyridazino[3,4-d]pyrimidine-7-thio-5(6H, 8H)-one (15). A mixture of compound **4** (2.0 g, 12.60 mmol) and benzil (2.65 g, 12.60 mmol) in absolute ethanol in the presence of triethylamine (5 drops) was heated under reflux for 2 hrs. The solid product was filtered, and recrystallized in DMF/water (1:1) to give 1.6 g of compound **15** with m.p. 191 °C; ^{1}H NMR (DMSO-d_6): δ 11.98 (s, 1H, NH), 11.76 (s, 1H, NH), 7.71-7.04 (m, 10H, aromatic); ^{13}C NMR (DMSO-d_6): 167.63 (C=S), 159.66 (C=O), 151.86 (C9), 150.10 (C3), 139.86 (C4), 136.13 (phenyl), 134.02, 129.74, 128.83, 128.14, 128.00, 127.65, 127.56, 111.32. Analysis

Calcd for $C_{18}H_{12}N_4OS$: C, 65.05; H, 3.64; N, 16.85. Found: C, 64.76; H, 3.61; N, 16.71.

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