A Facile One-pot Synthesis of Fused 2-Thiouracils: Dipyrimidinopyridine, Pyrazolo[5,4-d]pyrimidines, Pyrazolylpyrimidine, Indolodiazinopyrimidine and Pyridazino[6,5-d]pyrimidine

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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, pyrazolo[5,4-d]pyrimidines 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 pyridazino-pyrimidine 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 therapeutic 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.1,7 In general it has been found that the substitution on either the sulfur4 or the nitrogen5 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 dipyrimidinopyridine 3 in a good yield as in Scheme 1. 1H NMR shows the disappearance of NH2 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 method11 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

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

The formation of pyrazolopyrimidine 11 takes place using Vilsmeier reagents on compound 4. Thus, treatment of compound 4 with POCl3 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 1H-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. 13C-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 pyridazino-pyrimidine analogues 15 as in (Scheme 3), which was unequivocally confirmed by elemental analysis, 1H-NMR and 13C-NMR, which shows 14 peaks.

**Experimental Section**

All melting points were recorded on an electrothermal (Prolabo 9200) apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a JEOL JUM-LA 400 MHz spectrometer, 100 MHz. Chemical shifts δ are on parts per million (ppm) with (CD3)2SO-d6 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.8,10 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. H NMR (DMSO-d6): 11.56 (s, 2H, 2NH), 6.35 (s, 2H, NH3), 4.70 (s, 1H, CH(3)). 13C NMR (DMSO-d6): 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). Analysis Calcd. for C3H5N3OS: 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. H NMR (DMSO-d6): 11.93 (s, 2H, NH), 11.69 (s, 2H, NH), 6.78 (s, 4H, NH2), 3.10 (s, 2H, CH2); 13C NMR (DMSO-d6): 172.72 (2C=S), 163.21 (2C=O), 152.85, 163.37 (2C=O), 172.72 (2C=S). Analysis Calcd. for C8H10N6O2S2: C, 36.24; H, 3.38; N, 28.18. Found: C, 36.00; H, 3.38; 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. H NMR (DMSO-d6): 11.93 (s, 2H, NH (1,9)) 11.68 (s, 2H, NH (3,7)), 6.78 (s, 2H, CH2 (5)), 3.10 (s, 1H, NH (10)). 13C NMR (DMSO-d6): 15.74 (CH2), 89.08, 152.85, 163.37 (2C=S), 172.72 (2C=S). Analysis Calcd. for C4H5N4OS2: C, 36.24; H, 3.38; N, 28.69.

**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) in absolute ethanol was added and the mixture was refluxed in 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. H NMR (DMSO-d6): 11.62 (s, 1H, NH), 11.55 (s, 1H, NH), 6.39 (s, 2H, NH3), 4.72 (s, 1H, CH), 3.41 (s, 1H, NH (6)); 13C NMR (DMSO-d6): 174.46 (C=O), 161.61 (C=O), 154.28, 78.09. Analysis Calcd for C3H5N4OS: C, 30.38; H, 3.82; N, 35.43. Found: C, 30.2; H, 3.81; N, 35.3.

**6-Benzylidenehydrazino-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) were stirred at room temperature for 3 h. The solid product was filtered and recrystallized from ethanol.

5) Yield 92%; m.p. 290°C; 1H-NMR (DMSO-d6): 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). 13C NMR (DMSO-d6): 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. Analysis Calcd. for C11H10N4OS: 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; 1H-NMR (DMSO-d6): 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). 13C NMR (DMSO-d6): 172.73 (C=S), 162.92 (C=O), 162.21 (C=N), 153.36 (C=N), 137.86, 127.64, 126.38, 125.21, 190.18 (C5). Analysis Calcd. for C11H10N4OS: C, 53.65; H, 3.87; N, 21.99. Found: C, 53.43; H, 3.87; N, 21.99.

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, OCH3), 2.70 (s, 1H, NH). 13C NMR (DMSO-d6): 174.22 (C=S), 165.28 (C=O), 164.99 (C=N), 133.32, 97.56. Analysis Calcd. for C5H4N4OS: C, 35.72; H, 2.39; N, 25.68. Found: C, 35.52; H, 2.39; N, 25.68.

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). After cooling, the solid product was filtered, washed with water and recrystallized from ethanol to afford compounds 8-10.

8) Yield 65%; m.p. 195-97°C; 1H-NMR (DMSO-d6): 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). 13C NMR (DMSO-d6): 173.88, 160.67, 158.32, 154.02, 134.34, 130.32, 128.66, 127.22, 78.23. Analysis Calcd. for C12H7N5OS: C, 53.14; H, 2.62; N, 26.01. Found: C, 53.02; H, 2.62; N, 25.99.

9) Yield 72%; m.p. 215-16°C; 1H-NMR (DMSO-d6): 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). 13C NMR (DMSO-d6): 174.91 (C=S), 161.47 (C=O), 159.66, 154.38, 136.02, 132.77, 129.89, 128.95, 78.41. Analysis Calcd. for C12H7ClN2O2S: C, 47.41; H, 2.53; N, 20.10. Found: C, 47.27; H, 2.43; N, 20.12.

In conclusion, the one-pot synthesis of fused 2-thioxouracils has been successfully achieved with a general method, providing a convenient route for the preparation of these compounds. The reactions were carried out under mild conditions, and the products were obtained in good yields. Further studies on the biological activities of these compounds are currently underway.
Calcd for C_{18}H_{12}N_{4}O_{5}: C, 65.05; H, 3.64; N, 16.85. Found: C, 64.76; H, 3.61; N, 16.71.

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References

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