5-Aminouracil as a Building Block in Heterocyclic Synthesis: Part IV. One-pot Synthesis of 1*H*-Pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione Derivatives Using Controlled Microwave Heating

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An efficient and direct procedure for the synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4-dione derivatives using controlled microwave heating has been described. The products were characterized by elemental analyses, IR, ¹H NMR, ¹³C NMR and MS spectra.

Key words: 5-Aminouracil, Dimedone, Barbituric Acid, Thiobarbituric Acid, Controlled Microwave Heating, One-pot Synthesis, Pyrrolo[2,3-d]pyrimidine-2,4-dione

Introduction

Fused pyrimidinone derivatives have attracted the attention of numerous researchers over many years due to their important biological activities [1-3]. Among them, pyrrolo[2,3-d]pyrimidines, a class of 7-deazapurine analog, exhibit interesting biological activity in part due to their resemblance to pyrimidines and purines. For example, they have recently been reported as enzyme inhibitors [4], cytotoxic [5], antiinflammatory [6], anti-microbial [6], antibacterial [7], antifungal [7], anticancer [8], antitumor [9], antifolate [10], antiviral [11], vascular endothelial growth factor receptor-2 inhibitors [12], and antiangiogenic agents [12]. They also possess anti-HCV, anti-HIV type 1, anti-HSV, adenosine kinase inhibition, Aurora-A kinase inhibition and cAMP phosphodiesterase inhibition activity [13–15].

Recently, we have reported a simple and efficient synthesis of pyrimido[5,4-b]quinoline-2,4,9-triones **3** [16], **4** [17] and pyrido[3,2-d:6,5-d']dipyrimidines **6** [18] *via* the reaction of 5-aminouracil (1), aldehydes and dimedone (**2**) or barbituric acid derivatives **5** under microwave irradiation without catalyst, which could have interesting effects on biological targets (Scheme 1).

Considering the above reports and in continuation of our interest in the development of new and sim-



Scheme 1. Synthesis of pyrimido[5,4-b]quinolines 3, 4 and pyrido[3,2-d:6,5-d']dipyrimidines 6.

ple methods for the synthesis of polyfunctionally substituted heterocyclic compounds [16-28], we wish to report a novel and efficient one-pot method for the synthesis of pyrrolo[2,3-d]pyrimidine-2,4-dione and pyrimido[5,4-b]quinoline-2,4,9-trione derivatives with expected interesting biological activity.

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Results and Discussion

Thus, 5-aminouracil (1), dimedone (2) and phenylglyoxal hydrate (7) in DMF gave under controlled microwave heating for 20 min at 160 °C a solid product of molecular formula $C_{20}H_{19}N_3O_4$ (m/z = 365 (30%) $[M]^+$) which may be formulated as the pyrrolo[2,3-*d*]pyrimidine-2,4-dione **10** or pyrimido[5,4-*b*]quinoline-2,4,9(1*H*,3*H*,5*H*)-trione **11** (Scheme 2).

The product was assigned structure **10** on the basis of spectral data and the chemical transformations outlined below. Thus, its ¹H NMR spectrum revealed the presence of D₂O-exchangeable protons at $\delta = 10.36$, 10.53 and 11.95 ppm which are attributable to the three NH protons, 1-NH, 3-NH and 7-NH, respectively. Also, the structure assigned for compound **10** was fully supported by its ¹³C NMR spectrium. Further confirmation of structure **10** was achieved *via* the synthesis of its ethylated derivative **12** *via* the reaction of **10** with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate (Scheme 3).

A distinction between compounds **10** and **12** is clearly manifested in the spectroscopic data. For example, the ¹H NMR spectrum of compound **12** revealed no NH protons, and the presence of four ethyl groups indicated that the alkylation occurs at the N-1, N-3, N-7 and OH atoms. Furthermore, the structure assigned to **12** was fully supported by its mass spectrum, which showed a molecular formula $C_{28}H_{35}N_3O_4$ (m/z = 477 (35%) [M]⁺). With these spectroscopic data the proposed structure of **10** is identified. The formation of **10** was rationalized in terms of the initial formation of the intermediate **8** [29]. A subsequent reaction at the nucleophilic carbon atom C-6 in 5-aminouracil (**1**) leads to the formation of intermediate **9**,



Scheme 4. Synthesis of pyrimido[5,4-*b*]quinolines 11 and 15.

which was cyclized *via* loss of water to finally form pyrrolopyrimidine **10** (Scheme 2). The same product was obtained by refluxing 5-aminouracil (**1**), dimedone (**2**) and phenylglyoxal hydrate (**7**) in DMF for 10 h.

In addition, the structure of **10** was confirmed further by an alternative synthesis of its isomer **11** (Scheme 4). The reaction of phenylglyoxal hydrate (**7**) with enaminoketone **13** [16] in DMF under microwave irradiation at 160 °C for 20 min afforded 10-benzoyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-*b*]quinoline-2,4,9(1*H*,3*H*,6*H*)-trione (**11**) (Scheme 4). The structure of the product **11** was confirmed by elemental analysis and spectral data. The disappearance of signals for 10-H and 5-NH in the ¹H NMR spectrum indicated the formation of compound **11**.

We also studied the alkylation of **11** with ethyl iodide. The reaction was carried out at r. t. in DMF and in the presence of anhydrous potassium carbonate to afford the ethylated derivative **15** (Scheme 4). The structure of the product **15** was established by elemental analysis and spectral data. Its IR spectrum revealed absorption bands around 1654-1690 cm⁻¹, characteristic of a carbonyl function. The ¹H NMR spectrum revealed that the alkylation occurs at the N-1 and N-3 atoms. Thus, the ¹H NMR spectrum of com-

pound **15** contained signals from the N¹CH₂ (δ = 3.80) and N³CH₂ protons (δ = 4.00 ppm). Furthermore, the structure assigned to **15** was fully supported by its mass spectrum, which indicated the molecular formula C₂₄H₂₅N₃O₄ (m/z = 419 (35%) [M]⁺). Further confirmation of structure **15** was obtained *via* the reaction of ethylated enaminoketone **16** [17] with **7** in DMF under controlled microwave heating (Scheme 4).

As an extension of our synthetic methodology, 5aminouracil (1), phenylglyoxal hydrate (7) and barbituric acids 5a, b were also exposed to MW irradiation. The reaction proceeded similarly to give 17ab (Scheme 5). The proposed molecular structures of 17a, b are supported by elemental and spectral analyses. The fragmentation patterns of the mass spectra of 17a and 17b showed the molecular ion peaks $[M]^+$ at m/z = 369 (70%) and 353 (25%), respectively, in good agreement with the assigned structure. The IR, ¹H NMR as well as the ¹³C NMR spectra agreed with the proposed structures 17a, b. For example, the ¹H NMR spectrum of **17a** revealed five relatively sharp singlets at $\delta = 10.55, 10.69, 12.11, 12.13$ and 12.26 ppm assigned to the five NH groups, in addition to the signals for the dimedone and phenyl protons. Moreover, the ethylated derivative 18 was



Scheme 5. Synthesis of 17 and 18.

obtained by reacting **17a** with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate (Scheme 5). The structure of **18** was confirmed by its elemental and spectral analyses, which showed the molecular ion peak $[M]^+$ at m/z = 509 (100%). Also, the ¹H NMR spectrum of **18** displayed signals of five ethyl groups indicating that the alkylation occurred at the N-1, N-3, N-7, OH and SH atoms. The imide hydrogen atoms in thiobarbituric acid take part in tautomerism so that the alkylation of this compound leads to a mixture of *N*- and *S*-alkyl derivatives [30, 31]

Experimental Section

General procedures

Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by thin layer chromatography (TLC) on aluminum plates coated with silica gel with fluorescence indicator (Merck, 60 F₂₅₄) using CHCl₃-CH₃OH (10:5) as eluent. Microwave irradiation was carried out using the Milestone Start Labstation for microwave-enhanced chemistry. Infrared spectra were recorded in potassium bromide disks on a Jasco FT/IR-450 Plus infrared spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX spectrometer operating at 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR, with deuterated chloroform (CDCl₃) or dimethylsulfoxide ([D₆]DMSO) as solvent. Chemical shifts are reported in δ (ppm) and with TMS or the solvent signal as internal standard. Mass spectra were recorded on a Trace GC 2000/Finnigan Mat SSQ 7000 and a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were measured with a Vario EL III CHNOS Elemental Analyzer in the Microanalytical Center of Cairo University. Compounds **13** [16] and **16** [17] were synthesized using the published procedures.

Preparation of 5-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (10)

Method A: A mixture of 5-aminouracil (1) (0.127 g, 1 mmol), dimedone (2) (0.140 g, 1 mmol) and phenylglyoxal hydrate (7) (0.134 g, 1 mmol) in DMF (5 mL) was heated under reflux in a Milestone Microwave Labstation at 160 °C for 20 min. The solvent was evaporated under reduced pressure. The solid product was collected by filtration and recrystallized from ethanol; yield 76 %.

Method B: A solution of equimolar amounts of **1** (0.127 g, 1 mmol), **2** (0.140 g, 1 mmol) and **7** (0.134 g, 1 mmol) in DMF (10 mL) was refluxed for 10 h. Product **10** was isolated as described above; yield 70 %.

Pale-yellow powder, m. p. 335-337 °C. – IR (film): v = 3186, 3059, 2953, 1692 cm⁻¹. – ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 1.03$ (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 2.12 (brs, 2H, CH₂), 2.47 (brs, 2H, CH₂), 7.28 (t, 1H, J = 6.8 Hz, Ar-H), 7.31 (t, 2H, J = 7.2 Hz, Ar-H), 7.50 (d, 2H, J = 7.2 Hz, Ar-H), 10.36 (s, 1H, NH, D₂O-exchangeable), 10.53 (s, 1H, NH, D₂O-exchangeable), 11.95 (s, 1H, NH, D₂O-exchangeable). – ¹³C NMR (100 MHz, [D₆]DMSO): $\delta = 26.45$, 30.40, 31.22, 38.89, 40.28, 100.30, 105.93, 109.97,

126.93, 127.59, 128.02, 131.98, 135.74, 137.80, 151.64, 155.66, 162.05, 195.94. – MS (EI, 70 eV): m/z (%) = 366 (23) [M+1]⁺, 365 (100) [M]⁺. – C₂₀H₁₉N₃O₄ (365.38): calcd. C 65.74, H 5.24, N 11.50; found C 65.49, H 5.17, N 11.66

Preparation of 5-(2-ethoxy-4,4-dimethyl-6-oxocyclohex-1enyl)-1,3,7-triethyl-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**12**)

Ethyl iodide (2.496 g, 16 mmol) was added to a mixture of 10 (0.73 g, 2 mmol) and anhydrous potassium carbonate (1.104 g, 8 mmol) in DMF (20 mL). The reaction mixture was stirred for 80 h at r.t. and then poured into cold water and extracted with carbon tetrachloride $(3 \times 20 \text{ mL})$. The combined organic extracts were washed with water and dried (anhydrous magnesium sulfate). After evaporation of some of the solvent (~ 5 mL), petroleum ether (30 mL) was added, and the resulting precipitate was collected, dried and recrystallized from diphenylether-n-hexane to afford 12 (vield 50 %). Colorless solid, m. p. 220-222 °C. - IR (film): $v = 3064, 2968, 1683, 1642 \text{ cm}^{-1}. - {}^{1}\text{H} \text{ NMR}$ (400 MHz, $[D_6]DMSO$: $\delta = 0.92$ (s, 6H, 2CH₃), 1.11-1.14 (m, 12H, 4CH₃), 1.95 (d, 1H, J = 15.6 Hz, CH₂), 2.25 (d, 1H, J = 15.6 Hz, CH₂), 2.32 (d, 1H, J = 18 Hz, CH₂), 2.58 (d, 1H, J = 18 Hz, CH₂), 3.87 (q, 2H, J = 8 Hz, CH₂), 3.96 (q, 2H, J = 11 Hz, CH₂), 4.06 (q, 2H, J = 7 Hz, CH₂), 4.17 (q, 2H, J = 7 Hz, CH₂), 7.17-7.41 (m, 5H, ArH). – ¹³C NMR (100 MHz, [D₆]DMSO): δ = 13.23, 13.30, 15.29, 16.70, 25.81, 25.98, 27.17, 31.16, 31.31, 35.22, 38.66, 49.93, 63.73, 99.97, 100.61, 107.56, 109.23, 110.18, 120.64, 128.03, 128.68, 129.59, 130.03, 133.03, 141.96, 150.15, 154.21, 174.05, 196.99. – MS (EI, 70 eV): m/z (%) = 478 (40) [M+1]⁺, 477 (35) [M]⁺. – C₂₈H₃₅N₃O₄ (477.60): calcd. C 70.42, H 7.39, N 8.80; found C 70.59, H 7.37, N 8.66.

Preparation of 10-benzoyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)trione (11)

A mixture of 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)pyrimidine-2,4(1*H*,3*H*)-dione (**13**) (0.249 g, 1 mmol) and **7** (0.134 g, 1 mmol) in DMF (5 mL) was heated under reflux in a Microwave Labstation at 160 °C for 30 min. The solvent was evaporated under vacuum. The solid product was collected by filtration and crystallized from benzene, yield 60 %. Pale-brown powder, m. p. 282–285 °C. – IR (film): v = 3157, 3028, 2931, 1675, 1632 cm⁻¹. – ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 1.02$ (s, 6H, 2CH₃), 2.49 (s, 2H, CH₂), 3.22 (s, 2H, CH₂), 7.40–7.55 (m, 5H, Ar-H), 10.32 (s, 1H, NH, D₂O-exchangeable), 10.48 (s, 1H, NH, D₂O-exchangeable). – MS (EI, 70 eV): m/z (%) = 364 (40) [M+1]⁺, 363 (60) [M]⁺. – C₂₀H₁₇N₃O₄ (363.37): calcd. C 66.11, H 4.72, N 11.56; found C 65.89, H 4.75, N 11.61. Preparation of 10-benzoyl-1,3-diethyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-b]quinoline-2,4,9 (1H,3H,6H)-trione (15)

Method A: Ethyl iodide (0.624 g, 4 mmol) was added to a mixture of **11** (0.363 g, 1 mmol) and anhydrous potassium carbonate (0.276 g, 2 mmol) in DMF (10 mL). The reaction mixture was stirred for 70 h at r. t. and then poured into cold water and extracted with chloroform (3×20 mL). The combined organic extracts were washed with water and dried (anhydrous magnesium sulfate). After evaporation of some of the solvent (~ 10 mL), petroleum ether (40 mL) was added, and the resulting precipitate was collected, dried and recrystallized from petroleum ether-chloroform to give **14**; yield 43 %.

Method B: A mixture of 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-1,3-diethyl pyrimidine-2,4(1H,3H)dione (16) (0.710 g, 1 mmol) and 7 (0.134 g, 1 mmol) in DMF (5 mL) was heated under reflux in a Milestone Microwave Labstation at 160 °C for 50 min. The solvent was evaporated under vacuum. Product 14 was isolated by filtration and recrystallized as described above; yield 5 %.

Brown powder, m. p. 183 – 185 °C. – IR (film): v = 3060, 2954, 2877, 1690, 1654 cm⁻¹. – ¹H NMR (400 MHz, CDCl₃): $\delta = 1.05$ (s, 6H, 2 CH₃), 1.20 (t, 3H, J = 6 Hz, CH₃), 1.27 (t, 3H, J = 6 Hz, CH₃), 2.53 (s, 2H, CH₂), 3.35 (s, 2H, CH₂), 3.80 (q, 2H, J = 9 Hz, CH₂), 4.00 (q, 2H, J = 6 Hz, CH₂), 7.25 – 7.33 (m, 3H, Ar-H), 7.50 (d, 2H, Ar-H, J = 7.2 Hz). – MS (EI, 70 eV): m/z (%) = 419 (35) [M]⁺. – C₂₄H₂₅N₃O₄(419.47): calcd. C 68.72, H 6.01, N 10.02; found C 68.90, H 5.96, N 10.11.

Preparation of 6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-diones (**17a**, **b**)

A solution of equimolar amounts of **1** (0.127 g, 1 mmol), **7** (0.134 g, 1 mmol) and thiobarbituric acid **5a** (0.144 g, 1 mmol) and/or barbituric acid **5b** (0.128 g, 1 mmol) in DMF (5 mL) was heated under reflux in a Milestone Microwave Labstation at 160 °C for 20 min. The solvent was evaporated under reduced pressure. The solid product was collected by filtration and crystallized from the appropriate solvent.

5-(6-Hydroxy-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-6-phenyl-1H-pyrrolo[2,3d]pyrimidine-2,4(3H,7H)dione (**17a**)

Pale-brown crystals, yield 80 % (EtOH); m. p. > 360 °C. – IR (film): v = 3147, 3018, 2954, 1667 cm⁻¹. – ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 7.27$ (t, 1H, Ar-H, J = 6.2 Hz), 7.40 (t, 2H, Ar-H, J = 6.9 Hz), 7.49 (d, 2H, Ar-H, J = 7.2 Hz), 10.55 (s, 1H, NH, D₂O-exchangeable), 10.69 (s, 1H, NH, D₂O-exchangeable), 12.11 (s, 1H, NH, D₂O-exchangeable), 12.13 (s, 1H, NH, D₂O-exchangeable), 12.26 (s, 1H, HN, D₂O-exchangeable). – ¹³C NMR (100 MHz, [D₆]DMSO): δ = 86.57, 97.98, 109.25, 109.98, 126.75, 127.72, 128.25, 131.69, 136.54, 138.70, 151.58, 155.71, 161.33, 173.59, 200.11. – MS (EI, 70 eV): m/z (%) = 369.11 (70) [M]⁺, 370.12 (25.6), 371.22 (20). – C₁₆H₁₁N₅O₄S (369.35): calcd. C 52.03, H 3.00, N 18.96; found C 52.19, H 2.96, N 18.91.

5-(6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (17b)

Colorless powder, yield 76 % (DMF); m. p. > 350 °C. – IR (film): v = 3173, 3030, 2822, 1702, 1670 cm⁻¹. – ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 7.21$ (t, 1H, Ar-H, J = 7.0), 7.30 (t, 2H, Ar-H, J = 8), 7.68 (d, 2H, Ar-H, J = 7), 9.53 (s, 2H, NH, D₂O-exchangeable), 10.08 (s, 1H, NH, D₂Oexchangeable), 10.44 (s, 1H, NH, D₂O-exchangeable), 11.71 (s, 1H, NH, D₂O-exchangeable). – ¹³C NMR (100 MHz, [D₆]DMSO): $\delta = 100.01$, 109.72, 126.77, 127.35, 128.04, 132.16, 138.53, 151.15, 151.57, 155.74, 163.09. – MS (EI, 70 eV): m/z (%) = 355.2 (10) [M+2]⁺, 353.2 (25) [M]⁺. – C₁₆H₁₁N₅O₅ (353.29): calcd. C 54.39, H 3.14, N 19.82; found C 54.22, H 3.28, N 19.90.

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Synthesis of 5-(4-ethoxy-2-(ethylthio)-6-oxo-1,6-dihydropyrimidin-5-yl)-1,3,7-triethyl-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (18)

Ethyl iodide (3.79 g, 24 mmol) was added to a mixture of 17 (0.739 g, 2 mmol) and anhydrous potassium carbonate (1.65 g, 12 mmol) in DMSO (10 mL). The reaction mixture was stirred for 86 h at r. t. and then poured into cold water, the precipitate was collected by filtration and recrystallized from diethyl ether-petroleum ether to give 18 (yield 40%). Colorless solid, m. p. 230-233 °C. - IR (film): v = 3205, 3064, 2968, 1703, 1682 cm⁻¹. – ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 1.01$ (t, 3H, J = 9 Hz, CH₃), 1.15 (t, 3H, J = 7 Hz, CH₃), 1.25 (t, 3H, J = 7 Hz, CH₃), 1.31 (t, 3H, J = 7 Hz, CH₃), 1.36 (t, 3H, J = 11 Hz, CH₃), 3.16 (q, 2H, J = 8 Hz, CH₂), 3.76 (q, 2H, J = 8 Hz, CH₂), 3.94 (q, 2H, J = 10 Hz, CH₂), 4.14 (q, 2H, J = 7 Hz, CH₂), 4.21 (q, 4H, J = 7 Hz, CH2), 7.21-7.50 (m, 5H, ArH), 12.11 (s, 1H, NH). - MS (EI, 70 eV): m/z (%) = 508.25 (6.87), 509.20 (100) [M]⁺, 510.20 (33), 511.15 (11). – $C_{26}H_{31}N_5O_4S$ (509.62): calcd. C 61.28, H 6.13, N 13.74; found C 61.21, H 6.22, N 13.79.

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