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

Raafat M. Shaker[a,b], Kamal U. Sadek[b], Ebtisam A. Hafez[c], and Mohamed Abd Elrady[b]

[a] Current address: Chemistry Department, College of Science, Al-Jouf University, Sakaka, Saudi Kingdom
[b] Chemistry Department, Faculty of Science, Minia University, 61519 El-Minia, Egypt
[c] Chemistry Department, Faculty of Science, Cairo University, Giza-12613, Egypt

Reprint requests to Prof. Dr. Raafat M. Shaker. E-mail: rmshaker@yahoo.com

Z. Naturforsch. **2011**, *66b,* 843 – 849; received June 6, 2011

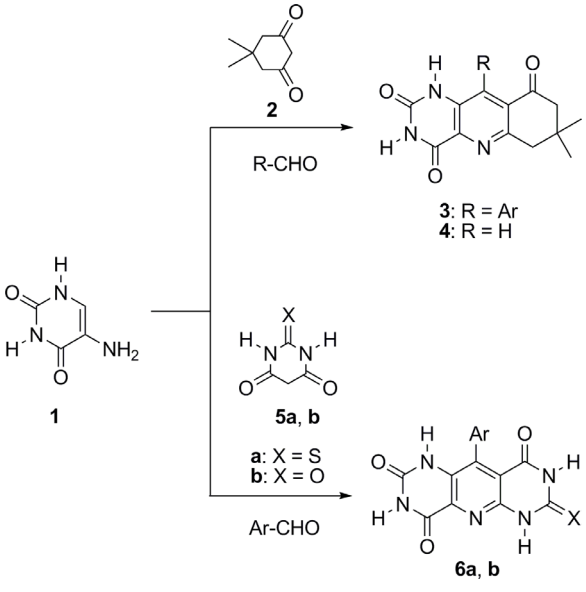
An efficient and direct procedure for the synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4-dione derivatives using controlled microwave heating has been described. The products were characterized by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and MS spectra.

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

Introduction

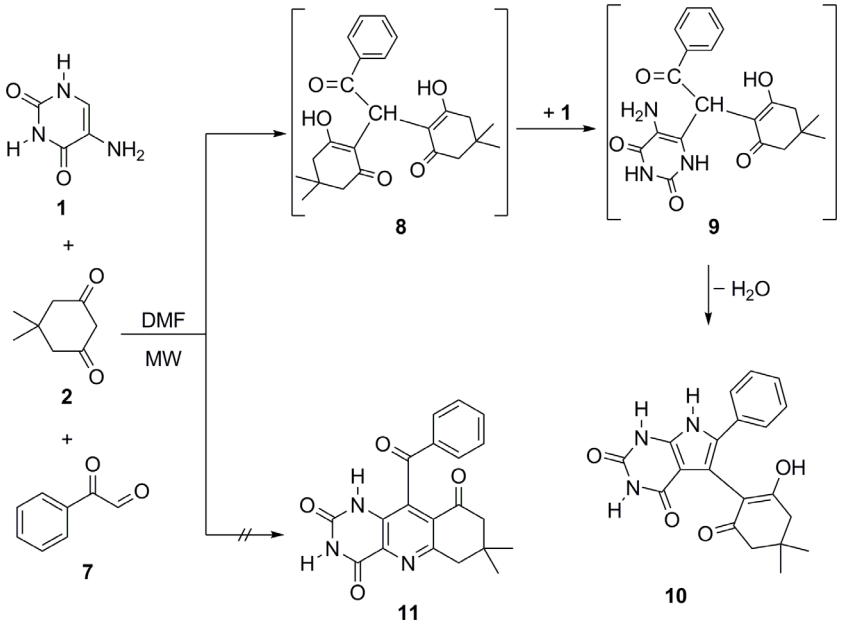
Fused pyrimidinone derivatives have attracted the attention of numerous researchers over many years due to their important biological activities [1 – 3]. Among them, pyrrolo[2,3-*d*]pyrimidines, a class of 7-deazapurine analog, exhibit interesting biological activity in part due to their resemblance to pyrimidines and purines. For example, they have recently been reported as enzyme inhibitors [4], cytotoxic [5], anti-inflammatory [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).

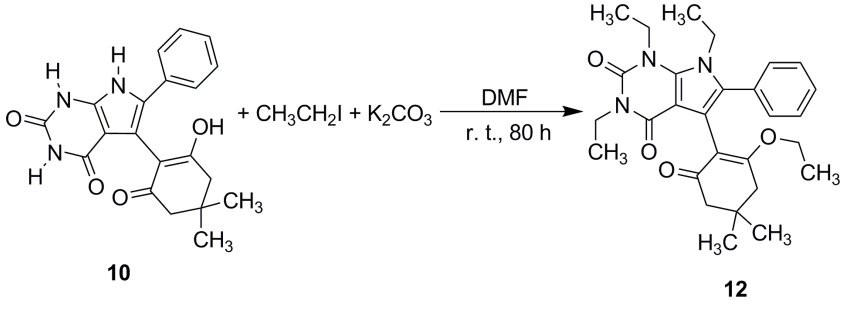


Scheme 1. Synthesis of pyrimido[5,4-*b*]quinolines **3**, **4** and pyrido[3,2-*d* : 6,5-*d*′]dipyrimidines **6**.

Considering the above reports and in continuation of our interest in the development of new and simple 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.



Scheme 2. Synthesis of 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**10**).



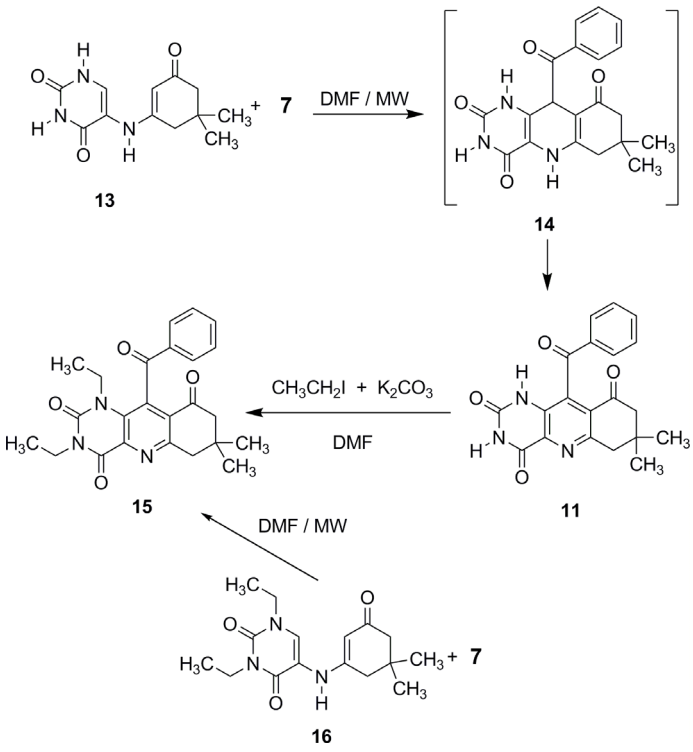
Scheme 3. Ethylation of **10**.

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 ^{1}H NMR spectrum revealed the presence of D_2O-exchangeable protons at δ = 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 ^{13}C 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 ^{1}H 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**,



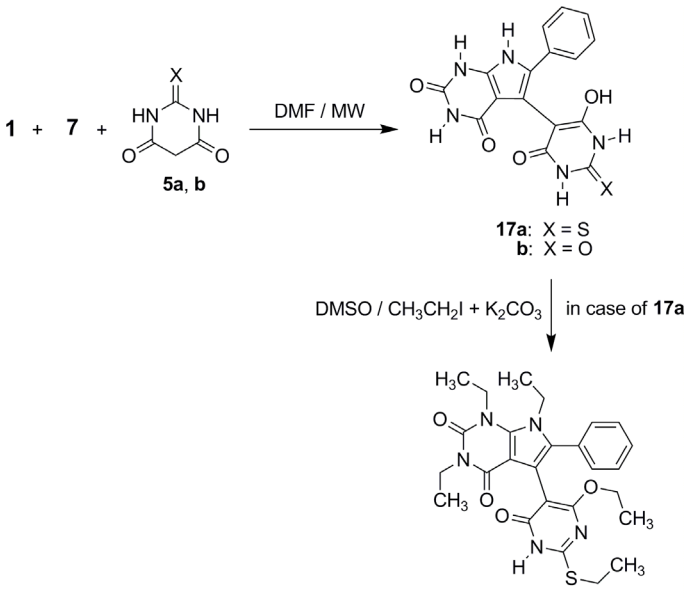
Scheme 4. Synthesis of pyrimido[5,4-*b*]quinolines **11** and **15**.

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 ^{1}H 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 ^{1}H NMR spectrum revealed that the alkylation occurs at the N-1 and N-3 atoms. Thus, the ^{1}H NMR spectrum of compound **15** contained signals from the N^1CH_2 (δ = 3.80) and N^3CH_2 protons (δ = 4.00 ppm). Furthermore, the structure assigned to **15** was fully supported by its mass spectrum, which indicated the molecular formula $C_{24}H_{25}N_3O_4$ (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, 5-aminouracil (**1**), phenylglyoxal hydrate (**7**) and barbituric acids **5a**, **b** were also exposed to MW irradiation. The reaction proceeded similarly to give **17a b** (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, ^{1}H NMR as well as the ^{13}C NMR spectra agreed with the proposed structures **17a**, **b**. For example, the ^{1}H NMR spectrum of **17a** revealed five relatively sharp singlets at δ = 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 ^{1}H 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 F_{254}) using $CHCl_3$-CH_3OH (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. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, with deuterated chloroform ($CDCl_3$) or dimethylsulfoxide ([D_6]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): ν = 3186, 3059, 2953, 1692 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.03 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.12 (brs, 2H, CH_2), 2.47 (brs, 2H, CH_2), 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, D_2O-exchangeable), 10.53 (s, 1H, NH, D_2O-exchangeable), 11.95 (s, 1H, NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 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) $[M]^+$. – $C_{20}H_{19}N_3O_4$ (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-1-enyl)-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 × 20 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** (yield 50 %). Colorless solid, m. p. 220 – 222 °C. – IR (film): ν = 3064, 2968, 1683, 1642 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 0.92 (s, 6H, 2CH$_3$), 1.11 – 1.14 (m, 12H, 4CH$_3$), 1.95 (d, 1H, J = 15.6 Hz, CH$_2$), 2.25 (d, 1H, J = 15.6 Hz, CH$_2$), 2.32 (d, 1H, J = 18 Hz, CH$_2$), 2.58 (d, 1H, J = 18 Hz, CH$_2$), 3.87 (q, 2H, J = 8 Hz, CH$_2$), 3.96 (q, 2H, J = 11 Hz, CH$_2$), 4.06 (q, 2H, J = 7 Hz, CH$_2$), 4.17 (q, 2H, J = 7 Hz, CH$_2$), 7.17 – 7.41 (m, 5H, ArH). – ^{13}C NMR (100 MHz, [D$_6$]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) $[M]^+$. – $C_{28}H_{35}N_3O_4$ (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): ν = 3157, 3028, 2931, 1675, 1632 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.02 (s, 6H, 2CH$_3$), 2.49 (s, 2H, CH$_2$), 3.22 (s, 2H, CH$_2$), 7.40 – 7.55 (m, 5H, Ar-H), 10.32 (s, 1H, NH, D$_2$O-exchangeable), 10.48 (s, 1H, NH, D$_2$O-exchangeable). – MS (EI, 70 eV): m/z (%) = 364 (40) $[M+1]^+$, 363 (60) $[M]^+$. – $C_{20}H_{17}N_3O_4$ (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(1*H*,3*H*)-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): ν = 3060, 2954, 2877, 1690, 1654 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 6H, 2 CH$_3$), 1.20 (t, 3H, J = 6 Hz, CH$_3$), 1.27 (t, 3H, J = 6 Hz, CH$_3$), 2.53 (s, 2H, CH$_2$), 3.35 (s, 2H, CH$_2$), 3.80 (q, 2H, J = 9 Hz, CH$_2$), 4.00 (q, 2H, J = 6 Hz, CH$_2$), 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) $[M]^+$. – $C_{24}H_{25}N_3O_4$(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): ν = 3147, 3018, 2954, 1667 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 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, D$_2$O-exchangeable), 10.69 (s, 1H, NH,

D_2O-exchangeable), 12.11 (s, 1H, NH, D_2O-exchangeable), 12.13 (s, 1H, NH, D_2O-exchangeable), 12.26 (s, 1H, HN, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]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). – $C_{16}H_{11}N_5O_4S$ (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): ν = 3173, 3030, 2822, 1702, 1670 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ = 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, D_2O-exchangeable), 10.08 (s, 1H, NH, D_2O-exchangeable), 10.44 (s, 1H, NH, D_2O-exchangeable), 11.71 (s, 1H, NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 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) $[M]^+$. – $C_{16}H_{11}N_5O_5$ (353.29): calcd. C 54.39, H 3.14, N 19.82; found C 54.22, H 3.28, N 19.90.

*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): ν = 3205, 3064, 2968, 1703, 1682 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.01 (t, 3H, J = 9 Hz, CH_3), 1.15 (t, 3H, J = 7 Hz, CH_3), 1.25 (t, 3H, J = 7 Hz, CH_3), 1.31 (t, 3H, J = 7 Hz, CH_3), 1.36 (t, 3H, J = 11 Hz, CH_3), 3.16 (q, 2H, J = 8 Hz, CH_2), 3.76 (q, 2H, J = 8 Hz, CH_2), 3.94 (q, 2H, J = 10 Hz, CH_2), 4.14 (q, 2H, J = 7 Hz, CH_2), 4.21 (q, 4H, J = 7 Hz, CH_2), 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.

Acknowledgement

The authors are grateful to the Alexander von Humboldt foundation for a donation of a Milestone Microwave Labstation which was of great help in completing this work.

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