5-Aminouracil as a Building Block in Heterocyclic Synthesis: Part III.
One-pot Synthesis of Novel Pyrimido[5,4-b]quinoline-2,4,9-triones
and Pyrimido[5,4-c]isoquinolines

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An efficient and direct procedure for the synthesis of pyrimido[5,4-b]quinoline-2,4,9-trione and
pyrimido[5,4-c]isoquinoline derivatives has been described. The products were characterized by ele-
mental analyses, IR, $^1$H NMR, $^{13}$C NMR and MS spectra.

Key words: 5-Aminouracil, Dimedone, One-pot Synthesis, Pyrimido[5,4-b]quinoline-2,4,9-trione,
Pyrimido[5,4-c]isoquinoline

Introduction

Polyfunctionalized heterocyclic compounds play
important roles in the drug discovery process, and anal-
ysis of drugs in late development or on the market
shows that 68 % of them are heterocycles [1]. There-
fore, it is not surprising that research on the synthesis
of polyfunctionalized heterocyclic compounds has re-
ceived significant attention. Pyrimidoquinolines have
been an object of great interest to organic, medicinal
and materials scientists over many years, as they are
present in a number of biologically active organic com-
ounds which exhibit antimalarial [2, 3], anticancer
[4], antitumor [5] antimicrobial [6], antiviral [7], anal-
gesic [8], anti-oxidant [8], and anti-inflammatory ac-
tivities [8, 9]. Furthermore, multi-component reactions
(MCRs) play an increasingly important role in organic
and medicinal chemistry for their convergence, pro-
ductivity, ease of execution, excellent yield, and broad
application in combinational chemistry [10 – 18].

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

Considering the above reports and in continuation
of our work in the development of new and simple
methods for the synthesis of polyfunctionally substi-
tuted heterocyclic compounds [17 – 28], we wish to
report a novel and efficient one-pot method for the
synthesis of pyrimido[5,4-b]quinoline-2,4,9-trione and
pyrimido[5,4-c]isoquinoline derivatives with the pur-
pose of investigating in the future their possible bio-
logical activity. The mechanism of the reaction has
been proved via the synthesis of a proposed inter-
mediate.

Results and Discussion

The reaction of 5-aminouracil (1), dimedone (3)
and paraformaldehyde (7) in DMF and in the pres-
ence of triethylamine as a catalyst gave a solid product of the composition C_{13}H_{13}N_{3}O_{3} (m/z = 259 (30%), [M]^+) which may be formulated as the pyrimido[5,4-b]quinoline-2,4,9-trione 8 or its isomer 9 (Scheme 2). The molecular structure of 8 was indicated by its $^1$H NMR spectrum which revealed three characteristic, relatively sharp singlets at 11.56, 11.25 and 7.93 ppm. The two former ones are assigned to the two NH groups, 3-NH and 1-NH, respectively, and the latter to H-10. Two singlets appear at 3.00 and 2.62 ppm corresponding to the two CH$_2$ groups at positions 6 and 8, respectively, in addition to the singlet for the two methyl groups. Moreover, the $^{13}$C NMR spectrum of 8 showed signals at $\delta_C =$ 28.41 (CMe$_2$), 33.02 (C-7), 41.88 (C-6), 50.37 (C-8), 129.01 (C-10), 133.73 (C-9a), 139.98 (C-4a), 144.62 (C-10a), 151.31 (C-6a), 162.08 (C-2), 163.31 (C-4), and 197.09 (C-9). With these spectroscopic data the proposed linear structure of 8 is identified. In the angular structure 9 the pyridine proton signal should have appeared at a higher field [29].

A proposed reaction mechanism that accounts for the multicomponent reaction is shown in Scheme 3. Thus, the reaction may occur via a condensation, addition, cyclization, and elimination mechanism. We assume the initial formation of the 2:1 dimedone/formaldehyde adduct 10, which gives the Knoevenagel adduct intermediate 11. A subsequent Michael-type addition reaction of the nucleophile C-6 in 5-aminouracil (I) leads to the formation of intermediate 12, which undergoes cyclization with loss of a water molecule and partial oxidation to render compound 8. Neither adduct 10 nor 11 were isolated in the reaction under study. To confirm the assumed three-component condensation route we synthesized 2,2′-methylene-bis(3-hydroxy-5,5-dimethyl-cyclohex-2-enone) (10) [30] and brought it into reaction with compound 1 under the previous conditions. The target product formed in approximately the same yield and was identical in all aspects to compound 8 (Scheme 3).

We also studied the alkylation of 8 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 13 (Scheme 4). The structure of the product 13 was proved by elemental analysis and spectral data. This compound is not the O-ethylation product. Its IR spectrum contains bands around 1662 – 1708 cm$^{-1}$, characteristic of carbonyl absorptions, and 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 13 contained signals from the N$^1$CH$_2$ ($\delta =$ 3.81) and N$^3$CH$_2$ protons ($\delta =$ 3.88 ppm). Furthermore, the structure assigned to 13 was fully supported by its mass spectrum, which showed a molecular formula C$_{17}$H$_{21}$N$_3$O$_3$ (m/z = 315 (35%), [M]$^+$). Further confirmation of structure 13 was achieved via the synthesis of the ethylated enaminoketone 15, prepared by ethylation of the enaminoketone 14 with ethyl iodide in DMF and in the
presence of anhydrous potassium carbonate. The IR, MS, \(^1\)H NMR as well as the \(^{13}\)C NMR spectra agreed with the proposed structure 15. Gentle heating of a dimethylformamide solution of 15 and dimethylformamide dimethyl acetal (16) at 125 – 135 °C for 18 h yielded a product identical in all aspects to compound 13 (Scheme 4).

In addition, the structure of 8 was confirmed further by an alternative synthesis of its isomer 9 (Scheme 5). Thus, reacting a mixture of 5-aminouracil (1), dimedone (3) and DMFDMMA (16) in DMF without catalyst under reflux for 8 h afforded the pyrimidine-2,4(1H,3H)-dione 18 (Scheme 5). The structure of compound 18 was confirmed by its elemental and spectral analyses, which showed the molecular ion peak at \(m/z = 277.14\) (98 %). Its \(^1\)H NMR spectrum showed characteristic singlets at \(\delta = 11.09\) and 11.57 ppm for two NH groups, a doublet at \(\delta = 12.29\) (J = 15 Hz) for an exocyclic NH group, a doublet at \(\delta = 8.36\) (J = 15 Hz) due to N-CH=, a singlet at \(\delta = 7.99\) due to CH-uracil, in addition to three singlet signals for the methyl and dimedone protons. Furthermore, the structure of compound 18 was confirmed by an independent synthesis of the same compound from an equimolar amount of 1 and 2-dimethylaminomethylidenecyclohexane-1,3-dione (17) in DMF under reflux to afford a product identical in all aspects to compound 18 (Scheme 5).

The formation of 18 can be described in terms of the initial formation of the intermediate 17. A reaction of the latter with 1, which is accompanied by elimination of the readily leaving dimethylamino group, gives rise to 18 (Scheme 5). Heating a dimethylformamide solution of compound 18 affords the pyrimido[5,4-c]isoquinoline 9, the \(^1\)H NMR spectrum of which revealed the absence of an exocyclic NH proton and the presence of a singlet at \(\delta = 8.45\) ppm due to a pyridine-CH proton. The structure of 9 was confirmed by its elemental and spectral analyses, which showed a molecular formula C\(_{13}\)H\(_{11}\)N\(_3\)O\(_3\) \((m/z = 259\) (83.3 %), \([M]^+\)). Comparison of the data of 9 with those of 8 showed differences in melting point, IR, and \(^1\)H NMR data which confirmed the structure of 9 for our product.

Moreover, the ethylated derivative 20 was obtained by reacting 9 with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate (Scheme 5). The structure of 20 was confirmed by its elemental and spectral analyses, which showed the molecular ion peak at \(m/z = 315\) (15 %). Also, the \(^1\)H NMR spectrum of 20 displayed no NH protons, but the presence of signals from the N\(^1\)CH\(_2\) (\(\delta = 3.86\)) and N\(^3\)CH\(_2\) protons (\(\delta = 4.10\) ppm). Further confirmation of structure 20 was obtained via the synthesis of compound 19, prepared by ethylation of compound 18. The structure of 19 was established by its correct elemental analysis and compatible spectroscopic data. Subsequent heating of 19 in refluxing DMF smoothly converted it to the final product 20 (Scheme 5). The identity of the products of the cyclization of 19 with those obtained by the ethylation of 9 was confirmed by comparison of their IR and \(^1\)H NMR spectra.

Finally, cyclization and chlorination of compound 18 using phosphoryl chloride gave the dichloro derivative 21 (Scheme 5). The structure of the latter product was confirmed on the basis of correct elemental analysis and spectral data. Thus, the IR and \(^1\)H NMR spectra of 21 revealed the absence of NH groups and signals attributable to the CH-uracil and NH protons of 18. Also, its MS gave the characteristic fragmentation pattern due to the presence of two chlorine atoms and showed the molecular ion peak at \(m/z = 296\) (19.80 %) in agreement with its molecular formula C\(_{13}\)H\(_{11}\)Cl\(_2\)N\(_3\)O.

In conclusion, the reported three-component one-step procedure is a simple, practical and very regioselective method for the synthesis of novel pyrimido[5,4-b]quinoline-2,4,9-trione and pyrimido[5,4-c]isoquinoline derivatives.
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 (10:1) as eluent. Infrared spectra were recorded in potassium bromide disks on a Jasco FT/IR-450 Plus infrared spectrophotometer. NMR spectra were obtained on a JNA-LAA 400 WB-FT spectrometer (300 MHz for 1H NMR, 75 MHz for 13C NMR), with deuterated chloroform (CDCl3) or dimethylsulfoxide ([D6]DMSO) as solvent. Chemical shifts are quoted in δ and are referenced to TMS or the solvent signal. Mass spectra were recorded on a Trace GC 2000/Finnag 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 10 [30], 14 [17] and 17 [31] were synthesized using the published procedures.

7,7-Dimethyl-7,8-dihydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)-trione (8)

Method A: A mixture of 5-aminoaracil (1) (0.13 g, 1 mmol), dimedone (3) (0.28 g, 2 mmol) and paraformaldehyde 7 (0.64 g, 2 mmol) along with triethylamine (0.05 g, 0.5 mmol) in DMF (10 mL) was refluxed for 25 h (TLC control using a solvent system of chloroform-methanol (5:2)). The solvent was evaporated under vacuum; the resulting solid was then collected and crystallized from dioxane; yield: 81%.

Method B: A solution of equimolar amounts of 2,2'-methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (10) (0.29 g, 1 mmol), 1 (0.13 g, 1 mmol) and triethylamine (0.05 g, 0.5 mmol) in DMF (10 mL) was refluxed for 25 h. Product 8 was isolated as described above; yield: 83%. Brown powder, m.p. 288 – 290 °C. – IR (film): ν = 3440, 2923, 1674 cm⁻¹. – 1H NMR (300 MHz, [D6]DMSO): δ = 1.03 (s, 6H, 2CH3), 2.62 (s, 2H, CH2), 3.00 (s, 2H, CH2), 7.93 (s, 1H, 6-H), 11.25 (s, 1H, NH), 11.56 (s, 1H, NH). – 13C NMR (75 MHz, [D6]DMSO): δ = 28.41, 33.22, 41.88, 50.37, 129.01, 133.73, 137.98, 144.62, 151.31, 162.08, 163.31, 197.09. – MS (EI, 70 eV): m/z (%) = 260 (16.7) [M+1]^+, 259 (30) [M]^+. – Anal. for C7H13N3O3 (259.26): calcd. C 60.22, H 5.05, N 16.21; found C 60.39, H 5.17, N 16.34.

Ethylation of 8 and 14

Ethyl iodide (2.81 g, 18 mmol) was added to a mixture of 8 and/or 14 (3 mmol) and anhydrous potassium carbonate (0.83 g, 6 mmol) in DMF (20 mL). The reaction mixture was stirred for 48 – 55 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 and/or n-hexane-benzene to give 13 (yield 40%), and/or 15 (yield 70%), respectively.

1,3-Diethyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)-trione (13)

Dark-brown powder, m.p. 209 – 212 °C. – IR (film): ν = 3521, 2924, 2877, 1708, 1662.5 cm⁻¹. – 1H NMR (300 MHz, [D6]DMSO): δ = 0.99 (s, 6H, 2CH3), 1.12 (t, 3H, J = 6 Hz, CH3), 1.23 (t, 3H, J = 6 Hz, CH3), 2.32 (s, 2H, CH2), 2.40 (s, 2H, CH2), 3.81 (q, 2H, J = 6 Hz, CH2), 3.88 (q, 2H, J = 6 Hz, CH2), 8.41 (s, 1H, 10-H). – MS (EI, 70 eV): m/z (%) = 316 (40) [M+1]^+, 315 (35) [M]^+. – Anal. for C17H23N3O3 (315.37): calcd. C 64.89, H 6.59, N 13.39; found C 64.89, H 6.59, N 13.39.

5-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)-1,3-diethylpyrimidine-2,4(1H,3H)-dione (15)

Yellow crystals, m. p. 238 – 240 °C. – IR (film): ν = 3205, 3106, 2954, 2877, 1708, 1654 cm⁻¹. – 1H NMR (300 MHz, CDCl3): δ = 1.05 (s, 6H, 2CH3), 1.19 (t, 3H, J = 6 Hz, CH3), 1.28 (t, 3H, J = 6 Hz, CH3), 2.18 (s, 2H, CH2), 2.31 (s, 2H, CH2), 3.80 (q, 2H, J = 9 Hz, CH2), 4.00 (q, 2H, J = 6 Hz, CH2), 5.41 (s, 1H, dimedone), 6.43 (s, 1H, CH uracil), 7.24 (s, 1H, NH). – 13C NMR (75 MHz, CDCl3): δ = 12.69, 14.23, 28.14, 32.70, 37.26, 43.77, 45.31, 50.11, 99.99, 114.35, 131.12, 148.86, 158.59, 160.09, 197.95. – MS (EI, 70 eV): m/z (%) = 305.15 (35.58) [M]^+, 290 (100) [M– CH3]^+. – Anal. for C16H21N3O3 (305.37): calcd. C 62.93, H 7.59, N 13.76; found C 62.82, H 7.71, N 13.81.

An alternative synthesis of compound 13

A solution of 15 (0.61 g, 2 mmol) and 16 (0.36 g, 3 mmol) in DMF (5 mL) was gently heated (125 – 135 °C) (TLC control using a solvent system of toluene-acetone (5:4)). After 18 h, product 13 was isolated as described above; yield 50%.

5-(((4,4-Dimethyl-2,6-dioxocyclohexylidene)methylamino)-pyrimidine-2,4(1H,3H)-dione (18)

Method A: A solution of 1 (0.25 g, 2 mmol), 3 (0.28 g, 2 mmol) and 16 (0.24 g, 2 mmol) in DMF (10 mL) was refluxed for 8 h (TLC control). The solvent was evaporated under vacuum; the resulting solid was then collected and crystallized from DMF; yield: 80%.

Method B: A solution of equimolar amounts of 17 (0.4 g, 2 mmol) and 1 (0.25 g, 2 mmol) in DMF (10 mL)
was refluxed for 8 h. Product 18 was isolated as described for method A; yield 85 %. Pale-yellow crystals, m. p. 350 – 352 °C. – IR (film): ν = 3127, 2873, 1651, 1581 cm⁻¹. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.99 (s, 6H, 2Me), 2.30 (s, 2H, CH₂), 2.37 (s, 2H, CH₂), 7.99 (s, 1H, CH uracil), 8.36 (d, 1H, J = 15 Hz, C=H), 11.09 (s, 1H, NH uracil), 11.57 (s, 1H, NH uracil). – MS (EI, 70 eV): m/z (%) = 278.28 (14) [M⁺]+, 277.14 (98) [M⁺]. – Anal. for C₁₃H₁₅N₃O₄ (352): calcd. C 61.25, H 6.95, N 12.60; found C 61.36, H 7.04, N 12.69.

5-(4,4-Dimethyl-2,6-dioxocyclohexylidene)methylamino)-1,3-diethylprismidine-2,4(1H,3H)-dione (19)

Ethyl iodide (1.87 g, 12 mmol) was added to a mixture of 18 (0.56 g, 2 mmol) and anhydrous potassium carbonate (0.83 g, 6 mmol) in DMF (20 mL). The reaction mixture was stirred for 36 h at r. t., concentrated to 3 mL and then poured into cold water. After stirring for 15 min, the precipitate was collected by filtration, washed with water, dried and crystallized from petroleum ether/chloroform; yield 55 %. Yellow crystals, m. p. 232 – 234 °C. – IR (film): ν = 3440, 2927, 2873, 1651, 1581 cm⁻¹. – ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (s, 6H, 2CH₃), 1.22 (t, 3H, J = 6 Hz, CH₃), 1.35 (t, 3H, J = 6 Hz, CH₃), 2.36 (s, 2H, CH₂), 2.42 (s, 2H, CH₂), 3.88 (q, 2H, J = 9 Hz, CH₂), 4.03 (q, 2H, J = 6 Hz, CH₂), 7.43 (s, 1H, uracil), 8.27 (d, 1H, J = 15 Hz), 12.45 (d, 1H, J = 9 Hz, NH). – ¹³C NMR (75 MHz, CDCl₃): δ = 12.64, 14.30, 28.46, 31.02, 37.28, 45.47, 51.30, 51.51, 115.73, 125.35, 127.97, 149.02, 158.36, 163.31, 197.40, 197.73. – MS (EI, 70 eV): m/z (%): 335.15 (8.01) [M+2]⁺, 334.15 (42.27) [M+1]⁺, 333.15 (100) [M]⁺. – Anal. for C₁₇H₁₅N₃O₃ (333): calcd. C 61.25, H 6.95, N 12.60; found C 61.36, H 7.04, N 12.69.

9,9-Dimethyl-9,10-dihydropyrimido[5,4-c]isoquinoline-2,4(1H,3H,8H)-trione (20)

Method A: This compound was prepared in 42 % isolated yield by ethylation of 9 using the procedure described for the synthesis of 13. The solid product was isolated and crystallized from n-hexane/benzene.

Method B: This compound was prepared in 50 % isolated yield by heating 19 in refluxing DMF for 60 h. The product 20 was isolated as described above. Dark-brown powder, m. p. 182 – 185 °C. – IR (film): ν = 2931, 2877, 1708, 1651, 1577 cm⁻¹. – ¹H NMR (300 MHz, CDCl₃): δ = 1.08 (s, 6H, 2Me), 1.26 (t, 3H, J = 6 Hz, CHMe), 1.35 (t, 3H, J = 6 Hz, CHMe) 2.65 (s, 2H, CH₂), 2.85 (s, 2H, CH₂), 3.86 (q, 2H, J = 9 Hz, CH₂), 4.10 (q, 2H, J = 6 Hz, CH₂), 8.27 (s, 1H, CH). – MS (EI, 70 eV): m/z (%): 315 (15) [M]⁺, 314 (10) [M–1]⁺. – Anal. for C₁₇H₁₃N₃O₃ (315): calcd. C 45.74, H, 6.71; found C 45.79, H, 6.82, N 13.8.

2,4-Dichloro-9,9-dimethyl-9,10-dihydropyrimido[5,4-c]isoquinoline-7(8H)-one (21)

Compound 18 (0.56 g, 2 mmol) was refluxed in phosphorus oxychloride (5 mL) for 12 h. The mixture was cooled and poured onto ice-water to give a precipitate which was filtered off, dried and recrystallized from petroleum ether/methylene chloride to afford 21. Yield 50 %. Brown powder, m. p. 222 – 224 °C. – IR (film): ν = 2958, 2831, 1697, 1512 cm⁻¹. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.07 (s, 6H, 2Me), 2.72 (s, 2H, CH₂), 2.86 (s, 2H, CH₂), 8.32 (s, 1H, CH). – MS (EI, 70 eV): m/z (%): 297 (21.05) [M+1]⁺, 296 (19.75) [M]⁺, 295.00 (13.25) [M–1]⁺. – Anal. for C₁₃H₁₁Cl₂N₃O (296): calcd. C 57.72, H 3.74, N 14.19; found C 57.81, H 3.81, N 14.25.


