Convenient Selective Synthesis of Substituted Pyrido[2,3-d]pyrimidones and Annulated Derivatives

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Z. Naturforsch. 2007, 62b, 104 – 110; received April 4, 2006

The reaction of 6-aminouracil (1) with the appropriate α,β-unsaturated ketones, gave the corresponding pyrido[2,3-d]pyrimidin-2,4-diones 3, 6, 8 and 10, respectively. Treatment of 1 with salicylaldehyde, 6-carboethoxy-3,5-diphenyl-2-cyclohexenone (13) or 2,6-bis(phenylmethylidene)cyclohexanone (15) afforded the corresponding pyrilmido[4,5-d]quinoline-2,4-diones 12, 14 and 16, respectively. Furthermore, a pyrido[2,3-d]pyrimidine incorporating 3,2’-bis(quinoline) derivative 18 was synthesized. Annulation of pyrido[2,3-d]pyrimidine with pyrazole or imidazole moieties was achieved via reaction of 1 with benzylidene derivatives of pyrazolone, imidazolone or 3-carboethoxycoumarin (23) to give 21, 22 and 24, respectively.

Key words: Uracil, Annulation, Biselectrophilic Reagent, Cyclocondensation

Introduction

The one-step assemblage of monocyclic as well as polycyclic heterocycles represents a practical approach in modern organic synthesis. These reactions are of particular interest in combinatorial chemistry [1] because they allow the production of vast arrays of molecules in an efficient mode. Recently, Quiroga [2] has reported the selective preparation of a number of condensed heterocycles as potential biologically active compounds. Amongst these, pyrido[2,3-d]pyrimidine derivatives known as deazalumazines [3, 4] present interesting biological properties. These compounds have been used as dihydrofolate reductase inhibitors and antitumor agents [5 – 9]; some of them have shown a broad spectrum of antimicrobial activity [10 – 13], diuretic properties [14] and activity against platelet aggregation [15].

The therapeutic importance of this molecular framework motivated us to develop selective procedures of synthesis in which constituents could be arranged in a pharmacophoric pattern to display a high degree of pharmacological activities.

Results and Discussion

From early studies [16 – 18], an empirical rule has emerged which specifies that in annulation reactions involving substituted 6-aminopyrimidines, which have multiple competing sites for possible ring-annulation and biselectrophiles, the 5-position of the pyrimidine is the most nucleophilic and attacks the most electrophilic carbon atom of the biselectrophile, followed by ring closure between the 6-amino group and the second electrophilic center. This experimental observation was supported by computational studies, which revealed a direct correlation between charge densities at the C-5 carbon atom of the 6-aminopyrimidine and their enamine-like nucleophilicity toward enones [19, 20]. However, unexpected reactions have also been observed in some cases, depending on the substitution in the pyrimidine, the biselectrophile, and the solvent used [21].

A wide variety of polycyclic molecules have been shown to interfere with the replication of DNA through intercalation between adjacent partially unwound base pairs as first described by Lerman [22]. Actinomycin [23], ethidium bromide [24], acridines [25] and proflavine [26] are known to bind to DNA by this intercalative process. This type of binding to DNA was also observed for other planar heterocyclic ring systems such as ellipticine, a pyridocarbazole derivative with a high degree of activity against leukemia [27 – 29]. Therefore, this study provides a convenient method for the selective synthesis of 7-styrylpyrido[2,3-d]pyrimidine 3 by reactions of 6-aminouracil 1 with 1,5-diphenyl-1,4-pentadien-3-one (2) in acetic acid in good yield via cyclocondensation reaction (Scheme 1). We have found that this reaction
was regioselective and no other compound was formed (TLC control). It is analogous to reactions of other aminopyrimidines and biselectrophiles [16, 30].

The constitution of 3 is supported by elemental analysis, IR, 1H NMR and MS spectra. The 1H NMR spectrum of 3 displayed signals corresponding to a methylene group (a doublet at $\delta = 2.13$), and a methine proton (triplet at $\delta = 4.01$). Its MS fragmentation pattern showed good agreement with the proposed structure.

The pyrimidine-2,4-dione ring is frequently encountered in drugs used for the treatment of hypothyroidy, hypertension, cancer and HIV infections [31]. Also, highly conjugated pyrimidine-2,4-dione derivatives have antiparasitic activities [32]. According to the interest toward pyrido[2,3-d]pyrimidines, considerable attention has been focused on the synthesis of highly conjugated pyrido[2,3-d]pyrimidines for biological evaluation.

Accordingly, it seemed interesting to explore the Michael addition of 6-amino-1,3-dimethyl-2,4-pyrimidinedione (1) to the highly conjugated $\alpha,\beta$-unsaturated ketone 4 to afford 6. The dihydropyridine adduct from a Hantzsch synthesis in this case afforded the fully oxidized (aromatic) pyridine derivative presumably due to the highly conjugated system formed (Scheme 2). The constitution of 6 was affirmed through its 1H NMR and MS spectra. The mass spectrum gave a molecular ion peak at $m/z = 369$ (M$^+$, 66%), 368 (M$^+$-1, 35%) and a base peak at $m/z = 292$.

In view of the interesting biological implication of nitrogen-containing heterocycles we aimed to synthesize novel bicyclic compounds which include an acetyl group at the pyridine ring. The synthesis of 6-acetyl-substituted pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione 8 was achieved by condensation of the 6-aminouracil derivative 1 with $m$-nitrobenzylidene-acetylacetone (7) (Scheme 3). Its 1H NMR spectrum shows a singlet at $\delta = 2.14$ for the methyl group, a singlet at $\delta = 3.09$ for three protons (COCH$_3$), a singlet at $\delta = 5.1$ for HC-Ar, a multiplet at $\delta = 7.5-8.06$ for four aromatic protons and a singlet at $\delta = 8.83$ for HC-CO. Additionally, the mass spectrometric fragmentation pattern of 8 coincides with the proposed structure.
Furthermore, the condensation of 1 with cinnamaldehyde in glacial acetic acid furnished compound 10 in low yield (Scheme 4). Compatible analytical and spectroscopic evidence was gained for the structure of compound 10. The mass spectra gave a molecular ion peak at $m/z = 267$ (M$^+$) and a base peak at $m/z = 266$ (M$^+$-1).

In a similar manner, 2-hydroxy-benzaldehyde was used to assure this finding. Thus, 5-hydroxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4-(1H, 3H)-dione (12) was synthesized by reaction of 1 with salicylaldehyde in acidic medium (Scheme 5). Its structure was confirmed by IR, $^1$H NMR and MS spectra.

It has been reported in the literature [33] that compound 1 reacted with an excess of ethyl acetoacetate to give 5-oxopyrido[2,3-d]pyrimidine in 2% yield in a basic medium or by thermal condensation [34].

In the present investigation it was also found that condensation of 1 with 6-carboethoxy-3,5-diphenyl-2-cyclohexenone (13) [35 – 37] as a $\beta$-ketoester (not as an $\alpha,\beta$-unsaturated ketone, because its $\beta$-position is blocked) furnished pyrimido[4,5-b]quinoline-2,4,5-(1H,3H,5aH)trione 14 (Scheme 6). Its structure was confirmed by elemental analysis and MS spectrum (see Experimental Section).

In addition, the reaction of 1 and dibenzylidencyclohexanone (15) [38] in acidic medium afforded pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione 16 as a sole product in high yield (Scheme 6). In contrast, Diaz [39] separated three adducts (one of them as a monoadduct and two isomeric bisadducts) from the reaction of compound 1 with dibenzylidencyclohexanone in the presence of Triton B as a base in moderate yields. The conformation of such skeletons was reported earlier [39].

The structural formula of 16 was deduced from spectral data. The $^1$H NMR spectrum showed signals at $\delta = 1.66, 2.09$ and 2.57 – 2.75 (three $\text{CH}_2$ groups), 3.14 and 3.54 (two $\text{N-CH}_3$ groups), 4.53 and 6.49 (two $\text{CH}$ protons) and also 7.20 – 7.35 (2 Ph and Ph–$\text{CH}=\text{CH}$) protons. In addition, the mass spectrum of compound 16 indicated a molecular ion peak at $m/z = 411$ (M$^+$, 6%) corresponding to the molecular formula $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$.

In addition, the interesting pharmacological activity of quinoline in different areas of chemotherapy [40] prompted us to prepare the 7-(quinolin-3-yl)-pyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione derivative 18 through the cyclocondensation of 1 with 3-cinnamoyl-1-phenyl-2,4(1H,3H)-quinolinedione (17).
Scheme 7. Its structure was confirmed by the $^1$H NMR spectrum which showed a singlet at $\delta = 2.08$ (CH$_2$), two singlet signals at $\delta = 3.36$ and 3.9 (2 NCH$_2$), a singlet at 3.78 (PhCH), multiplet at $\delta = 7.18$ – 7.63 for 14 aromatic protons, and finally a singlet at $\delta = 17.76$ ppm for enolic OH. In addition, the mass spectrum of compound 18 indicated a molecular ion peak at $m/z = 504$ (M$^+$, 8 %) and a base peak at 427 (M$^+$ – Ph).

No attention has been paid to the similar reaction with the benzylidenepyrazolone derivative 19 or the benzylidenehydantoin derivative 20 which can be used as key intermediates for the construction of a pyridopyrimidine moiety fused with pyrazole or with imidazole rings, respectively. The reaction of 1 with 19 [42] or 20 [43] in the presence of glacial acetic acid gave 21 and 22, respectively (Scheme 8). Formulation of structures 21 and 22 is based on elemental analysis, IR and mass spectra fragmentation.

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra measured using KBr discs on a Mattson 5000 FTIR spectrometer. $^1$H NMR data were obtained in CDCl$_3$ or DMSO solution on a Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts are reported in ppm ($\delta$) down-field from internal TMS. Mass spectra recorded on a GC-MS (Shimadzu QP-1000 EX). Reactions were monitored by thin layer chromatography (TLC) using silica gel (EM science) coated plates.

**Pyrido[2,3-d]pyrimidines 3, 6 and 10: general procedure**

A mixture of 6-amino-1,3-dimethyl-uracil (1 g, 6.5 mmol) and the appropriate $\alpha,\beta$-unsaturated compounds, namely, 1,5-diphenyl-1,4-pentadien-3-one (2), 1,5-diphenyl-1,3-pentadien-5-one (4) or cinnamaldehyde (6.5 mmol), in glacial acetic acid (20 mL) was refluxed for 1 h on a steam bath, kept overnight at r. t., diluted with water, then basified with ammonia. The precipitate formed was collected by filtration, then purified by crystallization from an appropriate solvent to give compounds 3, 6 and 10, respectively.

5,6-Dihydro-1,3-dimethyl-5-phenyl-7-styrylpyrido[2,3-d]-pyrimidine-2,4(1H,3H)-dione (3)

M. p. 129 – 130 $^\circ$C (acetic acid). – R$_f$ = 0.58 (pet. ether 40 – 60 $^\circ$C / ethyl acetate, 1:1). – Yield: 94 % (yellow crystals). – IR (KBr): $\nu = 3060, 2975$ (CH), $1637$ (CO), $1620$ cm$^{-1}$ (C=N). – $^1$H NMR (200 MHz, [D$_6$]-DMSO): $\delta = 2.13$ (d, $J = 6.4$ Hz, 2H), 2.80 (s, 3H), 3.09 (s, 3H), 4.01 (t, $J = 6.4$ Hz, 1H), 6.26 (d, $J = 16.5$ Hz, 1H), 6.93 – 7.28 (m, 11H). – MS (EI, 70 eV): $m/z$ (%) = 371 (94) [M$^+$], 370 (51) [M$^+$ – 1], 369 (4) [M$^+$ – 2], 294 (100), 244 (48), 217 (2), 205 (6), 191 (2), 153 (43), 153 (9). – C$_{23}$H$_{21}$N$_3$O$_2$ (371.42): calcd. C 74.37, H 5.69; found C 74.46, H 5.80.

1,3-Dimethyl-7-phenyl-5-styrylpyrido[2,3-d]-pyrimidine-2,4(1H,3H)-dione (6)

M. p. 185 $^\circ$C (ethanol). – R$_f$ = 0.65 (pet. ether 40 – 60 $^\circ$C / ethyl acetate 4:1). – Yield: 92 % (yellow crystals). – IR (KBr): $\nu = 2946$ (CH), 1673 (CO), 1620 cm$^{-1}$ (C=N). – $^1$H NMR (200 MHz, CDCl$_3$): $\delta = 3.26$ (s, 3H), 3.62 (s, 3H), 7.41 – 7.70 (m, 9H), 8.07 (s, 1H), 8.27 – 8.30 (m, 21H), 8.51 – 8.59 (m, 1H). – MS (EI, 70 eV): $m/z$ (%) = 369 (66) [M$^+$], 368 (35) [M$^+$ – 1], 292 (100), 242 (3), 215 (7), 192 (4), 186 (2), 155 (5), 153 (7). – C$_{23}$H$_{19}$N$_3$O$_2$ (369.42): calcd. C 74.78, H 5.18; found C 74.75, H 5.17.
1,3-Dimethyl-5-phenylpyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione (10)

M. p. 170 °C (methanol). – Rf = 0.7 (pet. ether 40 – 60 °C / ethyl acetate (1 : 2)). – Yield: 37 % (yellow crystals). – IR (KBr): v = 1709, 1600 (CO), 1584 cm⁻¹ (C=C). – MS (EL, 70 eV): m/z (%) = 267 (54) [M⁺], 266 (100), 238 (2), 200 (2), 181 (3), 155 (30), 127 (16), 81 (8). – C₁₈H₁₈N₄O₅ (370.35) calcd. C 58.37, H 4.89; found C 58.46, H 4.98.

6-Acetyl-5,6-dihydro-1,3,7-trimethyl-5-(3-nitrophenyl)pyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione (8)

A mixture of 6-amino-1,3-dimethyl-uracil (1) (1 g, 6.5 mmol) and m-nitrobenzylidene-acetylacetone (7) (6.5 mmol) in ethanol (30 mL) containing 3 drops of acetic acid was heated at reflux for 2 h. The reaction mixture was kept at r.t., diluted with H₂O whereby the precipitate formed was filtered off and crystallized from ethanol to furnish crystals. – IR (KBr): ν = 3138 (CH), 1693, 1668 (CO), 1592 cm⁻¹ (C=C). – ¹H NMR (200 MHz, CDCl₃): δ = 2.14 (s, 3H), 3.09 (s, 3H), 3.32 (s, 3H), 3.43 (s, 3H), 5.1 (s, 1H), 7.5 – 8.06 (m, 4H), 8.83 (s, 1H). – MS (EL, 70 eV): m/z (%) = 370 (10) [M⁺], 368 (6) [M⁺–2], 359 (3), 353 (21), 327 (47), 313 (7) 248 (100), 205 (28), 191 (15), 123 (5). – C₁₈H₁₈N₄O₃ (370.35) calcd. C 58.47, H 4.89; found C 58.46, H 4.98.

Pyrimido[4,5-b]quinolines 12 and 16; general procedure

A mixture of 6-amino-1,3-dimethyl-uracil (1) (1 g, 6.5 mmol) and salicyaldehyde or 2,6-dibenzylidene-cyclohexanone (7) (6.5 mmol) in glacial acetic acid (20 mL) was heated for 1 h on a steam bath, kept overnight at r.t., diluted with water, then basified with ammonia. The precipitate formed was collected by filtration, and then purified by crystallization from an appropriate solvent to give compound 12 and 16, respectively.

5-Hydroxy-1,3-dimethyl pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (12)

M. p. 240 °C (acetone). – Rf = 0.65 (pet. ether (40 – 60 °C) / ethyl acetate (1 : 2)). – Yield: 38 % (yellow crystals). – IR (KBr): v = 3570, 3519 (OH), 2956 (CH), 1708, 1659 cm⁻¹ (CO). – ¹H NMR (200 MHz, D₂O): δ = 3.32 (m, 3H), 3.56 (m, 3H), 5.05 (br, 1H), 7.27 (m, 4H). – MS (EL, 70 eV): m/z (%) = 257 (10) [M⁺], 230 (14), 120 (22), 123 (17), 215 (11), 54 (100). – C₁₃H₁₁N₂O₃ (257.24) calcd. C 60.69, H 4.31; found C 60.61, H 4.39.

9-Benzylidene-5,6a,7,8,9-hexahydro-1,3-dimethyl-5-phenylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (16)

M. p. 258 °C (acetic acid). – Rf = 0.57 (pet. ether (40 – 60 °C) / ethyl acetate (1 : 1)). – Yield: 93 % (yellow crystals). – IR (KBr): v = 3134 (CH), 1695, 1665 (CO), 1604 cm⁻¹ (C=C). – ¹H NMR (200 MHz, CDCl₃): δ = 1.66 (t, J = 8.0 Hz, 2H), 2.09 (t, J = 8.0 Hz, 2H), 2.57 – 2.75 (m, 2H), 3.14 (s, 3H), 3.54 (s, 3H), 4.53 (s, 1H), 6.49 (s, 1H), 7.20 – 7.35 (m, 1H). – MS (EL, 70 eV): m/z (%) = 411 (6) [M⁺], 410 (4) [M⁺–1], 409 (5), 334 (100), 320 (5), 256 (1), 91 (11), 77 (3). – C₂₆H₂₅N₃O₂ (411.50) calcd. C 75.89, H 6.12; found C 75.78, H 6.21.

6,7-Dihydro-1,3-dimethyl-6,8-diphenylpyrimido[4,5-b]quinoline-2,4,5(1H,3H,5aH)-trione (14)

A mixture of 6-amino-1,3-dimethyl-uracil (1) (0.34 g, 2.16 mmol), 6-carboethoxy-3,5-diphenyl-2-cyclohexenone (13) (2.16 mmol) in diphenyl ether (10 mL) was refluxed until disappearance of the starting materials as evidenced by TLC. After the reaction was over, removal of the solvent under vacuum followed by crystallization of the residue from ethanol afforded 14. – M. p. 306 °C (ethanol). – Rf = 0.66 (pet. ether (40 – 60 °C) / ethyl acetate (3 : 2)). – Yield: 51 % (brown crystals). – IR (KBr): v = 3134, 2875 (CH), 1708, 1658, 1641, 1612 cm⁻¹ (CO). – MS (EL, 70 eV): m/z (%) = 411 (77) [M⁺], 410 (23) [M⁺–1], 409 (3) [M⁺–2], 334 (100), 333 (7), 256 (8), 227 (7), 226 (6), 178 (4). – C₂₅H₂₃N₃O₃ (411.44) calcd. C 72.98, H 5.15; found C 72.29, H 5.05.

5,6-Dihydro-7-(1,2-dihydro-4-hydroxy-2-oxo-1-phenylquinol-3-yl)-1,3-dimethyl-5-phenylpyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione (18)

A mixture of 6-amino-1,3-dimethyl-uracil (1) (1 g, 6.5 mmol), 3-cinnamoyl-1-phenyl-2,4(1H,3H)-quinolinedione (2.4 g, 6.5 mmol) in glacial acetic acid (20 mL) was heated for 1 h on a steam bath, kept overnight at r.t., diluted with water, then basified with ammonia. The precipitate formed was collected by filtration, and then purified by crystallization from acetic acid to give 18. – M. p. 160 °C (acetic acid). – Rf = 0.63 (pet. ether (40 – 60 °C) / ethyl acetate (1 : 2)). – Yield: 97 % (yellow crystals). – IR (KBr): v = 3454 (OH intermolecular), 3057, 2952 (CH), 1712, 1671, 1645 cm⁻¹ (CO). – ¹H NMR (200 MHz, CDCl₃): δ = 2.08 (s, 2H), 3.36 (s, 3H), 3.78 (s, 1H), 3.9 (s, 3H), 7.18 – 7.63 (m, 14H), 9.05 (s, 1H), 17.76 (s, 1H). – MS (EL, 70 eV): m/z (%) = 504 (8) [M⁺], 502 (67), [M⁺–2], 427 (100), 367 (10), 308 (30), 237 (30), 196 (65). – C₉₀H₇₃N₅O₄ (504.52) calcd. C 71.41, H 4.79; found C 71.49, H 4.89.
Pyrido[2,3-d]pyrimidines 21 and 22, general procedure

A mixture of 6-amino-1,3-dimethyl-uracil (1 g, 6.5 mmol), and the benzylidenepyrazolone derivative 19 [43] or the benzylidenehydantoin derivative 20 [44] (6.5 mmol) in glacial acetic acid (20 mL) was heated for 1 h on a steam bath, kept overnight at room temperature, diluted with water, then basified with ammonia. The precipitate formed collected by filtration, and then purified by crystallization from the appropriate solvent to give 21 and 22.

5.4a-Dihydro-5,6,8-triphenyl-1,3-dimethyl-imidazolo[4',3':5,6]-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (22)

M. p. 112 °C (ethanol). – IR (KBr): ν = 2953 (CH), 1777, 1710, 1641 (CO), 1610 (C=N), 1597 cm⁻¹ (C=C). – MS (EI, 70 eV): m/z (%) = 477 (3) [M⁺], 565 (2), 439 (3), 412 (2), 353 (1), 307 (2), 267 (5), 190 (6), 112 (15), 210 (2), 104 (100). – C29H23N5O3 (477.5): calcd. C 70.43, H 4.85; found C 70.32, H 4.93.

5.6-Pyrido[2,3-d]-pyrimidone 22

M. p. 140 (acetic acid). – IR (KBr): ν = 3068 (CH), 1695, 1669 (CO), 1617 (C=N), 1582 cm⁻¹ (C=C). – MS (EI, 70 eV): m/z (%) = 399 (5) [M⁺], 368 (5) [M⁺], 334 (5), 284 (4) 262 (36), 89 (100). – C28H23N5O3 (399.44): calcd. C 69.16, H 5.30; found C 69.35, H 5.39.

Yield: 86 % (green crystals). – IR (KBr): ν = 3068 (CH), 1695, 1669 (CO), 1617 (C=N), 1582 cm⁻¹ (C=C). – MS (EI, 70 eV): m/z (%) = 477 (3) [M⁺], 565 (2), 439 (3), 412 (2), 353 (1), 307 (2), 267 (5), 190 (6), 112 (15), 210 (2), 104 (100). – C29H23N5O3 (477.5): calcd. C 70.43, H 4.85; found C 70.32, H 4.93.