Efficient Microwave-Assisted Synthesis of 5-Deazaflavine Derivatives

Jorge Trilleras 1,*, Luis Gabriel López 1, Dency José Pacheco 1, Jairo Quiroga 2,*, Manuel Nogueras 3,*, José M. de la Torre 3 and Justo Cobo 3

1 Grupo de Investigación en Compuestos Heterocíclicos, Programa de Química, Facultad de Ciencias Básicas, Universidad del Atlántico, A.A.1890 Barranquilla, Colombia
2 Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A. A. 25360 Cali, Colombia
3 Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain

* Author to whom correspondence should be addressed; E-Mails: jaiquir@univalle.edu.co (J.Q.); jorgetrilleras@mail.uniatlantico.edu.co (J.T.); mmontiel@ujaen.es (M.N.).

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Abstract: A series of pyrimido[4,5-b]quinolines (5-deazaflavines), were synthesized by microwave assisted intramolecular cyclization. The N4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes, were prepared by selective monoamination of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde with aliphatic and aromatic amines.

Keywords: pyrimidoquinolines; cyclocondensation; microwave; deazaflavines

1. Introduction

The 5-deazaflavine (pyrimido[4,5-b]quinoline) ring system I is of great interest because of its structural similarity to the pyrimido[4,5-b]quinoxaline ring system of the naturally-occurring flavines (II, Figure 1), with N-5 being replaced by CH and thus keeping the redox properties of I quite similar to those of compounds II. Surprisingly, not much has been reported on the synthesis and properties of pyrimido[4,5-b]quinolines. Flavo-enzymes require flavine mononucleotide (FMN) or flavine adenine dinucleotide (FAD) as a coenzyme and catalyze oxidation-reduction reactions in biological systems
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[1,2]. Some heterocyclic compounds containing a quinoline moiety are of importance owing to their biological activities, especially antimalarial, antibacterial, analgesic and antitumor agents [3-8].

Figure 1. 5-deazaflavine (pyrimido[4,5-b]quinoline) ring system I and pyrimido[4,5-b]quinoxaline ring system II.

In addition to their pharmaceutical applications, they are attractive for physicochemical applications since they exhibit a high fluorescence in both solution and solid state under exposure to white light, which makes them appropriate candidates for the design of electroluminescent materials, like organic light-emitting diodes (OLEDs) [9-15].

Synthetic methods to prepare pyrimidoquinoline derivatives using the pyrimidine moiety [16-20] as starting material have been reported and involve a three-component reaction induced by microwave irradiation or by conventional heating. We have recently reported a straightforward one-step route to the 5-deazaflavin system via cyclocondensation of \( N^4 \)-aryl-2,4-diamino-6-chloropyrimidine-5-carbaldehydes used as unique starting materials [21].

2. Results and Discussion

Heterocyclic systems containing an aldehyde or ketone function in a position suitable for closing a six-membered ring permit the access to fused systems by treatment with acid via cyclodehydration that results in the formation of a double bond conjugated with the heteroaromatic ring [22]. Here, we describe three pyrimido[4,5-b]quinoline derivatives that were prepared in good yields using a straightforward synthesis (Figure 2).

Figure 2. Pyrimido[4,5-b]quinoline derivatives synthesized.

In a first attempt \( N^4 \)-benzyl-\( N^4 \)-phenyl-2,4-diamino-6-chloropyrimidine-5-carbaldehyde (1a) and acetic acid were heated both under MW irradiation and by conventional heating. The reaction product corresponded to the deazaflavin analogue 10-benzyl-4-oxo-4,10-dihydropyrimido[4,5-b]quinolin-2(3H)-iminium chloride (2a), according to spectroscopic and MS analysis, that supposes the substitution of the chloro atom. Such a substitution appears to be entirely general in syntheses of this type, regardless of the nature of the acid employed [20,21]. Single crystal X-ray diffraction
analysis of compound 2a was used to corroborate the postulated structure [23]. Treatment of the salt 2a with aqueous NaOH (20%) was carried out to give the neutral derivative 4a in good yield (Scheme 1).

Scheme 1. Synthesis of pyrimido[4,5-b]quinolines derivatives 2-4.

Condensed aromatic systems are produced by cyclodehydration to give a double bond conjugated with the aromatic ring (Scheme 2). It seems likely that the acid is the most plausible source of the water component to nucleophilic aromatic substitution of the chloro atom by a hydroxyl group.

Scheme 2. Acid-catalysed Bradsher-type cyclodehydration of diaryl aldehydes 1.

To avoid the substitution of the chloro atom in order to maintain the possibility of adding complexity and molecular diversity to the molecule, the same reaction was carried out using an excess of 4-toluene sulfonic acid (PTSA). Thus, 1a (1.0 mmol) and an excess of PTSA monohydrate (1.3 mmol) were subjected to microwave irradiation (maximum power 300 W during 10 min at a controlled temperature of 573 K) using a focused microwave reactor (CEM Discover) or by conventional heating in refluxing ethanol. The reaction product was characterized from the spectroscopic data as the 1:1 salt 2-amino-10-benzylpyrimido[4,5-b]quinolin-4(10H)-one·PTSA (3a). The same type of salt 3b was obtained using the 2,4-diamino-6-chloropyrimidine-5-carbaldehyde (1b). It is interesting to note that when the reaction was carried out by conventional heating of aldehydes 1 and acid (PTSA), reactions proceeded rather similarly affording products 2a and 3. The only difference between those methods is
that with microwave irradiation the reaction time is shorter than by conventional heating, 10 vs. 60 min, respectively (Table 1).

**Table 1.** The synthesized pyrimidoquinolines (deazaflavin analogues) via cyclocondensation of compounds 1 under microwave irradiation and reflux in ethanol.

| Entry | Compound 1 | Reaction conditions | Compound yield % |
|-------|------------|---------------------|------------------|
|       | R                      | R'                  | MW (10 min) | A/Ethanol (60 min) |
|       |            |                     | 2a  | 3a-b  | 4a-c  | 2a  | 3a-b  | 4a-c  |
| a     | CH₂C₆H₅     | H                   | AcOH | -     | -     | 85  | -     | -     |
|       |             |                     | PTSA (1.3 mmol) | - | 70   | -    | 72  | -    |
|       |             |                     | (i) PTSA (1.3 mmol) | (ii) NaOH | - | 70   | -    | 68  | -    |
| b     | CH₃         | p-H₃C               | PTSA (1.3 mmol) | - | 70   | -    | 70  | -    |
|       |             |                     | (i) PTSA (1.3 mmol) | (ii) NaOH | - | 70   | -    | 68  | -    |
| c     | CH₃         | o-H₃C               | PTSA (0.2 mmol) | - | -    | 60   | -    | 62  |

The ¹H-NMR spectra of the salts 2a and 3 are characterized by two singlets for the NH₂ group protons as a result of the formation of the two cyclic N–H···Cl and N–H···O(PTSA) hydrogen bonds motifs, respectively. Treatment of the salts 2a and 3 with aqueous NaOH (20%) was carried out to give the neutral derivatives 4a,b in good yields. The derivative 4c was obtained directly from the reaction between 4-(N-methyl-N-o-tolylamino)-2-amino-6-chloropyrimidine-5-carbaldehyde (1c) and a catalytic amount of PTSA (0.2 mmol), so a 1:1 ratio of acid is needed for the formation of corresponding salt.

### 3. Experimental

#### 3.1. General

Melting points were determined in a Buchi Melting Point Apparatus and are reported uncorrected. The ¹H- and ¹³C-NMR spectra were measured at RT on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively, and using DMSO-d₆ as solvent and tetramethylsilane as internal standard. The mass-spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) which was operating at 70 eV. High Resolution Mass Spectra (HRMS) were recorded in a Waters Micromass AutoSpec NT spectrometer (STIUJA). The elemental analyses have been obtained using a LECO CHNS-900 and Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers.

*10-Benzyl-4-oxo-4,10-dihydropyrimido[4,5-b]quinolin-2(3H)-iminium chloride (2a). Microwave method:* A mixture of N⁴–benzyl–N⁴–phenyl–2,4–diamino–6–chloropyrimidine–5–carbaldehyde (1a, 1.0 mmol) and an excess of acetic acid (1.5 mL) were subjected to microwave irradiation (maximum power 300 W during 10 min at a controlled temperature of 573 K) using a focused microwave reactor (CEM Discover). The solid products were collected by filtration and washed with hot hexane to give yellow powder, yield 80%, m.p. > 300 °C. ¹H-NMR δ: 6.20 (s, 2H, CH₂); 7.27–7.35 (m, 5H, CH
phenyl); 7.68 (t, J = 7.5 Hz, 1H, H7); 7.93 (d, J = 8.8 Hz, 1H, H9); 8.01 (t, J = 8.3 Hz, 1H, H8); 8.39 (d, J = 8.0 Hz, 1H, H6), 8.54 (s, 1H, NH2), 9.19 (s, 1H, NH2), 9.45 (s, 1H, H5), 12.68 (s, 1H, NH). 13C–NMR δ: 48.9 (CH2); 116.2 (C4a); 118.3 (C9); 123.3 (C5a), 126.7 (C7), 127.1 CHo phenyl), 128.2 (CHp phenyl), 129.3 (CHm phenyl), 132.8 (C6); 135.3 (Ci phenyl), 137.1 (C8), 139.9 (C9a); 144.9 (C5), 157.3 (C10a); 158.3 (C2); 160.1 (C4). IR (KBr) cm⁻¹ 1712, 1654 (C=O

Conventional method: A mixture of N⁴–benzyl–N⁴–phenyl–2,4–diamino–6–chloropyrimidine–5–carbaldehyde (1a, 1.0 mmol) and an excess of acetic acid (1.5 mL) were heated under reflux in ethanol during 60 min, then allowed to cool. The solid product was collected and washed with hot hexane to give the corresponding derivative.

### 3.2. General procedure for the synthesis of pyrimido[4,5-b]quinolin-2(3H)-iminium-4-toluene-sulfonates

**Microwave method:** A mixture of N⁴-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes 1a,b (1.0 mmol) and an excess of PTSA (1.3 mmol) were subjected to microwave irradiation (maximum power 300 W during 10 min at a controlled temperature of 573 K) using a focused microwave reactor (CEM Discover). The solid products were collected by filtration and washed with hot hexane to give the corresponding derivatives.

**Conventional method:** A mixture of N⁴-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes 1a,b (1.0 mmol) and an excess PTSA (1.3 mmol) were heated under reflux in ethanol during 60 min, then allowed to cool. The solid product was collected and washed with hot hexane to give the corresponding derivatives.

**10-Benzyl-4-oxo-4,10-dihydropyrimido[4,5-b]quinolin-2(3H)-iminium-4-toluenesulfonate (3a).** A yellow powder, yield 70%, m.p. > 300 ºC. 1H-NMR δ: 2.29 (s, 3H, H3C-PTSA), 6.21 (s, 2H, CH2), 7.12 (d, J = 8.0 Hz, 2H, Hm’-PTSA), 7.27–7.33 (m, 5H, phenyl), 7.50 (d, J = 8.0 Hz, 2H, H0’-PTSA), 7.69 (t, J = 7.4 Hz, 1H, H7), 7.94 (d, J = 8.8 Hz, 1H, H6), 8.01 (t, J = 8.5 Hz, 1H, H8), 8.10 (s, 1H, NH2), 8.40 (d, J = 8.0 Hz, 1H, H9), 9.47 (s, 1H, H5), 9.16 (s, 1H, NH2), 12.39 (s, 1H, NH). 13C-NMR δ: 20.7 (CH3), 48.4 (CH2), 115.5 (C4a), 117.8 (C9), 122.8 (C5a), 125.4 (Cm’-PTSA), 126.2 (C7), 126.6 (Co’-PTSA), 127.6 (Cp), 128.0 (Co), 128.7 (Cm), 132.3 (C6), 134.8 (Ci), 136.7 (C8), 137.8 (Cp’-PTSA), 139.4 (C9a), 144.3 (C5), 145.3 (Ci’-PTSA), 156.8 (C10a), 157.4 (C4), 159.9 (C2). IR (KBr) cm⁻¹ 1714 (C=O, 1605 (C=C), 3407

**7,10-Dimethyl-4-oxo-4,10-dihydropyrimido[4,5-b]quinolin-2(3H)-iminium-4-toluenesulfonate (3b).** A yellow powder, yield 70%, m.p. > 300 ºC. 1H-NMR δ: 2.28 (s, 3H, CH3 PTSA), 2.52 (s, 3H, 7-CH3), 4.25 (s, 3H, 10-CH3), 7.09 (d, J = 8.0 Hz, 2H, Hm), 7.52 (d, J = 8.3 Hz, 2H, Ho), 7.97 (d, J = 8.8 Hz, 1H, H8), 8.06 (d, J = 8.5 Hz, 1H, H9), 8.14 (s, 1H, H6), 8.36 (s, 1H, NH2), 9.24 (s, 1H, H5), 9.58 (s, 1H, NH2), 11.93 (s, 1H, NH). 13C-NMR δ: 20.1 (7-CH3), 20.6 (CH3 PTSA), 33.6 (CH3 N-10), 114.9 (C4a), 117.4 (C9), 122.7 (C5a), 125.5 (Co), 127.9 (Cm), 130.9 (C6), 136.2 (C7), 137.5 (Cp), 138.5 (C8), 138.9 (C9a), 143.5 (C5), 145.9 (Ci), 155.8 (C10a), 156.9 (C4), 159.6 (C2). IR (KBr) cm⁻¹ 3407
(NH, s), 1709 (C=O, s), 1578 (NH, s). MS (70 eV) m/z (%) = 240 (C_{13}H_{12}N_4O, 64), 212 (45), 172 (PTSA, 30), 91 (100). Anal. Caled for C_{20}H_{20}N_4SO_4: C, 66.09; H, 5.27; N, 15.42. Found: C, 66.01; H, 5.20; N, 14.45.

Treatment of the salts 2a and 3 with aqueous NaOH (20%) was carried out to afford the neutral derivatives 4 in good yields.

2-Amino-10-benzylpyrimido[4,5-b]quinolin-4(10H)-one (4a). A yellow powder, yield 70%, m.p. > 300 °C. 1H-NMR δ: 6.06 (s, 2H, CH_2), 6.97 (s, 2H, NH_2), 7.23–7.25 (m, 3H, H_o, H_p), 7.30 (t, J = 7.5 Hz, 1H, H7), 7.70 (d, J = 8.78 Hz, 1H, H6), 7.77 (t, J = 7.28 Hz, 1H, H8), 8.14 (d, J = 7.76 Hz, 1H, H9), 8.90 (s, 1H, H5). 13C-NMR δ: 46.6 (CH_2), 116.1 (C6), 116.6 (C4a), 121.8 (C5a), 123.7 (C7), 126.2 (Co), 126.8 (Cp), 128.2 (Cm), 131.1 (C9), 133.6 (C8), 135.4 (C5), 138.8 (C9a), 140.0 (C5a), 145.9 (C10a), 157.7 (C10a), 1651 (C=O, s). IR (KBr) cm⁻¹ 3391 (NH, s), 1636 (C=O, s). MS (70 eV) m/z (%) = 302 (M⁺, 45), 91 (100). Anal. Caled for C_{18}H_{14}N_4O: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.47; H, 4.62; N, 18.55.

2-Amino-7,10-dimethylpyrimido[4,5-b]quinolin-4(10H)-one (4b). A yellow powder, yield 70%, m.p. > 300 °C. 1H-NMR δ: 2.46 (s, 3H, 7-CH_3), 4.07 (s, 3H, 10-CH_3), 6.84 (s, 2H, NH_2), 7.73 (d, J = 7.3 Hz, 1H, H8), 7.80 (d, J = 8.5 Hz, 1H, H9), 7.91 (s, 1H, H6), 8.75 (s, 1H, H5). 13C-NMR δ: 20.3 (7-CH_3), 32.4 (10-CH_3), 116.6 (C6), 122.3 (C5a), 130.7 (C9), 134.4 (C7), 136.5 (C8), 138.6 (C9a), 140.6 (C5), 157.7 (C10a). IR (KBr) cm⁻¹ 3446 (NH, s), 1651 (C=O, s). MS (70 eV) m/z (%) = 240 (M⁺, 84), 212 (62), 77 (45), 28 (100). Anal. Caled for C_{13}H_{12}N_4O: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.03; H, 5.10; N, 23.28.

2-Amino-9,10-dimethylpyrimido[4,5-b]quinolin-4(10H)-one (4c). A yellow powder, yield 60%, m.p. > 300 °C. 1H-NMR δ: 2.48 (s, 3H, 9-CH_3), 4.18 (s, 3H, 10-CH_3), 6.79 (s, 2H, NH_2), 7.37 (t, J = 7.53 Hz, 1H, H7), 7.67 (d, J = 7.03 Hz, 1H, H8), 7.91 (d, J = 7.53 Hz, 1H, H6), 8.72 (s, 1H, H5). 13C-NMR δ: 23.1 (9-CH_3), 38.0 (10-CH_3), 115.9 (C4a), 123.1 (C5a), 123.5 (C7), 126.1 (C9), 129.1 (C8), 137.7 (C6), 139.9 (C5), 140.6 (C9a), 159.8 (C10a), 166.9 (C2), 168.3 (C4). IR (KBr) cm⁻¹ 3419 (NH, s), 1644 (C=O, s). MS (70 eV) m/z (%) = 240 (M⁺, 15), 212 (7), 105 (64), 77 (100). Anal. Caled for C_{13}H_{12}N_4O: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.93; H, 4.98; N, 23.35.

4. Conclusions

In this work we are describing the synthesis of pyrimidoquinolines (deazaflavin analogues), via a simple, efficient, and versatile one-step method assisted by microwave irradiation. The reaction offers a strategy for the preparation of quinolines from N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes. Compared with other methods, this one has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents, and an environmentally friendly procedure. The chemical (fluorescence) and biological (antifungal and antitumor) properties of the new compounds obtained in these experiments are under investigation.
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Sample Availability: Samples of the compounds are available from authors.

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