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A straightforward synthesis of pyrimido[4,5-*b*]quinoline derivatives assisted by microwave irradiation

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ABSTRACT

Several pyrimido[4,5-*b*]quinolines, flavin analogues, have been prepared by assisted microwave intramolecular cyclization of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes. The reaction takes place with hydrolysis of amino-group and chlorine. Particularly valuable features of this method included the broader substrate scope and operational simplicity as well as increased safety for small-scale high-speed synthesis.

Since the turn of the century, the development of concise and effective methodologies for the preparation of libraries of small molecules for research in drug discovery has remained a major challenge.[1] A number of strategies have been developed to address this challenge. Among these, especially the microwave-assisted organic synthesis has received much attention because of its speed and the chemical formation of cleaner products compared with conventional heating. This method has been used as a tool for the functionalization of heterocycles.[2] The heterocycles are among the most common scaffolds in drugs and pharmaceutically relevant substances. Due to the pharmacophoric character and considerable wide structural diversity, large libraries of several heterocyclic compounds are typically used for high performance screening in the early stages of drug-discovery programs.

Pyrimido[4,5-*b*]quinolines (also known as 5-deazaflavins, **dF**) are important compounds because of their biological properties, which are known to depend mainly on the nature and position of the substituent. Quinoline derivatives display a broad range of biological activities such as antimalarial,[3] antitumor,[4] anthelmintic,[5] antibacterial,[6] antiasthmatic,[7] and antiplatelet.[8]

Relatively little is reported on the synthesis and properties of pyrimido[4,5-*b*]quinolines, although this system (**I**) is of interest because of its structural similarity to the pyrimido[4,5-*b*]quinoxaline ring system (**II**) of the naturally occurring flavins (Fig. 1). Flavo-enzymes require flavin mononucleotide (FMN) or flavin adenine dinucleotide (FAD) as a coenzyme and catalyze oxidation-reduction reactions in biological systems.[9]

Nevertheless, they have been attractive for physicochemical applications since they exhibit a high fluorescence in both solution and solid state under exposure to the white light,[10] which make them appropriate candidates in the design of electroluminescent materials, like organic light-emitting diodes (OLEDs).[10e–g]

Pyrimido[4,5-*b*]quinolines have been synthesized by diverse procedures which involve the cyclocondensation from 2-amino-quinoline-3-carboxamide with reagents such as formamide, acetic anhydride, phenyl isocyanate, phenyl isothiocyanate, and diethyl carbonate; from 2-amino-3-cyanoquinoline using reagents such as ammonia, urea, and formamide; or well reduction of 2-amino-3-cyanoquinoline to 2-amino-3-aminomethyl-quinoline, followed by cyclization with a variety of reagents.[11] The Skraup, Dobner von Miller, Friedländer, and Combes syntheses are also well-known methods for preparing quinolines.[12]

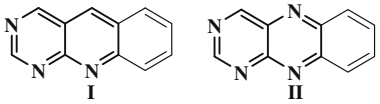

Figure 1.

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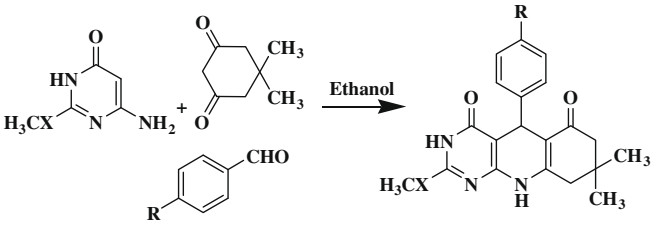


Scheme 1.

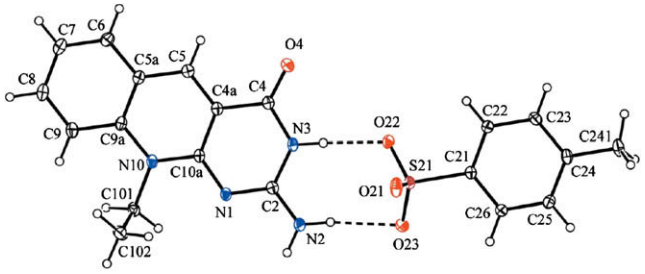


Figure 2. ORTEP drawing of compound **2a**.

Despite this, the search for simple, general, and efficient procedures for the preparation of these important heterocyclic compounds is still demanding.

Our group is interested in the development of synthetic strategies to obtain functionalized heterocycles.[13] We have concentrated much of our recent efforts in the preparation of such bioactive nitrogen-containing heterocycles, and reported simple and efficient procedures to prepare interesting molecules with biological properties such as pyrimido[4,5-*b*]quinolines (Scheme 1).[14]

In this Letter, we describe an efficient and straightforward synthesis of new pyrimido[4,5-*b*]quinoline derivatives with good yields. In a first attempt equimolar amounts of N^4-ethyl-N^4-phenyl-2,4-diamino-6-chloro-pyrimidine-5-carbaldehyde **1c** and 4-toluenesulfonic acid monohydrate were heated well under MW irradiation or by conventional heating. The reaction product according to X-ray analysis was the 1:1 salt: 2-amino-10-ethyl-4-oxo-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline:PTSA **2a** (Fig. 2).[15]

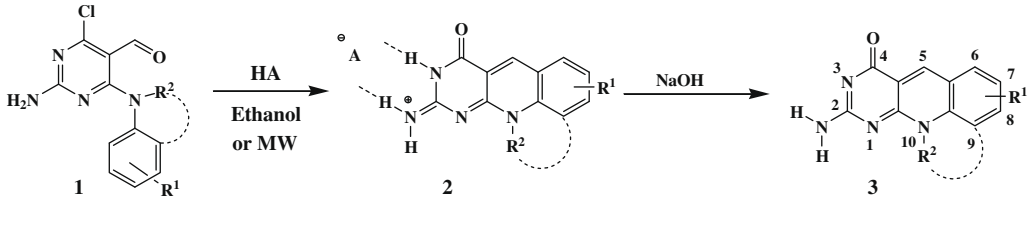
The same type of salts **2a** and **2b** were obtained when using the 2,4-diamino-6-chloro-pyrimidine-5-carbaldehydes **1a** and **1b**, respectively. The same result was obtained by changing the PTSA with the trifluoroacetic acid (Scheme 2). It is interesting to note that when the same reaction was carried out by conventional heating of aldehydes **1** and PTSA or excess of trifluoroacetic acid, reactions proceeded rather similarly rendering products **2** in equal yields. The only difference between those methods is that by microwave irradiation the reaction time is much shorter than by heating, 15 versus 60 min, respectively.[16]

^{1}H NMR spectra of these salts **2** are characterized by two singlets for protons of NH_2 group as an outcome of the formation of two N–H···O hydrogen bonds. Treatment of the salts **2** with aqueous NaOH (20%) was carried out to neutral derivatives **3** in moderate yields (Fig. 3).[16]

The attempt to directly obtain deazaflavines **3** proceeded to carry out the reaction in acetic acid. The intramolecular cyclization of 6-chloropyrimidine-5-carbaldehydes **1a–c** affords deazaflavin analogues **4**, with the hydrolysis of both Cl and NH_2 groups (Scheme 3). The same procedure was applied to various 6-chloropyrimidinecarbaldehydes[2a] **1d–i** obtaining the series of compounds **4a–i**.[17]

The structures of all new compounds were appropriately established by the usual spectroscopic methods. Single crystal X-ray diffraction analysis of some selected compounds was used to corroborate the postulated structures.[15,17]

To conclude, we have developed a simple, efficient, and versatile one-step method for the synthesis, assisted by microwave irradiation, of new pyrimidoquinolines (deazaflavin analogues). The



Entry	Reaction Conditions	Compound 3		Yield %
		R^1	R^2	
a-a'	PTSA or TFA	2-CH_2-CH_2-CH_2-		80
b-b'	PTSA or TFA	2-CH_2-CH_2-		50
c-c'	PTSA or TFA	H	CH_2CH_3	60

Yield reported to derivative **3**.

Scheme 2.

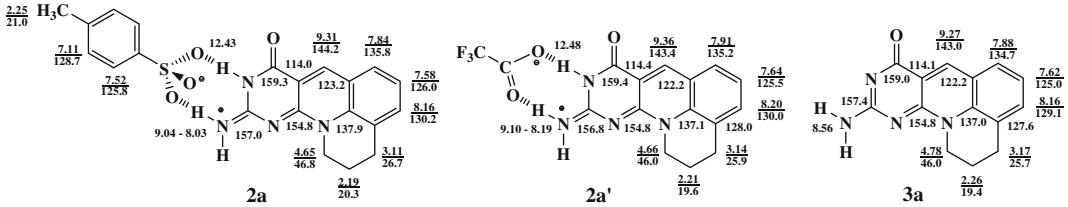
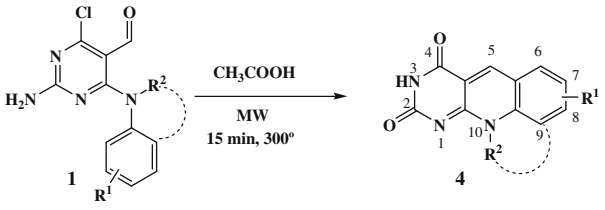


Figure 3. ^{1}H NMR/^{13}C NMR data of **2a**, **2a′**, and **3a** in ppm.



Entry	Compound 4		Yield %
	R^1	R^2	
a	H	2-$CH_2CH_2CH_2$-	70
b	H	2-CH_2CH_2-	70
c	H	CH_2CH_3	60
d	H	CH_3	70
e	H	CH_2-C_6H_5	80
f	7-CH_3	CH_3	70
g	9-CH_3	CH_3	70
h	7-OCH_3	CH_3	60
i	9-OCH_3	CH_3	70

Scheme 3.

reaction offers a potential strategy for the preparation of quinolines from N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes. All the newly obtained compounds exhibit a high fluorescence in both solution and solid state. These compounds present a privileged core from a biological point of view.

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16. *General procedure for the preparation of pyrimido[4,5-b]quinolines derivatives* **2** *and* **3**. *Microwave method*: A mixture of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes **1** (1.0 mmol) and PTSA (1.0 mmol) or excess of trifluoroacetic acid (1.5 mL) were subjected to microwave irradiation (maximum power 300 W during 15 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 hexanes to give the corresponding salt derivatives. *Conventional method*: A mixture of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes **1** (1.0 mmol) and PTSA (1.0 mmol) or excess of trifluoroacetic 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 hexanes to give the corresponding salt derivatives. (a) *Data for 2,3,4,10-tetrahydro-4-oxo-pyrido[3,2,1-ij]pyrimido[4,5-b]quinoline-2-iminium 4-toluenesulfonate* **2a**. Yellow solid, 80%. mp >300 °C. ^{1}H NMR (400 MHz DMSO-d_6 120 °C) δ (ppm): 2.19 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.11 (m, 2H, CH_2), 4.65 (t, 2H, CH_2), 7.11 (d, 2H, Hm, PTSA, J = 7.86 Hz), 7.52 (d, 2H, Ho, PTSA, J = 7.65 Hz), 7.58 (t, 1H, H7, J = 7.23 Hz), 7.84 (d, 1H, H6, J = 5.79 Hz), 8.03 (s, 1H, NH_2), 8.16 (d, 1H, H8, J = 6.82 Hz), 9.04 (s, 1H, NH_2), 9.31 (s, 1H, H5), 12.43 (s, 1H, NH). ^{13}C NMR δ (ppm): 21.0 (CH_3), 20.3 (CH_2), 26.7 (CH_2), 46.8 (CH_2), 114.0 (C4a), 123.2 (5a), 125.8 (Co, PTSA), 126.0 (C7), 128.7 (Cm, PTSA), 130.2 (C8), 135.8 (C6), 137.9 (C9a), 144.2 (C5), 154.8 (C10a), 157.0 (C2), 159.3 (C4). Anal. Calcd for $C_{21}H_{20}N_4O_4S$: C, 59.42; H, 4.75; N, 13.20. Found: C, 60.02; H, 4.68; N, 13.75; (b) *Data for 2,3,4,10-tetrahydro-4-oxo-pyrido[3,2,1-ij]pyrimido[4,5-b]quinoline-2-iminium trifluoroacetate* **2a′**. Yellow solid, 80%. mp >300 °C. ^{1}H NMR (400 MHz DMSO-d_6 120 °C) δ (ppm): 2.21 (m, 2H, CH_2), 3.14 (t, 2H, CH_2), 4.66 (t, 2H, CH_2), 7.64 (t, 1H, H7, J = 7.65 Hz), 7.91 (d, 1H, H6, J = 6.82 Hz), 8.19 (s, 1H, NH_2), 8.20 (d, 1H, H8, J = 7.86 Hz), 9.10 (s, 1H, NH_2), 9.36 (s, 1H, H5), 12.48 (s, 1H, NH). ^{13}C NMR δ (ppm): 19.6 (CH_2), 25.9 (CH_2), 46.0 (CH_2), 114.4 (C4a), 122.2 (C5a), 125.5 (C7), 128.0 (C9), 130.0 (C8), 135.2 (C6), 137.1 (C9a), 143.4 (C5), 154.8 (C10a), 156.8 (C2), 159.4 (C4). Anal. Calcd for $C_{16}H_{13}F_3N_4O_3$: C, 52.46; H, 3.58; N, 15.30. Found: C, 51.95; H, 3.78; N, 15.01; (c) After neutralization with NaOH solution (20%) compounds **3** were isolated by filtration. *Data for 2-Amino-2,3,4,10-tetrahydro-4-oxo-pyrido[3,2,1-ij]pyrimido[4,5-b]quinoline* **3a**. Yellow solid, 80%. mp >300 °C. ^{1}H NMR (400 MHz DMSO-d_6 120 °C) δ (ppm): 2.26 (m, 2H, CH_2), 3.17 (t, 2H, CH_2), 4.78 (t, 2H, CH_2), 7.62 (t, 1H, H7, J = 7.85 Hz), 7.88 (d, 1H, H6, J = 7.24 Hz), 8.16 (d, 1H, H8, J = 7.86 Hz), 8.56 (s, 2H, NH_2), 9.27 (s, 1H, H5). ^{13}C NMR δ (ppm): 19.4 (CH_2), 25.7 (CH_2), 46.0 (CH_2), 114.1 (C4a), 122.2 (C5a), 125.0 (C7), 127.6 (C9), 129.1 (C8), 134.7 (C6), 137.0 (C9a), 143.0 (C5), 154.8 (C10a), 157.4 (C2), 159.0 (C4). HR-MS calculated for $C_{14}H_{12}N_4O$ 252.1011 found 252.1002. Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.95; H, 4.39; N, 21.91.
17. *General procedure for the preparation of pyrimido[4,5-b]quinolines derivatives* **4**. A mixture of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes **1** (1.0 mmol) and an excess of glacial acetic acid (1.5 mL) were subjected to microwave irradiation (maximum power 300 W during 15 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 hexanes to give the pyrimido[4,5-*b*]quinolines derivatives **4**. *Data for 2,3,4,10-tetrahydro-2,4-dioxo-pyrido[3,2,1-ij]pyrimido[4,5-b]quinoline* **4a**. Yellow solid, yield 70%, mp >300 °C dec. ^{1}H NMR 400 MHz DMSO-d_6 rt δ (ppm): 2.27 (m, 2H, CH_2), 3.17 (t, 2H, CH_2), 4.70 (t, 2H, CH_2), 7.63 (t, 1H, H7, J = 7.78 Hz), 7.89 (d, 1H, H6, J = 7.27 Hz), 8.18 (d, 1H, H8, J = 8.03 Hz), 9.31 (s, 1H, H5), 11.06 (s, 1H, NH). ^{13}C NMR 100 MHz DMSO-d_6 rt δ (ppm): 20.4 (CH_2), 26.7 (CH_2), 47.0 (CH_2), 114.2 (C4a), 123.3 (C5a), 126.6 (C7), 130.2 (C8), 135.9 (C6), 136.0 (C9a), 144.2 (C5), 155.7 (C10a), 158.8 (C2), 159.9 (C4). IR (KBr) cm^{-1} 1704, 1660 (C=O *st*). MS (EI): 253 (21, M^+), 252 (100), 251 (60), 224 (26). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.32; H, 4.58; N, 16.19.