A FACILE ENTRY TO PYRIMIDO[4,5-b]QUINOLINES AND ITS THIO ANALOGUES

R.Nandha kumar, T. Suresh, A. Mythili and P.S. Mohan*
Department of Chemistry
Bharathiar University
Coimbatore – 641 046
India.

Abstract

Synthesis of pyrimido[4,5-b]quinolines and thiopyrimido[4,5-b]quinolines starting from 1,3-diaryl barbituric acid and 1,3-diaryl-2-thiobarbituric acid respectively, with anthranilic acid in the presence of polyphosphoric acid have been described. The structures of these compounds have been confirmed by their spectral and analytical data.

Introduction

In a thorough review of the literature work, it has been found that, incorporation of various fused heterocycles in pyrimidine nucleas enhances the biological activity[1,2]. Barbituric acids and its thio analogues have been employed as convenient starting materials for the synthesis of various fused pyrimidines e.g., pyrido[2,3-d;6,5-d]dipyrimidines[3,4], pyrimido[4,5-b]quinolines[5], thiazolo[4,5-b]quinolines [6]. Among these, biologically potent pyrimido[4,5-b]quinolines with significant therapeutic importance[7-9], have drawn our attention which leads in to a facile and a convenient one step route to a new derivative of these molecules in synthetically useful yields. Earlier reported methods[10-12], have applications limited to only specific derivatives such as 5-deazaflavins and lack generality in the synthesis of pyrimido[4,5-b]quinolines. Our endeavours found a novel method which paves a new path into a variety of 1,3-diaryl-5-hydroxy-2,4-dioxo pyrimido[4,5-b]quinolines in a single one pot convenient synthesis in much good yields.

Experimental

General Information

Thin layer chromatography was used to access the reactions and purity of products. Melting Points were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu – 8201 FT instrument in KBr disc and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H-NMR spectra were recorded in a AMX-400 MHz spectrometer in $CdCl_3$ solution; chemical shifts are expressed in ppm (δ) relative TMS, coupling constants (J) in Hz and signal multiplicities are represented by s (singlet) and m (multiplet). The elemental analysis were carried out in a Carlo Erba 1106 and Perkin Elmer model 240 C,H,N analyser. Mass spectra were recorded on a Jeol – 300 mass spectrometer.

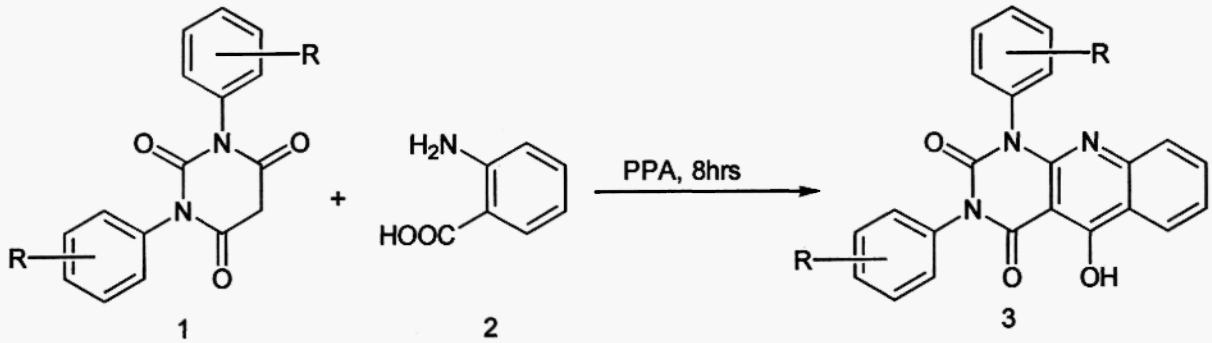
Typical procedure

1,3-diphenyl barbituric acid (0.01 mole), anthranilic acid (0.01 mole) and freshly prepared polyphosphoric acid (P_2O_5: 2.34 g, H_3PO_4: 0.65 ml) were mixed together and heated in an oil bath for 8 hours maintaining steadily at 140 °C. After completion of the reaction, inferred through TLC, it was poured in to 300 g of crushed ice. The compound mixture was then extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulphate. The column chromatography of the mixture yielded the desired product 3a during pet.ether-ethyl acetate (97:3) elution and was recrystallised with methanol.

Results and Discussions

The reaction between 1,3-diphenyl barbituric acid, anthranilic acid and PPA, for 8 hours at 140 °C, afforded the product 3a at 80 % yield (M.P.: 132 °C). It's IR spectrum showed strong absorption bands at 1685 cm^{-1}, 1670 cm^{-1} due to the carbonyl groups and 3300-3650 cm^{-1} absorption band due to the –OH group. The ^{1}H-NMR spectrum revealed a single proton singlet at δ 10.5 was accountable to the hydroxy proton. All the aromatic proton resonances exihibited the absorption between δ 7.10 - 8.15. The mass spectrum pointed out the molecular ion peak at m/z 381. The elemental analysis was also in accordance with the molecular formula $C_{23}H_{15}O_3N_3$. All the above spectral data accredited the compound 3a as 1,3-diphenyl-5-hydroxy-2,4-dioxo pyrimido[4,5-b]quinolines.(Scheme I, Table 1).

SCHEME 1:



1,3 a : R = H
b : R = 2-CH3
c : R = 4-CH3
d : R = 2-OCH
e : R = 4 - Cl

Table 1: Physical and spectral data of 1,3-diphenyl-5-hydroxy-2,4-dioxo pyrimido[4,5-b]quinolines **3**

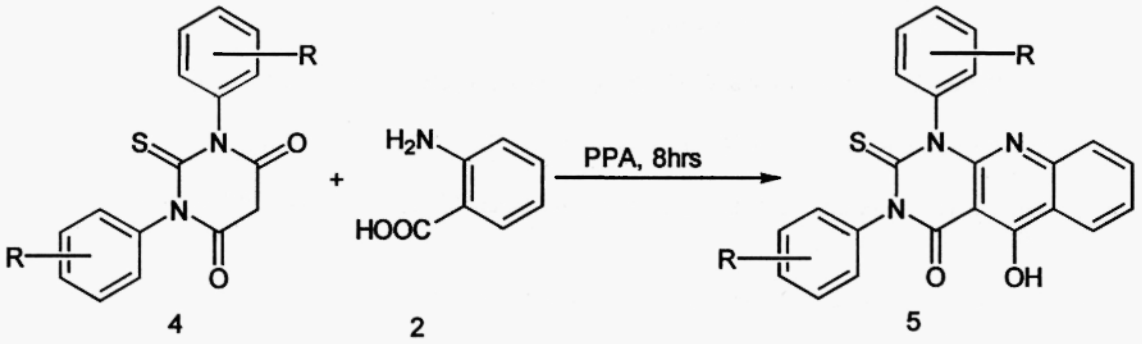
Compound	M.P. (°C)	Yield(%)	IR (KBr) (γ_{max} cm^{-1})	MS (70 eV) m/e(m+)	Molecular Formula	Analysis(%)			^{1}H-NMR ($CdCl_3$)δ/ppm
							Calcd	Found	
3a	132	80	1685	381	$C_{23}H_{15}O_3N_3$	C	72.44	72.10	10.5 (s, 1H, -OH)
			1670			H	3.96	3.83	7.10-8.15 (m, 14H, Ar-H)
			3480			N	11.02	10.95	
3b	129	75	1695	409	$C_{25}H_{19}N_3O_3$	C	73.34	73.21	10.7 (s, 1H, -OH)
			1649			H	4.68	4.56	2.5 (s, 6H, 2xCH_3).
			3390			N	10.26	10.15	7.20 – 8.10 (m, 12H, Ar-H)
3c	110	74	1680	409	$C_{25}H_{19}N_3O_3$	C	73.34	73.12	11.10 (s, 1H, -OH)
			1640			H	4.68	4.65	2.34 (s, 6H, 2xCH_3)
			3350			N	10.26	10.22	7.10 – 8.88 (m, 12H, Ar-H)
3d	135	72	1697	441	$C_{25}H_{19}N_3O_5$	C	68.02	67.95	10.09 (s, 1H, -OH)
			1645			H	4.33	4.23	3.80 (s, 6H, 2xOCH_3)
			3520			N	9.52	9.46	7.20 – 8.70 (m, 12H, Ar-H)
3e	109	42	1680	450	$C_{23}H_{13}N_3O_3Cl_2$	C	61.35	61.31	10.5 (s, 1H, -OH)
			1645			H	2.91	2.84	7.40 – 9.02 (m, 12H, Ar-H)
			3590			N	9.33	9.27	

Table 2: Physical and spectral of 1,3-diphenyl-5-hydroxy-2-thio-4-oxo pyrimido[4,5-b]quinolines **5**

Compound	M.P. (°C)	Yield(%)	IR(KBr) ($\gamma_{max}cm^{-1}$)	MS(70 eV) m/z(m+)	Molecular Formula	Analysis(%)		^{1}H-NMR ($CdCl_3$)δ/ppm
						Calcd	Found	
5a	96	75	1600	397	$C_{21}H_{15}N_3O_2S$	C 69.52	69.48	δ 12.8 (s, 1H, -OH)
			1323			H 3.80	3.85	δ 6.8 – 8.3 (m, 14H, Ar-H)
			3250			N 10.57	10.52	
5b	117	72	1612	425	$C_{25}H_{19}N_3O_2S$	C 10.55	10.41	δ 12.6 (s, 1H, -OH)
			1323			H 4.50	4.35	δ 2.3 (s, 6H, 2xCH_3)
			3300			N 9.88	9.71	δ 7.10 – 9.10 (m, 12H, Ar-H)
5c	110	71	1615	425	$C_{25}H_{15}N_3O_2S$	C 70.55	70.61	δ 12.5 (s, 1H, -OH)
			1323			H 4.50	4.68	δ 2.5 (s, 6H, 2xCH_3)
			3290			N 9.88	9.92	δ 6.7 – 8.7(m, 12H, Ar-H)
5d	138	68	1620	457	$C_{25}H_{15}N_3O_4S$	C 65.64	65.49	δ 12.9 (s, 1H, -OH)
			1325			H 4.18	4.10	δ 3.9 (s, 6H, 2xOCH_3)
			3320			N 9.19	9.11	δ 6.9 – 8.5 (m, 12H, Ar-H)
5e	106	54	1610	466	$C_{23}H_{13}N_3O_2SCl_2$	C 59.24	59.36	δ 12.6 (s, 1H, -OH)
			1271			H 2.83	2.94	δ 6.8 – 9.10 (m,12H, Ar-H)
			3280			N 9.01	9.08	

Having achieved the desired product by the above mentioned technique, our efforts were extended to its thio analogues, 1,3-diphenyl 2-thio barbituric acid also. The products obtained were discernable with IR, ^{1}H-NMR, mass and elemental analysis. (Scheme 2, Table II).

SCHEME 2:



4,5 a : R = H
b : R = 2-CH3
c : R = 4-CH3
d : R = 2-OCH3
e : R = 4 - Cl

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