SYNTHESIS OF NEW COUMARINYL 1,4-BENZOTHIAZINES

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Abstract:

1-(4'-Methyl-7'/5'-hydroxy coumarin-6'/8'-yl)-3-(naphth-1-'yl / thein-2'-yl)-1,3-propanediones **2**a-h have been condensed with 2-aminobenzenethiol in DMSO to get the title products, 2-(naptho-1'yl /thieno-2'-yl)-3-(5'/7'-hydroxy-4'-methyl coumarin-6'/8'-yl)-4,*H*-1,4-benzothiazines **3**a-h. The required 1,3-propanediones **2**a-h were synthesized starting from respective coumarins **1**a-d. The structures of the title compounds and intermediates were confirmed with the help of their spectral and elemental analyses.

Introduction

Coumarins are natural products found in number of plant sources and constitute a family of pharmaceutically active compounds1. A number of coumarin derivatives endowed with large number of biological activities2 such as antihelmintic, hypnotic, insecticidal, anticoagulant and coronary vasodilator. Some of the coumarins have displayed CNS depressant3 and anti-HIV4activities. It is pertinent to mention here that potent antibiotics like chartreusin5, coumermyucine6 and novobiocin7 are coumarin derivatives.

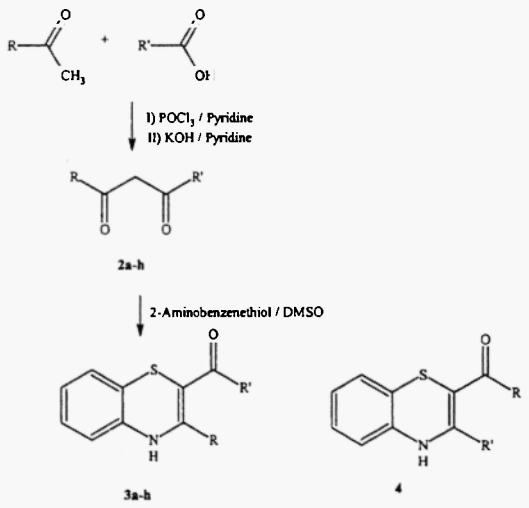
1,4-Benzothiazines exhibit a number of pharmacological activities such as antihistaminic, anti-inflammatory, CNS depressant, diuretics, antihypertensive and blood pressure depressant8. The detail review on the chemistry, synthetic methods and pharmacological/ biological significance of 1,4-benzothiazines has been published by Gupta et al8. Semotiadil9, 1,4-benzothiazine derivative is clinically used as antihypertensive and antianginal agent.

In view of the biological importance of the coumarin and 1,4-benzothiazine derivatives and in continuation of our earlier interest10-13 to incorporate heteryl moieties in 1,4-benzothiazine nucleus here in we report the synthesis of new coumarinyl 1,4-benzothiazines (Scheme-1).

Results and Discussion :

The required starting materials, 8-acetyl-7-hydroxy coumarin, 6-acetyl-7-hydroxy coumarin and 6-acetyl-5-hydroxy coumarin were prepared by following literature procedures14-16. The hydroxy group of the coumarins was first aroylated using 1-naphthoic acid / thiophene-2-carboxylic acid in presence of POCl3 and pyridine. Thus obtained O-esters were subsequently treated with potassium hydroxide in pyridine maintaining Baker-Venkatraman transformation conditions so as to obtain the respective 1,3-propanediones, 1-(4'-methyl-7'/5'-hydroxy coumarin-6'/8'-yl)-3-(naphth-1-'yl / thein-2'-yl)-1,3-propanediones **2**a-h. These 1,3-diketones (2a-h) on cyclocondensation with 2-aminobenzenethiol in DMSO gave the title products, 2-(naptho-1'yl /thieno-2'-yl)-3-(5'/7'-hydroxy-4'-methyl coumarin-6'/8'-yl)-4,*H*-1,4-benzothiazines **3**a-h.

In this condensation there was possibility of formation of two isomers, **3** and **4**. TLC showed the formation of single product. The cyclocondesed product 3c obtained from 2c and 2-aminobenzenethiol was scanned for IR, 1HNMR and MS . MS of 3c gave m/z peak at 111 which can be attributed to thienoyl cation radical and there was no peak at m/z 231 for 6-ethyl-4-methyl-7-hydroxy coumraino-8'-yl cation radical. This MS data therefore supported to assign the structure to the to cyclocondensed product as 3a-h and not 4a-h.



Where, R = 7-Hydroxy-4-methyl-coumarin-6-yl,
5-Hydroxy-4-methyl-coumarin-6-yl,
7-Hydroxy-4-methyl-coumarin-8-yl,
6-Ethyl-7-hydroxy-4-methyl-coumarin-8-yl,
R' = Naphth-1'-yl, Thien-2'-yl

Scheme-I

Experimental :

Melting points were taken in open capillary tube and are uncorrected. IR, 1HNMR and Mass spectra were scanned on Perkin Elmer FTIR spectrophotometer, Brucker FT 300 spectrophotometer at 300 MHz and Finnigan MAT 1020 mass spectrometer, respectively. Chemical shifts are expressed in δ (ppm). Melting points and other data are presented in Table I.

Synthesis of 1-(6'-ethyl-4'-methyl-7'-hydroxy coumarin-8'-yl)-3-thien -2'-yl-1,3-propanedione (2c)

8-Acetyl-6-ethyl-4-methyl-7-hydroxy coumarin (0.01 mole) and thiophene 2-carboxylic acid (0.012 mole) were dissolved in dry pyridine (25 mL) and the solution was cooled to 0oC. Phosphorous oxychloride (1mL) was then added drop wise to the solution maintaining temperature below 10oC. After complete addition the reaction mixture was stirred at room temperature for 12 hr. It was then neutralized with hydrochloric acid. Thus obtained solid was extracted with ether. Ether layer was then washed with cold sodium hydroxide solution and finally with water. Ether layer was separated and dried over anhydrous magnesium sulphate and ether was removed and thus obtained crude ester was dissolved in dry pyridine (15 mL). The solution was cooled to 0oC. Powdered potassium hydroxide (0.04 mole) was added in to the solution in portion at 5oC and after complete addition of KOH, the reaction mass was allowed to stir at 10oC for 30 min. and then it was kept at room temperature for 4 hr with occasional shaking. The reaction mass was poured on ice-hydrochloric acid mixture. Thus obtained solid was filtered, washed with water, dried and crystallized from ethanol, **IR** (KBr, cm-1): 3410 (OH stretching), 3111 (CH stretching aromatic), 2915 (CH stretching, aliphatic), 1735 (cyclic C=O stretching), 1657 (C=O stretching), 1640 (C=O stretching, chelated), 1609 (C=C aromatic stretching) and 1186 (C-O stretching); **1HNMR** (CDCl3): 1.23 (t, 3H, CH2-C*H*3, J = 8Hz), 2.44 (s, 3H, CH3, J = 8Hz), 2.74 (q, 2H, C*H*2CH3, J = 8Hz), 4.93 (s, 1H, C*H*=C-OH, enolic form of 1,3-diketone), 7.13-7.90 (m, 5H, ArH), 13.46 (s, 1H, OH, exchangeable with D2O) and 13.64 (s, 1H, OH, enolic, exchangeable with D2O); **MS**, m/z (% intensity): 356 (50 M+.), 285 (10), 245 (6.6), 231 (13), 202 (22.66), 174 (6.6), 131 (11.33), 111(100), 91 (26.66), 77 (27.33) and 69 (23.33).

Table I : Characterisation data of compounds 2a-h and 3a-h.

Sr. No.	R	R'	M.P. in °C	Yield %	Molecular Formula	Mol. Wt.	Nitrogen %	
							Found	Calcd.
2a	7-Hydroxy-4-methyl-coumarin-8-yl	1-Naphthyl	164	61	$C_{23}H_{16}O_5$	372	-	-
2b	6-Ethyl-7-hydroxy-4-methyl-coumarin-8-yl	1-Naphthyl	150	72	$C_{25}H_{20}O_5$	400	-	-
2c	6-Ethyl-7-hydroxy-4-methyl-coumarin-8-yl	2-Thienyl	186	68	$C_{19}H_{16}O_5S$	356	-	-
2d	7-Hydroxy-4-methyl-coumarin-8-yl	2-Thienyl	202	62	$C_{17}H_{12}O_5S$	328	-	-
2e	5-Hydroxy-4-methyl-coumarin-6-yl	2-Thienyl	195	71	$C_{17}H_{12}O_5S$	328	-	-
2f	5-Hydroxy-4-methyl-coumarin-6-yl	1-Naphthyl	187	65	$C_{23}H_{16}O_5$	372	-	-
2g	7-Hydroxy-4-methyl-coumarin-6-yl	2-Thienyl	180	62	$C_{17}H_{12}O_5S$	328	-	-
2h	7-Hydroxy-4-methyl-coumarin-6-yl	1-Naphthyl	200	67	$C_{23}H_{16}O_5$	372	-	-
3a	7-Hydroxy-4-methyl-coumarin-8-yl	1-Naphthyl	156	70	$C_{25}H_{19}NO_4S$	477	2.87	2.94
3b	6-Ethyl-7-hydroxy-4-methyl-coumarin-8-yl	1-Naphthyl	180	64	$C_{31}H_{23}NO_4S$	505	2.61	2.77
3c	6-Ethyl-7-hydroxy-4-methyl-coumarin-8-yl	2-Thienyl	294	58	$C_{25}H_{19}NO_4S_2$	461	2.89	3.04
3d	7-Hydroxy-4-methyl-coumarin-8-yl	2-Thienyl	174	67	$C_{23}H_{15}NO_4S_2$	401	3.33	3.49
3e	5-Hydroxy-4-methyl-coumarin-6-yl	2-Thienyl	270	73	$C_{23}H_{15}NO_4S_2$	401	3.31	3.49
3f	5-Hydroxy-4-methyl-coumarin-6-yl	1-Naphthyl	280	69	$C_{29}H_{19}NO_4S$	477	2.86	2.94
3g	7-Hydroxy-4-methyl-coumarin-6-yl	2-Thienyl	194	60	$C_{23}H_{15}NO_4S_2$	401	3.32	3.49
3h	7-Hydroxy-4-methyl-coumarin-6-yl	1-Naphthy	230	56	$C_{29}H_{19}NO_4S$	477	2.90	2.94

The other 1,3-propanediones of the series were prepared by following above procedure. Melting points, yields, and other data are given in Table I.

Synthesis of 2-(thieno-2'-yl)-3-(6'-ethyl-7'-hydroxy-4'-methyl coumarin-8'-yl) 4*H*-1,4-benzothiazine (3c)

A mixture of **2c** (0.005 mole) and 2-aminobenzenethiol (0.005mole) was dissolved in dimethyl sulphoxide (5 mL) and the solution was refluxed at 170-180oC on an oil bath for 3 hr. Reaction mass was cooled to room temperature and poured on ice water with vigorous stirring. The obtained solid was filtered, washed with water and crystallized from 1,4-dioxane, **IR** (Nujol, cm-1): 3270-3210 (OH and NH stretchings), 1705 (cyclic C=O stretching), 1652 (C=O stretching) and 1610 (C=C aromatic stretching); **1HNMR** (CDCl3 + DMSO*d*6): 1.4 (t, 3H, CH2-C*H*3, J = 8Hz), 2.52 (s, 3H, CH3), 3.0 (q, 2H, C*H*2CH3, J = 8Hz), 6.3-7.79 (m, 9H, Ar-H) and signals due to OH and NH are not seen up to 8.5 ppm; **MS**, m/z (%intensity): 461 (2, M+. unstable), 338 (93.33), 310 (43.33), 230 (51.33), 215 (29.33), 202 (92.66), 187 (28), 174 (46.66), 134 (22.66), 111(35.33, thiophenoyl cation), 108 (100), 91 (71.33) and 69 (38).

The other 1,4-benzothiazines of the series were prepared by following above procedure. Melting points, yields, and other data are given in Table I.

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