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Note

Synthesis of 3-(6-aryl-pyridin-2-yl)- and 8-(6-aryl-pyridin-2-yl) coumarins

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Mannich bases of 3-acetyl coumarin **1** and 4-methyl-7-methoxy-8-acetyl coumarin **4** on reaction with substituted phenacyl bromide pyridinium salts **2a-f** in the presence of ammonium acetate in refluxing acetic acid afford the title 3-(6-aryl-pyridin-2-yl)- and 8-(6-aryl-pyridin-2-yl) coumarins (**3a-f** and **5a-f**) in moderate to good yields.

Keywords: Coumarins, pyridinium salts, Mannich bases

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Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing heterocycles and a large number of coumarin derivatives are used in drugs and dyes. The incorporation of other heterocyclic moiety either as a substituent group or as a fused component into parent coumarin alters the property of parent coumarin and converts it into a more useful product. Among heterocyclic substituted coumarins, 3-pyridyl and 4-pyridyl substituted coumarins[1-3] are known for their diverse physiological activities. The literature methods reported for the preparation of these 3-pyridyl and 4-pyridyl coumarins involve either Perkin or Pechmann reaction and are one pot syntheses. Thus however these reported methods are simple they do not provide substitution in pyridine part. Hence with a view to developing new methods which can provide pyridyl coumarins having substitution in pyridine nucleus, we had earlier reported[4,5] synthesis of various 3 and 8-pyridyl substituted coumarins having mono and diaryl substitution in pyridine part. In mono aryl pyridyl substituted coumarins work[5] we had synthesized various 3-(6-aryl-pyridin-2-yl)- and 8-(6-aryl-pyridin-2-yl) coumarins. The compounds were prepared by reacting 3-coumarinoyl methyl pyridinium bromide and 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide with various Mannich bases derived from acetophenones, under Kroehnke's reaction condition[6,7]. In the present work the same compounds have been synthesized by interchanging the functionality of reacting components. Thus, instead of reacting coumarinoyl methyl pyridinium salts with Mannich bases of acetophenones, the Mannich bases derived from 3-acetyl coumarin and 4-methyl-7-methoxy-8-acetyl coumarin have been reacted with phenacyl bromide pyridinium salts under Kroehnke's reaction condition. (**Scheme 1**). The compounds synthesized in the present work (**3a-f** and **5a-f**) were characterized by analytical and spectral data. They were found identical with those prepared earlier[5]. It is important to mention over here that the yield (35-60%) of the compounds (**3a-f** and **5a-f**) obtained in the present work was almost same as the earlier work.

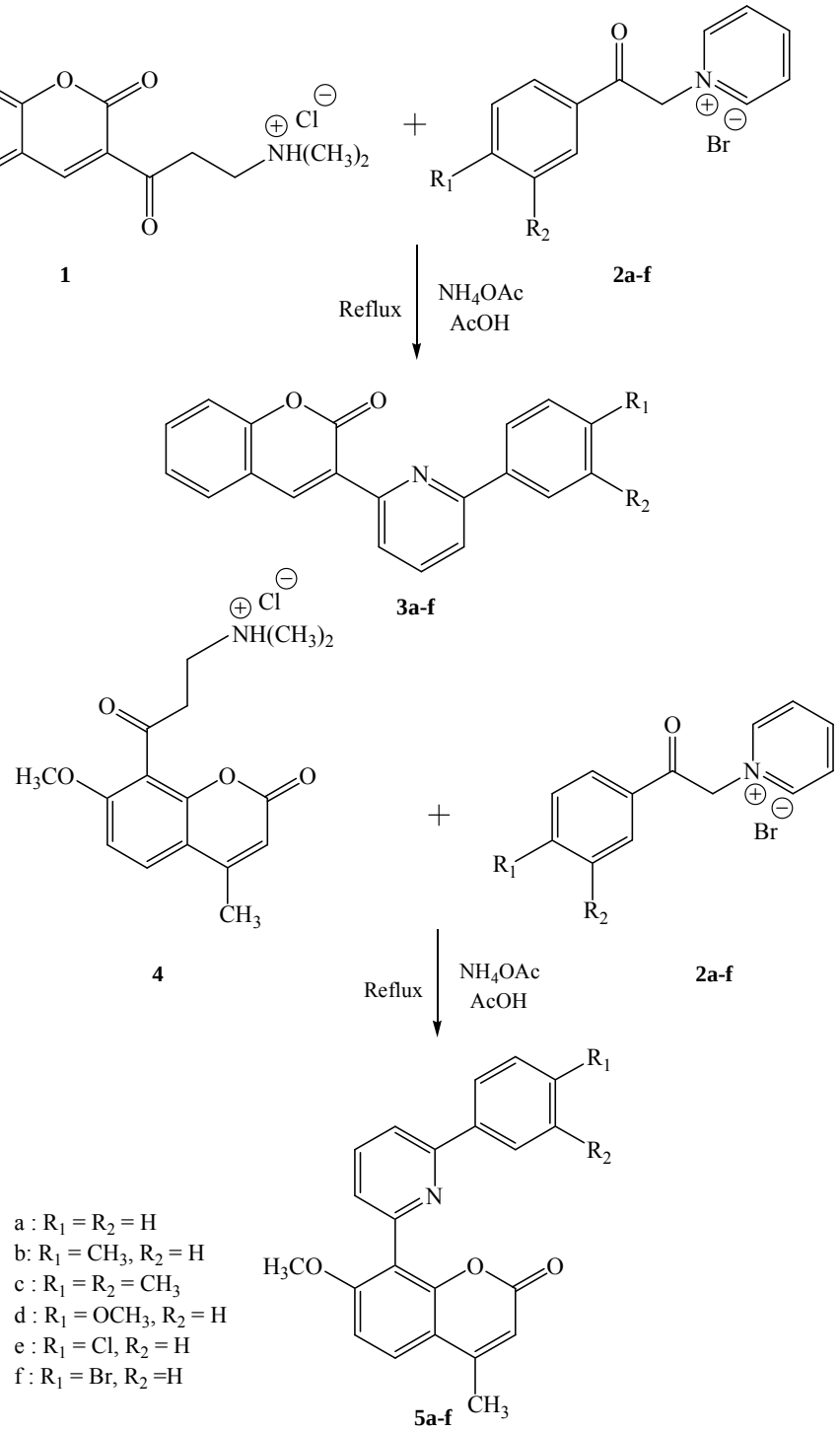
Experimental Section

All melting points are uncorrected. IR spectra were recorded in KBr on a Nicolet 400D spectrophotometer and ^{1}H NMR in $CDCl_3$ on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. The pyridinium salts **2a-f** were prepared by literature procedure[8].

Preparation of Mannich bases of 3-acetyl coumarin 1 and 4-methyl-7-methoxy-8-acetyl coumarin 4: General Procedure

In a 250 mL round bottom flask was placed dimethylamine hydrochloride (0.13 mole), powdered paraformaldehyde (0.13 mole) and appropriate coumarins (0.1 mole). To this mixture, was added ethanol (20 mL) and catalytic amount of HCl (0.5 mL). The reaction mixture was refluxed on a water bath for 3 hr and while still warm it was poured into dry acetone (200 mL) and left in a referigerator overnight. The crystalline product separated was filtered, washed with dry acetone (chilled) and dried under vacuum at 45-50°C for 4-5 hr.

Compound 1: Yield 65%, m.p. 198ºC (dec.) Found: C, 59.7; H, 5.2; N, 4.9. $C_{14}H_{15}NO_3Cl$ requires C, 59.8; H, 5.3; N, 5.0%); IR: 1725 (δ-lactone carbonyl of coumarin, 1670 (ketone carbonyl), 2620 and 3000 cm^{-1} (N-H stretching of tertiary amine and C-H stretching); ^{1}H NMR (D_2O): 2.9 (6H, s,



Scheme I

-$N(CH_3)_2$), 3.4-3.8 (4H, poorly resolved multiplet, -CO-CH_2-CH_2-N<), 7.1-8.0 (4H, m, Ar-H), 8.6 δ (1H, s, C_4-H).

Compound 4: Yield 60%, m.p. 220ºC (dec.) Found: C, 59.0; H, 5.6; N, 4.3. $C_{16}H_{19}NO_4Cl$ requires C, 59.1; H, 5.8; N, 4.3%); IR: 1720 (δ-lactone carbonyl of coumarin), 1675 (ketone carbonyl), 2660 and 3000 cm^{-1} (N-H stretching of tertiary amine and C-H stretching); ^1H NMR (D_2O): 2.1 (3H, s, -CH_3), 2.9 (6H, s, -$N(CH_3)_2$), 3.2-3.7 (4H, poorly resolved

Table I — Characterization data of compounds **3a-f** and **5a-f**

Compd *	m.p. (ºC)	Yield (%)	Mol. formula	Found (%) (Calcd.) C	H	N	^{1}H NMR (δ, ppm)
3a	147	56	$C_{20}H_{13}NO_2$	80.1 (80.2	4.4 4.3	4.7 4.6)	7.4-8.4 (12H, m, Ar-H), 8.9 (1H, s, C_4 -H)
3b	164	58	$C_{21}H_{15}NO_2$	80.3 (80.4	4.7 4.8	4.5 4.4)	2.4 (3H, s, -CH_3), 7.3-8.5 (11H, m, Ar-H), 8.9 (1H, s, C_4 -H)
3c	155	60	$C_{22}H_{17}NO_2$	80.6 (80.7	5.1 5.2	4.1 4.2)	2.3 and 2.4 (6H, 2 x s, 2 x -CH_3), 7.1-8.4 (10H, m, Ar-H), 8.9 (1H, s, C_4 -H)
3d	168	35	$C_{21}H_{15}NO_3$	76.6 (76.5	4.6 4.5	4.3 4.2)	3.8 (3H, s, -OCH_3). 6.8-8.4 (11H, m, Ar-H), 8.9 (1H, s, C_4 -H)
3e	257	55	$C_{20}H_{12}ClNO_2$	72.0 (71.9	3.5 3.6	4.3 4.2)	7.3-8.1 (11H, m, Ar-H), 8.8 (1H, s, C_4 -H)
3f	209	54	$C_{20}H_{12}BrNO_2$	63.6 (63.5	3.3 3.2	3.8 3.7)	7.3-8.4 (11H, m, Ar-H), 8.9 (1H, s, C_4 -H)
5a	214	52	$C_{22}H_{17}NO_3$	77.0 (76.9	5.0 4.9	4.1 4.0)	2.4 (3H, s, -CH_3), 3.8 (3H, s,-OCH_3), 6.1 (1H, s, C_3-H), 6.9-8.0 (10H, m, Ar-H)
5b	235(d)	60	$C_{23}H_{19}NO_3$	77.3 (77.2	5.4 5.3	3.8 3.9)	2.3 (6H, s, 2 × -CH_3), 3.8 (3H, s, -OCH_3), 6.1 (1H, s, C_3-H), 6.9-7.9 (9H, m, Ar-H)
5c	181	55	$C_{24}H_{21}NO_3$	77.5 (77.6	5.6 5.7	3.8 3.7)	2.3 and 2.4 (9H, 2 × s, 3 × -CH_3), 3.8 (3H, s, -OCH_3),6.1 (1H, s, C_3-H), 7.0-7.9 (8H, m, Ar-H)
5d	195	48	$C_{23}H_{19}NO_4$	74.0 (73.9	5.0 5.1	3.6 3.7)	2.3 (3H, s, -CH_3), 3.8 (6H, s, two-OCH_3), 6.1 (1H, s, C_3-H), 6.9-7.9 (9H, m, Ar-H)
5e	245(d)	57	$C_{22}H_{16}ClNO_3$	70.0 (69.9	4.3 4.2	3.6 3.7)	2.4 (3H, s, -CH_3), 3.9 (3H, s, -OCH_3), 6.1(1H, s, C_3-H), 7.0-8.1 (9H, m, Ar-H)
5f	236	59	$C_{22}H_{16}BrNO_3$	62.6 (62.5	3.9 3.8	3.2 3.3)	2.3 (3H, s, -CH_3), 3.8 (3H, s,-OCH_3), 6. 1(1H, s, C_3-H), 6.8-7.9 (9H, m, Ar-H)

*All compounds exhibited the characteristic IR bands at 3000 (C-H stretching of pyridine ring), 1600-1500 (C=C aromatic and C=N of pyridine) and 1710-1730 cm^{-1} (δ-lactone carbonyl of coumarin)

multiplet, -CO-CH_2-CH_2-N<), 3.8 (3H, s, -OCH_3), 5.9 (1H, s, C_3-H), 6.9 (1H, d, J = 8 Hz, C_5-H), 7.5 δ (1H, d, J = 8 Hz, C_6-H).

Synthesis of 3-(6-aryl-pyridin-2-yl) coumarins 3a-f and 4-methyl-7-methoxy-8-(6-aryl-pyridin-2-yl) coumarins 5a-f: General procedure. To a well stirred solution of Mannich base of appropriate coumarin (**1** or **4)** (0.006 mole) in glacial acetic acid (15 mL) was added ammonium acetate (5.0 g, 0.06 mole) and appropriate phenacyl bromide pyridinium salt **2a-f** (0.004 mole) in glacial acetic acid (10 mL). The reaction mixture was stirred at room temperature for 15 min and then refluxed in an oil bath at 140-45ºC for 6 hr and left overnight. The reaction mixture was poured in water (75 mL) and the crude solid obtained was extracted with chloroform (3 × 30 mL). The organic layer was washed with 10% $NaHCO_3$ (50 mL), water (50 mL) and dried (Na_2SO_4). Excess chloroform was distilled *in vacuo* and liquid left was adsorbed on silica gel and column chromatographed using 15% hexane-benzene as an eluent to give **3a-f** and 5% ethyl acetate-benzene as an eluent to give **5a-f** in 35-60% yield. The compounds were characterized by analytical and spectral data (**Table I**).

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