A Novel Synthesis of 4-Aminomethylcoumarins

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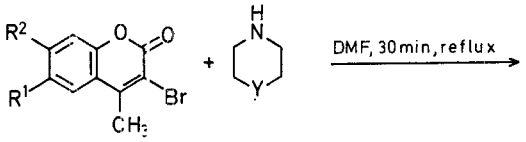
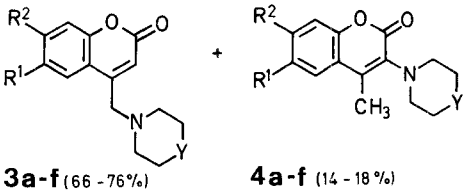
The paper describes the synthesis of 4-aminomethylcoumarins starting with easily accessible corresponding 3-bromo-4-methylcoumarins and a secondary amine. In this reaction, the formation of 3-amino-4-methylcoumarins as a minor product, is also observed.

The reported biological activities[1-4] and fluorescent properties of 4-aminomethylcoumarins (**3**) make them attractive targets for synthesis. The known methods either involve reaction of 4-halomethylcoumarins with the appropriate secondary amine[1,2,5,6] or direct introduction of the aminomethyl group at the desired position on the 3-hydroxycoumarin using formaldehyde and a secondary amine[3]. The major drawback of the first method is the difficulty in obtaining the 4-halomethylcoumarins which are also reported to be light sensitive[5]. These are prepared either directly by condensation of the corresponding phenol with ethyl 4-haloacetoacetate[1,2,7] or by an indirect method involving conversion of 4-methylcoumarin into 4-chloromethylcoumarin[6] and also from coumarin-4-acetic acid by halogenation and decarboxylation[8]. In the second method the presence of a 3-hydroxy group in coumarin is essential for the reaction to proceed, thus restricting its applicability.

In the present communication, we report a new and convenient method for the synthesis of these compounds **3** starting with easily accessible 3-bromo-4-methylcoumarins **1**. The reaction of **1** with secondary amines **2** such as morpholine and piperidine in dimethylformamide gives the 4-aminomethylcoumarins **3** in more than 65% yield (Table



1 $R^1, R^2 = H, CH_3$ **2** Y = O, CH_2



3a-f (66-76%) **4a-f** (14-18%)

3,4	R^1	R^2	Y
a	CH_3	H	O
b	H	CH_3	O
c	H	H	O
d	CH_3	H	CH_2
e	H	CH_3	CH_2
f	H	H	CH_2

Table 1. 4-Aminomethylcoumarins **3a–f** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (Nujol)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
3a	66	162°	$C_{15}H_{17}NO_3$ (259.3)	1740 (C=O), 1380 (C—N)	2.4 (s, 3H, CH_3); 2.52 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.59 (br. d, 2H, CH_2); 3.7 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 6.44 (br. s, 1H, 3-H); 7.1–7.4 (m, 2H, 7-H, 8-H); 7.5 (br. s, 1H, 5-H)
3b	68	141°	$C_{15}H_{17}NO_3$ (259.3)	1740 (C=O), 1380 (C—N)	2.4 (s, 3H, CH_3); 2.52 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.6 (br. s, 2H, CH_2); 3.7 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 6.42 (br. s, 1H, 3-H); 6.95–7.1 (m, 2H, 6-H, 8-H); 7.65 (d, J = 9 Hz, 1H, 5-H)
3c	72	146°	$C_{14}H_{15}NO_3$ (245.3)	1735 (C=O), 1375 (C—N)	2.4 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.68 (br. s, 2H, CH_2); 3.75 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 6.5 (br. s, 1H, 3-H); 7.0–7.7 (m, 3H, 6-H, 7-H, 8-H); 7.8 (dd, J = 9 Hz, 2 Hz, 1H, 5-H)
3d	76	140°	136–7°[6]	1745 (C=O), 1380 (C—N)	1.3–1.8 (m, 6H, 3′-CH_2, 4′-CH_2, 5′-CH_2); 2.39–2.6 (m, 7H, 2′-CH_2, 6′-CH_2, CH_3); 3.54 (br. d, 2H, CH_2); 6.5 (bs, 1H, 3-H); 7.1–7.35 (m, 2H, 7-H, 8-H); 7.55 (br. s, 1H, 5-H)
3e	72	95°	81–82°[6]	1745 (C=O), 1380 (C—N)	1.3–1.9 (m, 6H, 3′-CH_2, 4′-CH_2, 5′-CH_2); 2.38–2.6 (m, 7H, 2′-CH_2, 6′-CH_2, CH_3); 3.55 (br. s, 2H, CH_2); 6.45 (br. s, 1H, 3-H); 7.0–7.2 (m, 2H, 6-H, 8-H); 7.68 (d, J = 9 Hz, 1H, 5-H)
3f	70	90°	$C_{15}H_{17}NO_2$ (243.3)	1750 (C=O), 1380 (C—N)	1.4–1.8 (m, 6H, 3′-, 4′-, 5′-CH_2); 2.4–2.65 (m, 4H, 2′-, 6′-CH_2); 3.59 (br. s, 2H, CH_2); 6.52 (br. s, 1H, 3-H); 7.1–7.6 (m, 3H, 6-H, 7-H, 8-H); 7.82 (dd, J = 9 Hz, 2 Hz, 1H, 5-H)

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.38, N ±0.40.
[c] Recorded on a Perkin-Elmer 337 spectrophotometer.
[d] Recorded on a 90 MHz Perkin-Elmer R-32 instrument.

Table 2. 3-Aminocoumarins **4a–f** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b]	I.R. (Nujol)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
4a	14	177°	$C_{15}H_{17}NO_3$ (259.3)	1720 (C=O), 1370 (C—N)	2.4 (s, 3H, 6-CH_3); 2.5 (s, 3H, 4-CH_3); 3.09 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.8 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 7.1–7.4 (m, 3H, 5-H, 7-H, 8-H)
4b	19	151°	$C_{15}H_{17}NO_3$ (259.3)	1710 (C=O), 1360 (C—N)	2.44 (s, 3H, 7-CH_3); 2.49 (s, 3H, 4-CH_3); 3.08 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.78 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 7.0–7.5 (m, 3H, 5-H, 6-H, 8-H)
4c	17	155°	$C_{14}H_{15}NO_3$ (245.3)	1730 (C=O), 1370 (C—N)	2.52 (s, 3H, CH_3); 3.12 (t, J = 5 Hz, 4H, 2′-CH_2, 6′-CH_2); 3.82 (t, J = 5 Hz, 4H, 3′-CH_2, 5′-CH_2); 7.2–7.7 (m, 4H_{arom})
4d	18	126°	$C_{16}H_{19}NO_2$ (257.3)	1730 (C=O), 1380 (C—N)	1.5–1.75 (br. s, 6H, 3′-CH_2, 4′-CH_2, 5′-CH_2); 2.39 (s, 3H, 6-CH_3); 2.42 (s, 3H, 4-CH_3); 2.9–3.1 (m, 4H, 2′-CH_2, 6′-CH_2); 7.1–7.35 (m, 3H, 5-H, 7-H, 8-H)
4e	18	105°	$C_{16}H_{19}NO_2$ (257.3)	1725 (C=O), 1370 (C—N)	1.5–1.8 (br. s, 6H, 3′-CH_2, 4′-CH_2, 5′-CH_2); 2.4 (s, 3H, 7-CH_3); 2.45 (s, 3H, 4-CH_3); 2.9–3.15 (m, 4H, 2′-CH_2, 6′-CH_2); 7.0–7.1 (m, 2H, 6-H, 8-H); 7.42 (d, J = 9 Hz, 1H, 5-H)
4f	17	101°	$C_{15}H_{17}NO_2$ (243.3)	1735 (C=O), 1375 (C—N)	1.5–1.8 (br. s, 6H, 3′-CH_2, 4′-CH_2, 5′-CH_2); 2.5 (s, 3H, CH_3); 3.0–3.2 (m, 4H, 2′—CH_2, 6′-CH_2); 7.1–7.6 (m, 4H_{arom})

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.29, H ±0.37, N ±0.23.
[c] Recorded on a Perkin-Elmer 337 spectrophotometer.
[d] Recorded on a 90 MHz Perkin-Elmer R-32 instrument.

1). A side product is also formed in the above reaction which is characterised as the 3-aminocoumarin **4** (Table **2**). The mechanism for the formation of **3** and **4** from **1** is still not clear.

The present method involving easily accessible starting materials, milder reaction conditions and wider applicability is more advantageous than the earlier ones.

Table 3. 3-Bromo-4-methylcoumarins **1a–c** prepared[a]

Product No.	Yield [%]	m.p.[b] [°C]	Molecular Formula Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
1a	79	157°	$C_{11}H_9BrO_2$[d] (253.2)	2.44 (s, 3H, 6-CH_3); 2.52 (s, 3H, 4-CH_3); 7.05–7.4 (m, 3H, 5-H, 7-H, 8-H)
1b	89	135°	138°[9]	2.41 (s, 3H, 7-CH_3); 2.52 (s, 3H, 4-CH_3); 7.0–7.1 (m, 2H, 6-H, 8-H); 7.45 (d, 1H, 5-H, J = 9 Hz)
1c	89	112°	114°[10]	2.61 (s, 3H, CH_3); 7.2–7.7 (m, 4H_{arom})

[a] I.R. (Nujol): ν = 1750 (C=O), 760 cm^{-1} (C—Br).
[b] Uncorrected.
[c] Recorded on a 90 MHz Perkin-Elmer R-32 instrument.
[d] calc. C 52.18 H 3.58 Br 31.60
found 52.56 3.80 32.01

3-Bromo-4-methylcoumarins 1; General Procedure:
A solution of bromine (3.2 g, 0.02 mol) in glacial acetic acid (10 ml) is added dropwise with stirring to a solution of the appropriate 4-methylcoumarin (0.01 mol) in glacial acetic acid (20 ml). The stirring is continued for 2 h. The mixture is then poured in ice-cold water (300 ml), stirred with a solution of sodium hydrogen sulphite till the yellow colour disappears, filtered, and the solid thus obtained is crystallised from hexane/ethanol to give white needles of **1** (Table 3).

4-Aminomethylcoumarins 3 and 3-Aminocoumarins 4; General Procedure:
A solution of the appropriate 3-bromo-4-methylcoumarin **1** (0.002 mol) and the secondary amine (0.008 mol) in dimethylformamide (5 ml) is refluxed for 30 min. The mixture is cooled and poured in water (100 ml). The precipitated solid is filtered, dried, and column chromatographed on silica gel column using ethyl acetate/hexane (1:4) as eluent. The earlier fractions give 3-aminocoumarins **4** (Table 2) as the minor compounds while the later fractions furnish 4-aminomethylcoumarins **3** (Table 1). All the compounds are crystallised from hexane/ethanol to furnish white needles.

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