Microwave assisted synthesis of 4-aryl/alkylaminocoumarins

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4–Aryl and 4–alkylaminocoumarins were prepared by reaction of 4–hydroxycoumarin with amines under microwave irradiation in solvent-free conditions in good to excellent yields.

Keywords: aminocoumarins, arylcoumarins

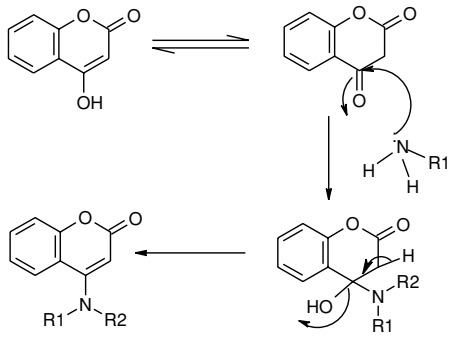
Coumarins constitute an important class of oxygen hetrocycles.[1] Many compounds containing the coumarin nucleus, both naturally occurring and synthetic, are known to exhibit pharmacological activity.[2-7] Aminocoumarins have become important raw materials for the production of biologically active molecules such as pyrrolocoumarins[8] and pyrano[3,2-*f*][2]benzothiophenes.[9] It has been reported that 4-arylaminocoumarins[10] can be synthesised by converting 4-hydroxycoumarins into respective 4-chlorocoumarins and subsequent replacements of reactive chloro group by amino function compounds. But above procedure suffers from drawback such as extended reaction time, low yields due to multi-step reaction and toxic solvents.

Ideal synthesis involved preparation of target molecules in one step, in quantitative yields from readily available and inexpensive starting materials in resource effective and environmentally acceptable process. Another major current challenge before chemists is to develop synthetic methodology where optimal value of resource is achieved and consumption of energy is minimised. To achieve these goals the use of microwave energy has been found to be a useful tool. Rapid, ecofriendly chemical transformations[11] with excellent yields have resulted and there have been many reports[12] of remarkable decreases in reaction time for the reactions carried out using domestic microwave oven. Hence we would like to report the synthesis of 4-alkyl/aryl aminocoumarins by simple two component condensation of 4-hydroxycoumarin with amines using microwave irradiation (MW) under solvent free conditions.

The reaction of 4-hydroxycoumarin and an amine **(2b)** was carried out under thermal conditions gave 4-(4-methoxyphenylamino)coumarin **(3b)** in low yield (45 %), same transformation under microwave irradiation at a power output of 600 W, gave the title compound **(3b)** in high yield (90 %) in short reaction time (20 s). The large difference in yields (MW >> Δ) may be a consequence of the polar transition state (Scheme 1) interaction[13] with electric field component of microwave irradiation. In order to optimize the microwave power, the reaction mixture was exposed to the electromagnetic field at different power levels. This step allowed us to determine adequate conditions of incident power and irradiation time. The experiments were conducted at different power levels to compare product yield (Table 1).

The microwave irradiation time increased the yields of product (Table 2, entries 1–3). However, the irradiation time prolonged did not give higher yields (Table 2, entries 4–5).

When the reaction was followed by GC no any side product formation due to ring opening was found.[14] Similarly on refluxing a solution of 4-hydroxycoumarin in morpholine for 8 h furnished enamine[15] **(3h)**, same reaction in microwave gave product in 30 s. A variety of amines including ammonium acetate, aliphatic and aromatic amines were condensed with 4-hydroxycoumarin to establish the general behaviour of this reaction under microwave conditions (Table 3). Aliphatic primary amines such as allylamine, propylamine, 2-aminoethanol as well as methyl amine, ethylamine as water solution,



Scheme 1

Table 1 Effect of microwave power on the yield

Entry	Microwave power/W	Reaction time/s	Yield/%[a]
1	100	20	0
2	300	20	15
3	500	20	70
4	600	20	90
5	800	20	92

[a]Yields listed refer to pure isolated product **3b** based on compound **1**.

Table 2 Effect of microwave irradiation (600W) time on the yield

Entry	Reaction time/s	Yield/%[a]
1	5	10
2	10	35
3	15	65
4	20	90
5	40	93

[a]Yields listed refer to pure isolated product **3b** based on compound **1**.

the aromatic secondary amines as *N*-methylaniline and the secondary aliphatic amine as diisobutylamine did not give any reaction under the described experimental conditions. We have also prepared 4-aminocoumarin using ammonium acetate as a source of amine in high yield (92%), also when hexamethylenetetramine use as amine source 3,4-dihydro-2*H*,5*H*-[1]benzopyrano[3,4-*e*][1,3]oxazin-5-one **(3g)** was obtained in good yield (72%).

In conclusion, the present procedure for the amination of 4-hydroxycoumarin has attractive features which will make a useful and important addition to present methodologies. Improved yield, enhanced reaction rates, solvent-free and carrier-free conditions are the main advantages of this procedure, all these factors combine to make it a green synthesis.

Experimental

All experiments were carried out in a domestic Kenstar Microwave Oven (OM-9918C, 900W), without subjecting the oven to any

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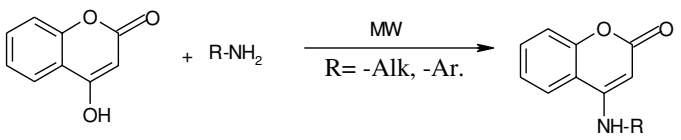
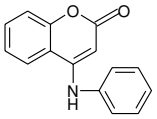
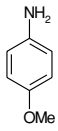
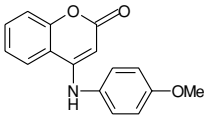
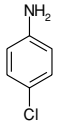
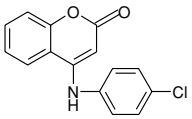
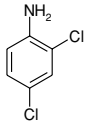
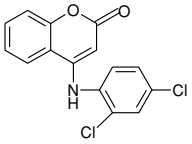
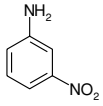
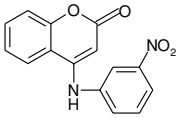
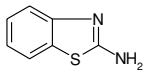
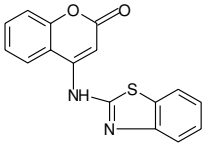
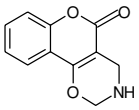
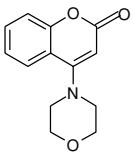
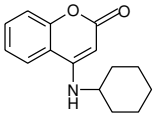
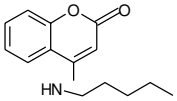
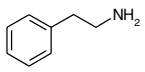
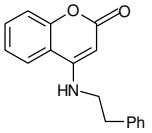
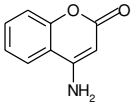
Table 3 Preparation of 4-Aryl and 4-alkylaminocoumarins by reaction of 4-hydroxycoumarin with amines in the absence of solvent



1 **2** **3**

Entry	Compound (**2**)	Product (**3**)	Time/s	Yield[a]/%'
a			25	94
b			20	90
c			30	92
d			35	88
e			30	85
f			25	90
g	Hexamine		35	72
h			30	85
i			30	92
j	n-C_5H_{11} NH_2		25	88
k			25	89
l	CH_3COONH_4		30	92

[a]Yields listed refer to pure isolated product based on compound **1**.

modifications. IR spectra were recorded on a Perkin Elmer 1310 instrument while ^{1}H NMR spectra were recorded on a Bruker AC 300F NMR spectrometer (300MHz) with TMS as an internal standard. Silica gel-G was used for TLC. Analysis of gas chromatography was performed using a Hewlett Paxkard 5890 Series II with a 6ft × 1/8 in 10% Carbowax 20 M columns. The following procedure is general one.

A mixture of 4-hydroxycoumarin (1 mmol), an amine (1 mmol) in a 25ml conical flask and placed in a microwave oven (Kenstar OM-9918C, 900W) under ambient pressure for specified time (Table 3). The reaction was monitored by TLC. The reaction mixture was then dissolved in methanol (5ml) and the solution was treated with 0.1M aqueous sodium hydroxide (3ml) with stirring afforded almost pure the desired 4-aryl or 4-alkylaminocoumarins in good to excellent yields which was further purified by crystallisation from aqueous ethanol.

4-Phenylaminocoumarin **(3a)**: M.p. 265 °C (lit.[16] m.p. 267–268 °C). IR (KBr): 3220, 2980, 2960, 2860, 1706, 1665, 1550, 1340, 1285 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.01, s, 1H; 7.30–8.35, m, 9H; 8.65, br s, 1H.

4-(4'-Methoxyphenylamino)coumarin **(3b)**: M.p. 242 °C (lit.[16] m.p. 245–246 °C). IR (KBr): 3235, 2955, 1655, 1460, 1345, 1290, 1225 cm^{-1}. ^{1}H NMR (DMSO-d_6):δ =3.80, s, 3H; 5.12, s, 1H; 6.70, d (*J*=6.9Hz), 2H; 6.45, d (*J*=6.9Hz), 2H; 7.30–8.32, m, 4H; 8.82, br s, 1H.

4-(4'-Chlorophenylamino)coumarin **(3c)**: M.p. 306 °C (lit.[16] m.p. 306–307 °C). IR (KBr): 3250, 2899, 1650, 1490, 1388, 1295, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.30, s, 1H; 7.12, d (*J*=7.6 Hz), 2H; 7.24, d (*J*=7.6 Hz), 2H; 7.34–8.33, m, 4H; 9.10, br s, 1H.

4-(2',4'-Dichlorophenylamino)coumarin **(3d)**: M.p. 322 °C. IR (KBr): 3220, 2920, 1650, 1482, 1354, 1277, 1262 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 4.95, s, 1H; 7.0–7.92, m, 7H; 8.95, br s, 1H. Anal. Calcd for $C_{15}H_9NO_2Cl_2$: C, 58.85; H, 2.96; N, 4.58; Cl, 23.16. Found: C, 58.82; H, 2.94; N, 4.60; Cl, 23.14.

4-(3'-Nitrophenylamino)coumarin **(3e)**: M.p. 252 °C. IR (KBr): 3291, 2935, 1666, 1556, 1373, 1282, 1255 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 4.98, s, 1H; 7.40–8.21, m, 7H; 9.10, br s, 1H. Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.81; H, 3.60; N, 9.95.

4-(1,3-benzothiazol-2-ylamino)coumarin **(3f)**: M.p. 246 °C. IR (KBr): 3350, 2900, 1666, 1490, 1373, 1282, 1255 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.10, s, 1H; 7.36–8.32, m, 8H; 9.20, br s, 1H. Anal. Calcd for $C_{16}H_{10}N_2O_2S$: C, 65.29; H, 3.42; N, 9.52. Found: C, 65.31; H, 3.45; N, 9.51.

3,4-dihydro–2H,5H-[1]benzopyrano[3,4-e][1, 3]oxazin-5-one **(3g)**: M.p. 285 °C. IR (KBr): 3250, 2859, 1659, 1410, 1373, 1295, 1252 cm^{-1}. ^{1}H NMR (DMSO-d_6):δ = 2.60, br s, 1H; 3.25, s, 2H; 5.22, s, 2H; 7.15–7.54, m, 4H. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.00; H, 4.45; N, 6.90.

4-Morpholinocoumarin **(3h)**: M.p. 149 °C (lit[15]. m.p. 150–152 °C). IR (KBr): 3020, 2980, 1700, 1600, 1550, 1400, 1340, 1290, 1250, 1100 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.25, t (*J* = 4.5Hz), 4H; 3.93, t (*J* = 4.5Hz), 4H; 5.73, s, 1H; 7.61–7.22, m, 4H.

4-Cyclohexylaminocoumarin **(3i)**: M.p. 220 °C. IR (KBr): 3030, 2955, 1685, 1460, 1295, 1235 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.5, bs, 10H; 2.82, m, 1H; 5.15, s, 1H; 7.36–8.30, m, 5H. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.02; H, 7.06; N, 5.75.

4-Pentylaminocoumarin **(3j)**: M.p. 170 °C (lit.[16] m.p. 169–171 °C). IR (KBr): 3020, 2980, 1610, 1550, 1456, 1340, 1290, 1250 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.96, t (*J* = 6.5Hz), 3H; 1.32–1.55, m, 6H; 2.85, t (*J* = 6.5Hz), 2H; 5.18, br s, 2H; 7.61–7.22, m, 4H.

4-Phenethylaminocoumarin **(3k)**: M.p. 171 °C (lit.[16] m.p. 169–171°C). IR (KBr): 3250, 2955, 1650, 1515, 1425, 1340, 1288, 1260 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.8–3.0, m, 5H; 5.18, s, 2H; 7.2–8.22, m, 9H.

4-Aminocoumarin **(3l)**: M.p. 199 °C. IR (KBr): 3250, 2955, 1650, 1515, 1425, 1340, 1288, 1260cm^1. ^{1}H NMR (DMSO-d_6): δ = 5.18, br s, 3H; 7.2–8.22, m, 4H. Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.05; H, 4.40; N, 8.70.

The author is grateful to Professor B.P. Bandgar, S.R.T.M.U. University, Nanded (M. S.), India for helpful suggestions and Dr A.R Joseph, Bar-Ilan University, Israel for spectral analysis. Special thanks to the University of Mumbai for providing the financial assistance (APD/237/2187 of 2004, project number 16).

Received 28 May 2005; accepted 15 July 2005
Paper 05/3275

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