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Synthesis of novel carboxylated benzoxazolylcoumarins

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Six novel coumarins containing carboxylic ester or acid groups were prepared. The compounds were characterised by the usual methods. In a few cases the fluorescence data were obtained.

Coumarins are a family of compounds that have been studied extensively for their practical applications,[1] as textile dyes,[2] optical brighteners, laser dyes, sensitisers in phototherapy, biological labels. Coumarin derivatives have been also used in making fluorogenic enzyme substrates.[3]

Disperse dyes containing an electron-donating group, such as N,N-diethylamino, and an heterocyclic residue in position 3 are widely used as optical brighteners for polyester, polyamide and polyvinyl chloride plastics.[4]

Several 7-hydroxycoumarins substituted in position 3 are efficient laser dyes and the lasing range is amplified if there is an heterocyclic ring at this position.[5]

Recently, we have been working with compounds containing S, N or O heterocycles linked to a benzoxazole.[6-8] In this paper we report the synthesis of coumarinyl-benzoxazole derivatives with carboxylic groups on the benzoxazole moiety (Fig. 1). This type of compound would enlarge the scope of the potential applications for industrial [9] or biological purposes. [3]

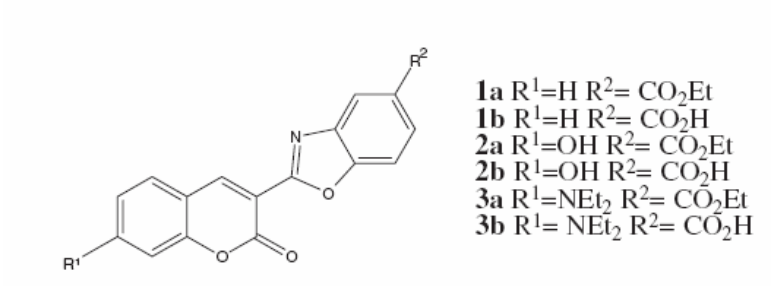
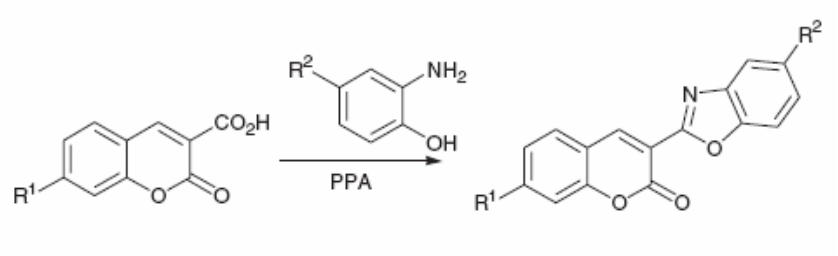


Fig. 1 Structures of compounds **1–3.**

Three different methods were used in attempts to improve the yield in the preparation of compounds **1**–**3** (Schemes 1–3). The final cyclisation in method 1 was achieved in polyphosphoric acid as described by Carpignano.[10] When a carboxylated coumarin was heated with 3-amino-4-hydroxybenzoic acid at high temperature with PPA (Scheme1, R^2=CO_2H), decarboxylation was

observed thus giving low to moderate yields (Table 1, **1b**, **2b** and **3b**). To overcome this problem ethyl *ortho*-aminobenzoate was prepared and used in the same way, (Scheme 1, R^2=CO_2Et). The final compounds were obtained in partially hydrolysed form. An extreme case was one of the preparations of **3a**, where the final mixture contained only a small amount of the product. After purification the ester, **3a**, was obtained in 10% yield still contaminated with the acid (the hydrolysis occurred during purification) and the main product of this reaction (40%) was 7-*N*,*N*-diethylcoumarin.



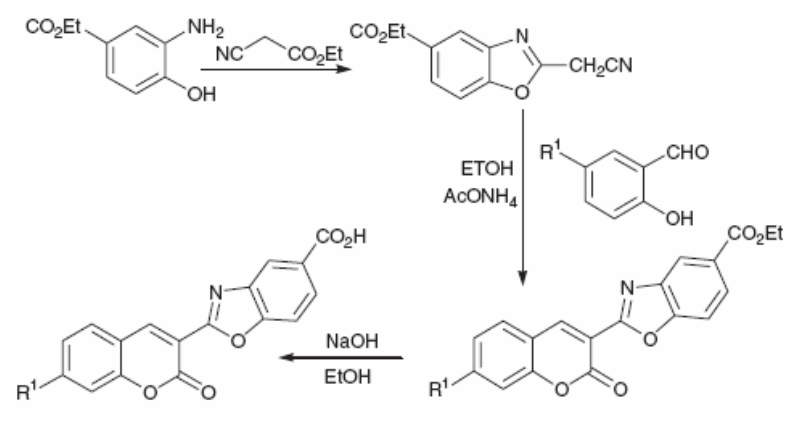
Scheme 1

Table 1 Yields, purification details and physical properties of dyes

Dye	Method	Yield (%)[a]	Purification solvent[b]	Appearance
1a	1	56	B	Ligh gray solid
	3	64[c]	-	
1b	1	7	B	Light yellow solid
2a	1	10	A	Yellow solid
	2	36		
2b	1	32	C	Yellow solid
		77[d]		
3a	1	23	B	Dark yellow solid
3b	1	42	D	Dark yellow solid
	2	50	D[e]	Light brown solid

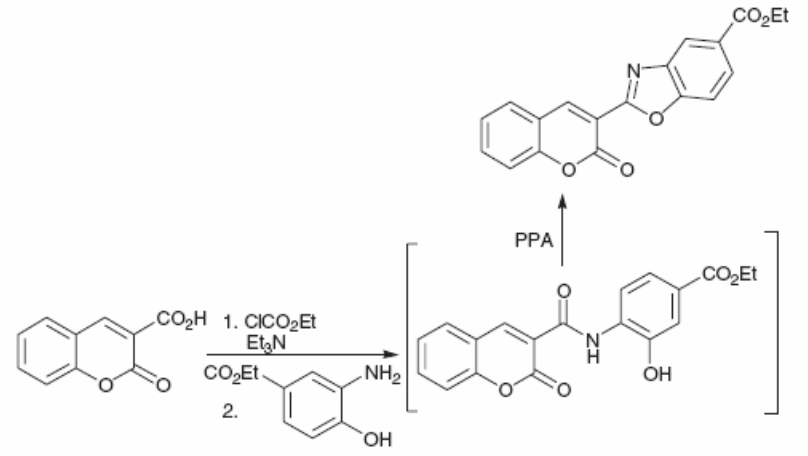
[a]After purification [b]A: DMF-MeOH; B: DMF- acetone; C: MeOH; D: acetone; E: Diethyl ether; F: $CHCl_3$/ether; [c]Mixture of acid and ester in 1:1 proportion [d]Obtained by hydrolysis of **2a**. [e]Contaminated with 7-*N*,*N*-diethylcoumarin-3-carboxylic acid.

A second method was used in which the suitable 2-cyanomethylbenzoxazole was prepared first and then reacted with the corresponding *ortho*-hydroxybenzaldehyde (Scheme 2).[5,11] The yield for compound **2a** improved by this method. Attempts to purify compound **3b** further led to decomposition mainly to the 7-*N*,*N*-diethylcoumarin-3-carboxylic acid possibly due to hydrolysis of the oxazole ring.[12]



Scheme 2

The third route started from the same coumarin as method 1. This was activated by reaction with ethylchloroformate to the mixed anhydride and then this was reacted with the corresponding substituted *ortho*-aminophenol (Scheme 3). The crude amide which was formed was then heated with PPA in order to obtain the final compound. This method was used for the preparation of **1a**, but the final mixture contained both **1a** and **1b** in 1:1 proportion, as deduced by NMR. (Table 1).



Scheme 3

All the compounds were characterised by spectroscopic methods. The fluorescence spectra were obtained except for compound **3b**. It was not possible to obtain **3b** in a pure enough form for fluorescence analysis (Table 2).

Table 2 Spectroscopic data for fluorescent compounds

	UV- Visible[a]			
	Absorption		λmax (nm)	
	λmax (nm)	ε ($mol^{-1}/dm^3/cm^{-1}$)	Excitation	Emission
1a	347	11554	350	439
1b	352	11 444	350	450
2a	447	23504	447	475
2b	445.5	19398	447	476
3a	429	24000	450	490

[a]Absorption and fluorescence spectra were measured in ethanol.

Examination of Table 2 shows that the introduction of a donating group in the coumarin ring gave a bathochromic shift in the absorption spectra (100 nm for **2a** and 82 nm for **3a**).

Fig. 2 shows the absorption and emission spectra of **1b**, which was the compound that gave the larger Stokes shift in this study (Table 2).

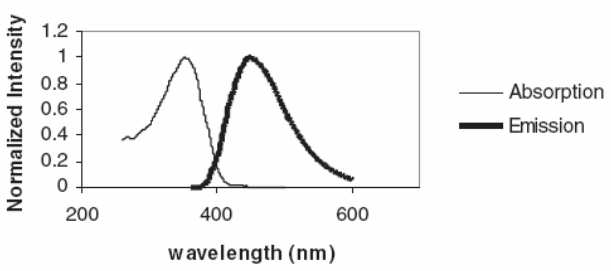


Fig. 2 Absorption and emission spectra of **1b** in ethanol.

Experimental

The infrared spectra were determined in Nujol and on a Perkin Elmer FTIR-1600 or Shimadzu UV-3101 PC spectrometers. ^{1}H NMR spectra were obtained on a Varian Unity Plus Spectrometer at 300 MHz, and Me_4Si or the solvent peak was used as reference. Electron impact mass spectra were recorded on a Unicam GC/MS 120 by direct insertion.

FAB and high resolution mass spectra were run on a VG Ultima HRMS or an Auto Spec E spectrometer. UV-visible spectra were determined on a Hitachi U-2000. Fluorescence spectra were determined on a SPEX FLUOROLOG-2 analyser, with double monochromator and an emission Xenon lamp of 4450 watts. Elemental analyses were carried out on a Leco CHNS 932 instrument. All melting points were measured on a Gallenkamp apparatus and are uncorrected. TLC was carried out on plates coated with 0.25 mm thick silica gel 60 F_{254}. Column chromatography was performed on silica gel (<230 mesh).

Synthesis of carboxylated chromen-3-yl-benzoxazole: general procedures

Method 1

A mixture of coumarin (0.5 mmol), the suitable *ortho*-aminophenol (2.5 mmol) and polyphosphoric acid (10 g) was heated at 160 °C for 1.5–2 hours. After cooling, water (40ml) and then a 5M NaOH solution (20 ml) were added. The precipitate was filtered, washed with water and dried at 60°C. After analysis by TLC (thin layer chromatography) it was purified by crystallisation or chromatography.

Method 2

A mixture of ethyl cyanoacetate (5 mmol) and the corresponding *ortho*-aminophenol (5 mmol) was heated at 180°C in an oil bath for 2 hours. After cooling ammonium acetate (5 mmol), ethanol (5 ml) and the corresponding hydroxybenzaldehyde (5 mmol) were added and the mixture was refluxed for 30 minutes. A mixture of water and ethanol (15ml, 2:1) was added and the precipitate was filtered.

In the preparation of **3b** DMF was used as solvent. After cooling water was added and the precipitate was filtered.

Preparation of 2-(2'-Oxo-2'H-chromen-3'-yl)-benzoxazole-5-carboxylic acid ethyl ester (**1a**) by *Method 3*

To an ice cold suspension of coumarin-3-carboxylic acid (1 mmol) in acetone (10 ml) ethyl chloroformate (0.15 ml, 1.2 mmol) and triethylamine (0.164 ml, 1.2 mmol) were added. The initially orange suspension turned light yellow and a white solid precipitated after 10 minutes. The triethylamine hydrochloride was filtered off and, the appropriate *ortho*-aminophenol (1 mmol) was added to the filtrate.The mixture was stirred at room temperature overnight. The yellow suspension was evaporated to dryness and a yellow solid (the amide) was obtained which was pure by TLC. PPA (ca 5 g) was added to the amide and the mixture was heated at 150–170 °C for 4 hours. After cooling, water was added, a reddish-orange solution was formed and then 5M NaOH solution was added until the pH was 7. A yellow oil separated that solidified overnight. This solid was purified by crystallisation.

2-(2'-Oxo-2'H-chromen-3'-yl)-benzoxazole-5-carboxylic acid ethyl ester **(1a)**: The compound does not melt below 350 °C. δ_H (Acetone-d_6) 1.44 (3H, t *J* 7.0 Hz, $CH_2\mathit{CH_3}$), 4.43 (2H, q *J* 7.0 Hz, $\mathit{CH_2}CH_3$), 7.48–7.56 (2H, m, 6' and 8'-H), 7.84 (1H, dt *J* 8.0 Hz, 7'-H), 7.89 (1H, d *J* 8.8 Hz, 7-H), 8.05 (1H, dd *J* 8.0 and 1.5 Hz, 5'-H), 8.20 (1H, dd *J* 8.8 and 1.5 Hz, 6-H), 8.45 (1H, d *J* 1.5 Hz, 4-

H), 9.06 (1H, s, 4'-H). EI (*m/z* %) 358(M^++Na, 9) 336(M^++H, 100) *336→308(336–328) 264(336–372) 308→290 280 264. ν_{max} 1744, 1707, 1607 cm^{-1}. Calc. for $C_{19}H_{13}N_2O_5$ 335.0794. Found 335.0782.

*2-(2'-Oxo-2'*H*-chromen-3'-yl)-benzoxazole-5-carboxylic* **(1b)**: The compound does not melt below 350 °C. δ_H (DMSO-d_6) 7.46 (1H, t *J* 8.0 Hz, H-6'), 7.50 (1H, d *J* 8.0 Hz, H-8'), 7.77 (1H, dt *J* 8.0 and 1.5 Hz, H-7'), 7.93 (1H, d *J* 8.4 Hz, H-7), 8.02 (1H, dd *J* 8.0 and 1.5 Hz, H-5'), 8.08 (1H, dd 8.4 and 1.5 Hz, H-6), 8.35 (1H, br s, H-4), 9.14 (1H, s, H-4'), 13.20 (1H, very br s, COO*H*). EI (*m/z*, %) 307(M+, 90) 279(18) 235(32) 206(10) 91(40) 73(80) 56(100). ν_{max} 3474 (br), 1747, 1704, 1606 cm^{-1} Calc. for 308.0559 $C_{17}H_{10}NO_5$. Found 308.0550 (FAB^+).

*2-(7'-Hydroxy-2'-oxo-2'*H*-chromen-3'-yl)-benzoxazole-5-carboxylic acid ethyl ester* **(2a)**: m.p. 257–260 °C. δ_H ($CDCl_3$) 1.35 (3H, t *J* 7.2 Hz, CH_2CH_3), 4.55 (2H, q *J* 7.2 Hz, CH_2CH_3), 6.79 (1H, d *J* 1.8 Hz, 8'-H), 6.88 (1H, dd *J* 8.5 and 1.8 Hz, 6'-H), 7.84 (1H, d *J* 8.5 Hz, 5'-H), 7.90 (1H, d *J* 8.7 Hz, 7-H), 8.05 (1H, dd *J* 8.5 and 1.5 Hz, 6-H), 8.31 (1H, d *J* 1.5 Hz, 4-H), 8.99 (1H, s, 4'-H), OH not observed). EI (*m/z*, %) 351(M+, 3) 379(9) 306(6) 278(2) 250(2) 189(2) 162(4). ν_{max} 3514–3114 (br), 3309, 1701, 1617 cm^{-1}. Calc. For $C_{19}H_{13}NO_6$. H_2O C, 61.79; H, 4.07, N, 3.79. Found C, 61.34; H, 4.56; N, 3.87.

*2-(7'-Hydroxy-2'-oxo-2'*H*-chromen-3'-yl)-benzoxazole-5-carboxylic acid* **(2b)**: 1M NaOH (1.35 ml, 1.35 mmol) was added under stirring to a soln. of compound **2a** (0.315 g, 0.897 mmol) in ethanol (15 ml) at room temperature. After stirring for 4 hours the mixture was cooled in an ice-water bath and acidified to pH 3 with 5M HCl. After storage in the cold overnight the precipitate was collected on a filter, washed thoroughly with water and air dried to yield a brown solid (0.224 g, 77%). Purification by PLC (ethyl acetate/light petroleum, 1:1) yielded the title compound as a yellow solid; decomposes without melting above 300 °C; δ_H (DMSO-d_6) 6.95 (1H, d *J* 8.2 Hz, 6'-H), 7.15 (1H, d *J* 8.2 Hz, 5'-H), 7.32 (1H, s , 8'-H), 7.75 (1H, d *J* 8.2 Hz, 7-H), 7.82 (1H, d *J* 8.2 Hz, 6-H), 8.90 (1H, s, 4-H), 9.90 (1H, s, 4'-H), 11.10 (1H, s, OH). The second OH signal is not observed. ν_{max} 3408, 1704, 1614 cm^{-1}. Calc. for $C_{17}H_{10}NO_6$ 324.0508. Found 324.0508 (M^++1, FAB^+).

*2-(7'-Diethylamino-2'-oxo-2'*H*-chromen-3'-yl)-benzoxazole-5- carboxylic acid ethyl ester* **(3a)**: Decomposes without melting above 270 °C. δ_H ($CDCl_3$) 1.20 (6H, t *J* 7.5 Hz, 2x CH_2CH_3), 1.42 (3H, t *J* 7.5 Hz, CH_2CH_3), 3.50 (4H, q *J* 7.5 Hz, 2x CH_2CH_3), 4.40 (2H, q *J* 7.5 Hz, CH_2CH_3), 6.56 (1H, d *J* 1.8 Hz, 8'-H), 6.68 (1H, dd *J* 8.2 and 1.8 Hz, 6'-H), 7.44 (1H, d *J* 8.2 Hz, 5'-H), 7.90 (1H, d *J* 9.0 Hz, 7-H), 8.10 (1H, dd *J* 9.0 and 1.5 Hz, 6-H), 8.50 (1H, d *J* 1.5 Hz, 4-H), 8.64 (1H, s, 4'-H).

EI (*m/z*, %) 406(6) 391(3) 363(5) 204(15) 91(22). ν_{max} 3070, 1704, 1621, 1602 cm^{-1}. Calc. for $C_{23}H_{22}N_2O_5$ 406.1529. Found 406.1527.

*2-(7'-Diethylamino-2'-oxo-2'*H*-chromen-3'-yl)-benzoxazole-5-carboxylic acid* **(3b)**: Decomposes without melting above 250 °C. δ_H(DMSO-d_6) 6.60 (1H, d *J* 2.0 Hz, 8'-H), 6.80–6.88 (1H, m, 6'-H), 7.65 (1H, d *J* 9.0 Hz, 5'-H or 7-H), 7.70 (1H, d *J* 9.0 Hz, 5'-H or 7-H), 8.00 (1H, dd *J* 9.0 and 2.1 Hz, 6-H), 8.20 (1H, d *J* 2.0 Hz, 4-H), 8.64 (1H, s, OH), 8.82(1H, s, 4'-H). EI (*m/z*, %) 406(6) 391(3) 363(5) 204(15) 91(22).ν_{max} 3378, 1702, 1611 cm^{-1}. Calc. For $C_{21}H_{19}N_2O_5$ 379.1294. Found 379.1280 (M^++1, FAB^+).

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