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Contributed Paper

Syntheses and UV Spectroscopic Study of Mono- and Dialkyloxy-4-methylcoumarins

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ABSTRACT

Mono- and dialkyloxy-4-methylcoumarins were successfully synthesized starting from dihydroxy-4-methylcoumarins and an alkyl bromide, butyl bromide or octyl bromide, at 1:1 molar ratio. The alkylation of 5,7-dihydroxy-4-methylcoumarin gave 5,7-dialkyloxy-4-methylcoumarin and two monoalkyloxy-4-methylcoumarins with substitution at 5 and 7 positions. For 6,7- and 7,8-dihydroxy-4-methylcoumarins, the corresponding dialkyloxy-4-methylcoumarins and only monoalkyloxy-4-methylcoumarins at the 7 position were obtained. UV absorption studies of the dihydroxy-4-methylcoumarins and their mono- and dialkyloxy products showed a red shift of the maximum absorption wavelengths compared to 4-methylcoumarins. Additionally, substitution of a hydroxyl or alkyloxy group at the 6-position caused a further red shift. The dimerization degree from decreasing of UV absorbance revealed that it depended on the substitution positions. Among all these coumarin derivatives, 5,7-dibutyloxy-4-methylcoumarin exhibited the highest dimerization degree.

Keywords: monoalkyloxycoumarin, dialkyloxycoumarin, dimerization, substitution effect

1. INTRODUCTION

Coumarins are widespread in nature and well known as physiologically active compounds. Coumarin derivatives have been used in many medical treatments, such as antibacterial [1], antiviral including anti-HIV agents [2, 3], and drug devices [4]. Coumarins have been attracted in material applications because of their excellent photochemical properties. The photodimerization of coumarins is one of the most desirable properties. Coumarins can undergo photodimerization via a [2+2]-cycloaddition after irradiation with wavelength longer than 300 nm. In addition, irradiation at 254 nm leads to the reversal of the cyclobutane based dimer [5, 6].

The reversible photo-induced dimerization of coumarin moieties incorporated into polymers has received great interest in a large variety of applications

[7], such as photoresponsive polymers [8-11], polymeric micelles [12-15], self-healing polymers [16-17], polymeric drug delivery [18-20], and self-assembled polymers [21-23].

In many of these applications, however, the coumarin moieties were normally parent coumarin or 7-hydroxy-coumarin. There have been a few reports on the photochemical properties of mono- and dialkyloxy substituted coumarins where alkyloxy coumarins were used. Ramamurthy et al. [24, 25] reported the effect of alkyloxy substitution for the formation of the coumarin dimer. In aqueous and micellar systems, a simple coumarin yielded 6-21% of dimer after 20-22 hours of irradiation while the alkyloxy coumarins showed dimer yields up to 75% after 45 hours of irradiation. The photostability of hydroxy and alkyloxy substituted 4-methylcoumarins were studied by Jivaramonaikul et al. [26]. It was determined that in the 7,8-substitution and the 5,7-substitution, the dihydroxy substitution showed the highest degree of photostability while in the 6,7-substitution, the alkyloxy substitution demonstrated the highest photostability.

Since the dimerization degree and photostability are important in the applications of substituted coumarins, we reported the successful syntheses and characterization of fourteen mono- and dialkyloxy-4-methylcoumarin derivatives via an alkylation reaction. The UV absorption and the dimerization degree of each derivatives were studied and compared to address the effect of hydroxy and alkyloxy substitutions at various positions on the benzene ring of the coumarin structure on dimerization.

2. MATERIALS AND METHODS

2.1 Chemicals and Instruments

All commercially available chemicals and solvents were purchased and used without further purification. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on BRUKER® NMR spectrometer and Varian spectrometer with DMSO-d_6 as solvent. FTIR spectra were recorded on NICOLET 6700 FTIR spectrometer. UV absorption spectra were recorded on VARIAN CARY 100 Conc. Spectrometer. UVP Black-Ray B-100 UV 100 watts was used as a UV source at 365 nm. Melting points were measured on BIBBY SMP10 and ELECTROTHERMAL 120VAC Fuse type with Digital Thermometer (Fluke).

2.2 Experiments

2.2.1 Preparation of dihydroxy coumarins*

To synthesize 5,7-dihydroxy-4-methyl-coumarin (H5H7), phloroglucinol (1.00 g, 8 mmol), oxalic acid (0.41, 3 mmol) and ethyl acetoacetate (1.00 mL) were added into a 100 mL round bottom flask. The liquid mixture was stirred in an oil bath at temperature 85 °C for 1.5 hours. The reaction was monitored by TLC. After cooling to room temperature, the precipitates were filtered and washed with cold water. The product was recrystallized in ethanol. Similarly, 7,8-dihydroxy-4-methylcoumarin (H7H8) was synthesized as described above, except that phloroglucinol was replaced with pyrogallol.

5,7-Dihydroxy-4-methylcoumarin (H5H7). Pale yellow crystals (60%), mp. 296-300 °C, FTIR-ATR (neat, cm^{-1}) 3413, 3115, 3029, 2989, 1655. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.52 (1H, s, ArO<u>H</u>), 10.29 (1H, s, ArO<u>H</u>), 6.23 (1H, s, Ar<u>H</u>), 6.14 (1H, s, Ar<u>H</u>), 5.83 (1H, s, CH_3CC<u>H</u>), 2.45 (3H, s, CC<u>H_3</u>).

7,8-Dihydroxy-4-methylcoumarin (H7H8). Pale orange crystals (58%), mp.

242-243 °C, FTIR-ATR (neat, cm^{-1}) 3215, 3103, 2986, 1643, 1577. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (1H, s, ArOH), 9.30 (1H, s, ArOH), 7.08 (1H, d, J = 8.6 Hz, ArH), 6.80 (1H, d, J = 8.6 Hz, ArH), 6.10 (1H, s, CH_3CCH), 2.35 (3H, s, CCH_3).

2.2.2 Preparation of alkyloxy coumarins*

5,7-Dihydroxylcoumarin (H5H7) (0.14 g, 7 mmol) was reacted with butyl bromide (0.75 mL, 7 mmol) or octyl bromide (1.20 mL, 7 mmol) in DMF using potassium carbonate (7 mmol) as a base. The solution was stirred in oil bath at temperature 90 °C overnight. The solution was extracted with ethyl acetate 20 mL, and washed with water 3 times. The crude product was evaporated to remove the ethyl acetate. The crude product was separated by silica gel column chromatography using 3:2 hexanes:ethyl acetate as mobile phase. The TLC showed three types of products and a trace of starting material for both reactions.

5,7-Dibutyloxy-4-methylcoumarin (B5B7). Pale yellow powder (27%), mp. 69-72 °C, FTIR-ATR (neat, cm^{-1}) 2955, 2929, 2869, 1715, 1597. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.50 (1H, s, ArH), 6.41 (1H, s, ArH), 5.95 (1H, s, CH_3CCH), 4.02 (4H, t, J = 5.5 Hz, $2OCH_2CH_2$), 2.46 (3H, s, CCH_3), 1.70 (4H, m, $2CH_2CH_2CH_2$), 1.42 (4H, m, $2CH_2CH_2CH_3$), 0.92 (6H, m, $2CH_2CH_3$).

7-Butyloxy-5-hydroxy-4-methylcoumarin (B7H5). White powder (13%), mp. 165-168 °C, FTIR-ATR (neat, cm^{-1}) 3155, 3069, 2955, 2923, 1669, 1594. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.66 (1H, s, ArOH), 6.42 (1H, s, ArH), 6.32 (1H, s, ArH), 5.94 (1H, s, CH_3CCH), 4.00 (2H, t, J = 6.2 Hz, OCH_2CH_2), 2.50 (3H, s, CCH_3), 1.70 (2H, m, $CH_2CH_2CH_2$), 1.42 (2H, m, $CH_2CH_2CH_3$), 0.94 (3H, t, J = 6.6 Hz, CH_2CH_3).

5-Butyloxy-7-hydroxy-4-methylcoumarin (B5H7). White powder (12%), mp. 179-183 °C, FTIR-ATR (neat, cm^{-1}) 3310, 3126, 3066, 2955, 2923, 2869, 1675. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.51 (1H, s, ArOH), 6.30 (1H, s, ArH), 6.27 (1H, s, ArH), 5.89 (1H, s, CH_3CCH), 3.97 (2H, t, J = 6.2 Hz, OCH_2CH_2), 2.45 (3H, s, CCH_3), 1.74 (2H, m, $CH_2CH_2CH_2$), 1.44 (2H, m, $CH_2CH_2CH_3$), 0.92 (3H, t, J = 7.8 Hz, CH_2CH_3).

5,7-Dioctyloxy-4-methylcoumarin (O5O7). Pale yellow powder (24%), mp. 47-50 °C, FTIR-ATR (neat, cm^{-1}) 2917, 2851, 1720, 1603. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.54 (1H, s, ArH), 6.46 (1H, s, ArH), 6.00 (1H, s, CH_3CCH), 4.05 (4H, t, J = 7.0 Hz, $2OCH_2CH_2$), 2.50 (3H, s, CCH_3), 1.74 (4H, m, $2CH_2CH_2CH_2$), 1.42 (4H, m, $2CH_2CH_2CH_2$), 1.27 (16H, m, $2CH_2(CH_2)_4CH_3$), 0.87 (6H, t, J = 6.6 Hz, $2CH_2CH_3$).

5-Hydroxy-4-methyl-7-octyloxycoumarin (H5O7). White powder (10%), mp. 151-154 °C, FTIR-ATR (neat, cm^{-1}) 3075, 2914, 2851, 1666, 1600. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.66 (1H, s, ArOH), 6.41 (1H, s, ArH), 6.31 (1H, s, ArH), 5.94 (1H, s, CH_3CCH), 3.99 (2H, t, J = 6.2 Hz, OCH_2CH_2), 2.50 (3H, s, CCH_3), 1.71 (2H, m, $CH_2CH_2CH_2$), 1.40 (2H, m, $CH_2CH_2CH_2$), 1.28 (8H, m, $CH_2(CH_2)_4CH_3$), 0.87 (3H, t, J = 6.0 Hz, CH_2CH_3).

7-Hydroxy-4-methyl-5-octyloxycoumarin (H7O5). White powder (15%), mp. 157-161 °C, FTIR-ATR (neat, cm^{-1}) 3338, 3123, 3072, 2937, 2917, 2849, 1677, 1603. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.51 (1H, s, ArOH), 6.34 (1H, s, ArH), 6.30 (1H, s, ArH), 5.92 (1H, s, CH_3CCH),

4.00 (2H, t, J = 5.5 Hz, OC$\underline{H}_2$CH$_2$), 2.50 (3H, s, CC$\underline{H}_3$), 1.78 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.44 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.28 (8H, m, CH$_2$(C$\underline{H}_2$)$_4$CH$_3$), 0.87 (3H, t, J = 5.8 Hz, CH$_2$C$\underline{H}_3$).

The alkylation of 6,7-dihydroxy-4-methylcoumarin (H6H7) and 7,8-dihydroxy-4-mehylcoumarin (H7H8) were carried out in the same manner as described for H5H7.

6,7-Dibutyloxy-4-methylcoumarin (B6B7). Pale yellow powder (18%), mp. 77-80 °C, FTIR-ATR (neat, cm^{-1}) 2957, 2935, 2872, 1703. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.20 (1H, s, Ar$\underline{H}$), 7.01 (1H, s, Ar$\underline{H}$), 6.24 (1H, s, CH$_3$CC$\underline{H}$), 4.10 (4H, m, 2OC$\underline{H}_2$CH$_2$), 2.45 (3H, s, CC$\underline{H}_3$), 1.76 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_2$), 1.52 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_3$), 0.96 (6H, t, J = 7.0 Hz, CH$_2$C$\underline{H}_3$).

7-Butyloxy-6-hydroxy-4-methylcoumarin (H6B7). Pale yellow powder (40%), mp. 156-159 °C, FTIR-ATR (neat, cm^{-1}) 3166, 3075, 2957, 2923, 2866, 1686. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25 (1H, s, ArO$\underline{H}$), 7.05 (1H, s, Ar$\underline{H}$), 7.00 (1H, Ar$\underline{H}$), 6.17 (1H, s, CH$_3$CC$\underline{H}$), 4.07 (2H, t, J = 5.4 Hz, OC$\underline{H}_2$CH$_2$), 2.34 (3H, s, CC$\underline{H}_3$), 1.74 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.48 (2H, m, CH$_2$C$\underline{H}_2$CH$_3$), 0.94 (3H, t, J = 6.6 Hz, CH$_2$C$\underline{H}_3$).

4-Methyl-6,7-dioctyloxycoumarin (O6O7). Pale yellow powder (25%), mp. 54-57 °C, FTIR-ATR (neat, cm^{-1} 2952, 2920, 2849, 1726. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.12 (1H, s, Ar$\underline{H}$), 7.00 (1H, s, Ar$\underline{H}$), 6.16 (1H, s, CH$_3$CC$\underline{H}$), 4.00 (4H, m, 2OC$\underline{H}_2$CH$_2$), 2.37 (3H, s, CC$\underline{H}_3$), 1.69 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_2$), 1.41 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_2$), 1.23 (16H, m, 2CH$_2$(C$\underline{H}_2$)$_4$CH$_3$), 0.83 (6H, t, J = 7.0 Hz, 2CH$_2$C$\underline{H}_3$).

6-Hydroxy-4-methyl-7-octyloxycoumarin (H6O7). Pale yellow powder (40%), mp. 111-112 °C, FTIR-ATR (neat, cm^{-1}) 3284, 2949, 2923, 2854, 1686. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.30 (1H, s, ArO$\underline{H}$), 7.07 (1H, s, Ar$\underline{H}$), 7.00 (1H, s, Ar$\underline{H}$), 6.20 (1H, s, CH$_3$CC$\underline{H}$), 4.07 (2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 2.36 (3H, s, CC$\underline{H}_3$), 1.76 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.44 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.28 (8H, m, CH$_2$(C$\underline{H}_2$)$_4$CH$_3$), 0.90 (3H, t, J = 6.2 Hz, CH$_2$C$\underline{H}_3$).

7,8-Dibutyloxy-4-methylcoumarin (B7B8). White powder (15%), mp. 71-72 °C, FTIR-ATR (neat, cm^{-1}) 2952, 2940, 2869, 1706, 1600. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.40 (1H, d, J = 8.8 Hz, Ar$\underline{H}$), 7.08 (1H, d, J = 8.6 Hz, Ar$\underline{H}$), 6.20 (1H, s, CH$_3$CC$\underline{H}$), 4.08 (2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 3.97 (2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 2.37 (3H, s, CC$\underline{H}_3$), 1.73 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.65 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.46 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_3$), 0.90 (6H, m, 2CH$_2$C$\underline{H}_3$).

7-Butyloxy-8-hydroxy-4-methylcoumarin (B7H8). White powder (30%), mp. 149-150 °C, FTIR-ATR (neat, cm^{-1}) 3233, 2958, 2869, 1578. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.35 (1H, s, ArO$\underline{H}$), 7.40 (1H, d, J = 8.6 Hz, Ar$\underline{H}$), 6.95 (1H, d, J = 8.6 Hz, Ar$\underline{H}$), 6.20 (1H, s,z,H CH$_3$CC$\underline{H}$), 4.06 (2H, t, J = 7.0 Hz, OC$\underline{H}_2$ CH$_2$), 2.43 (3H, s, CC$\underline{H}_3$), 1.75 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.55 (2H, m, CH$_2$C$\underline{H}_2$CH$_3$), 1.00 (3H, t, J 7.8 Hz, CH$_2$C$\underline{H}_3$).

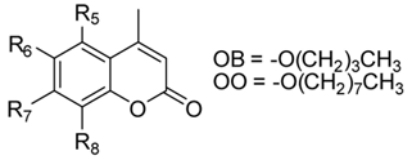
4-Methyl-7,8-dioctyloxycoumarin (O7O8). Pale yellow powder (25%), 38-41 °C, FTIR-ATR (neat, cm^{-1}) 2955, 2918, 2846, 1712. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45 (1H, d, J = 9.0 Hz, Ar$\underline{H}$), 7.10 (1H, d, J = 9.0 Hz, Ar$\underline{H}$), 6.22 (1H, s, CH$_3$CC$\underline{H}$), 4.10

(2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 4.00 (2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 2.40 (3H, s, CC$\underline{H}_3$), 1.76 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.70 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.47 (4H, m, 2CH$_2$C$\underline{H}_2$CH$_2$), 1.28 (16H, m, 2CH$_2$(C$\underline{H}_2$)$_4$CH$_3$), 0.87 (6H, t, J = 6.6 Hz, 2CH$_2$C$\underline{H}_3$).

8-Hydroxy-4-methyl-7-octyloxycoumarin (H8O7). Pale yellow powder (37%), mp. 106-108 °C, FTIR (neat, cm^{-1}) 3419, 2944, 2918, 2852, 1704, 1606. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.24 (1H, s, ArO$\underline{H}$), 7.18 (1H, d, J = 8.6 Hz, Ar$\underline{H}$), 7.03 (1H, d, J = 8.2 Hz, Ar$\underline{H}$), 6.20 (1H, s, CH$_3$CC$\underline{H}$), 4.08 (2H, t, J = 6.2 Hz, OC$\underline{H}_2$CH$_2$), 2.39 (3H, s, CC$\underline{H}_3$), 1.76 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.44 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.28 (8H, m, CH$_2$(C$\underline{H}_2$)$_4$CH$_3$), 0.87 (3H, t, J = 7.4 Hz, CH$_2$C$\underline{H}_3$).

*The chemical structure of all synthesized products is presented in Table 1.

Table 1. Syntheses and UV spectroscopic data of coumarin derivatives.



Compound	R_5	R_6	R_7	R_8	Yield[a] (%)	λ_{max} (nm)	ε ($M^{-1}cm^{1}$)	Dimerization data[b]	
								DD[c] (%)	Time (min)
4-methyl	H	H	H	H	-	310[d]	-	-	-
H7	H	H	OH	H	-	324	18600	56	1160
H5H7	OH	H	OH	H	-	323	12500	79	170
B5H7	OB	H	OH	H	12	324	15800	82	80
B7H5	OH	H	OB	H	13	320	16500	73	210
B5B7	OB	H	OB	H	27	324	17000	86	50
H7O5	OO	H	OH	H	15	324	15200	82	40
H5O7	OH	H	OO	H	10	321	14900	74	250
O5O7	OO	H	OO	H	24	321	14600	84	80
H6H7	H	OH	OH	H	-	347	10000	74	120
B7H6	H	OH	OB	H	40	345	12500	67	50
B6B7	H	OB	OB	H	18	343	12500	65	510
H6O7	H	H	OO	H	40	345	11200	73	80
O6O7	H	OO	OO	H	25	339	12200	74	630
H7H8	H	H	OH	OH	-	321	11600	50	1030
B7H8	H	H	OB	OH	30	317	13300	27	1140
B7B8	H	H	OB	OB	15	317	14700	5	1030
H8O7	H	H	OH	OH	37	318	13800	14	1140
O7O8	H	H	OO	OO	25	318	15800	6	1140

[a] Isolated yield from the alkylation reaction.

[b] Measured when no more change in absorption was observed.

[c] DD = dimerization degree; %DD = $(1-A_t/A_0) \times 100$ where A_0 and A_t are the initial absorbance and the absorbance at given irradiation time, respectively.

[d] Taken from reference no. 26.

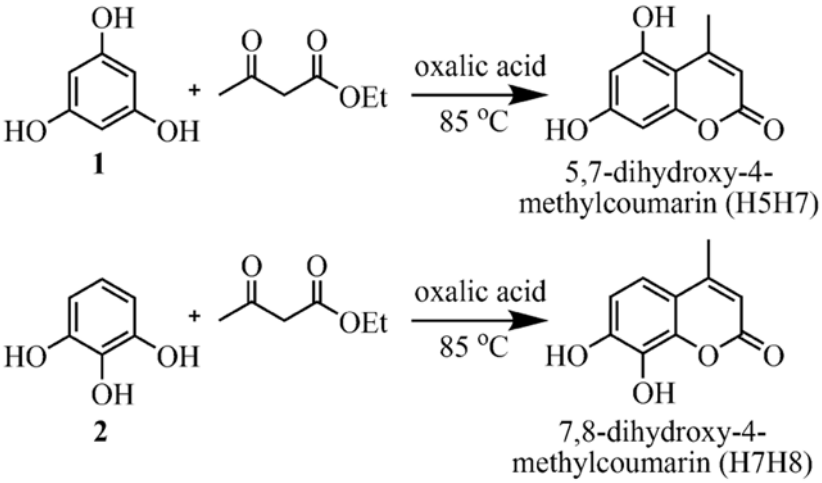
2.2.3 UV absorption study and the dimerization degree of mono- and dialkyloxy-coumarins

The 5×10^{-5} M solution of each of seventeen coumarin derivatives in DMSO was irradiated with UV light at 365 nm. After the given irradiation time, the absorbance of each solution at its maximum wavelength was recorded. The irradiation was continued until no change in the absorbance was observed. The dimerization degree (DD) was then calculated by $(1\text{-}A_t/A_0)\times100$, where A_0 and A_t are the initial absorbance and the absorbance at given irradiation time.

3. RESULTS AND DISCUSSIONS

3.1 Syntheses of Dihydroxycoumarins

5,7-Dihydroxy-4-methylcoumarin (H5H7) and 7,8-dihydroxy-4-methylcoumarin (H7H8) were successfully synthesized via the Pechmann condensation reaction from phloroglucinol (**1**) and pyrogallol (**2**), with 60% and 58% yields, respectively, as shown in Scheme 1. Their structures were clearly identified by the FTIR absorption spectra with the stretching vibration of C=O at 1650 cm^{-1}, aromatic C-H stretching at higher 3000 cm^{-1} and broad absorption band for O-H stretching in the range of 2800-3400 cm^{-1}. Their ^1H NMR spectra exhibited the characteristic olefinic proton at δ 6.1 ppm and the two hydroxyl protons in the range of δ 9-11 ppm. The commercially available 6,7-dihydroxy-4-methylcoumarin (H6H7) was also taken as another material in this study.



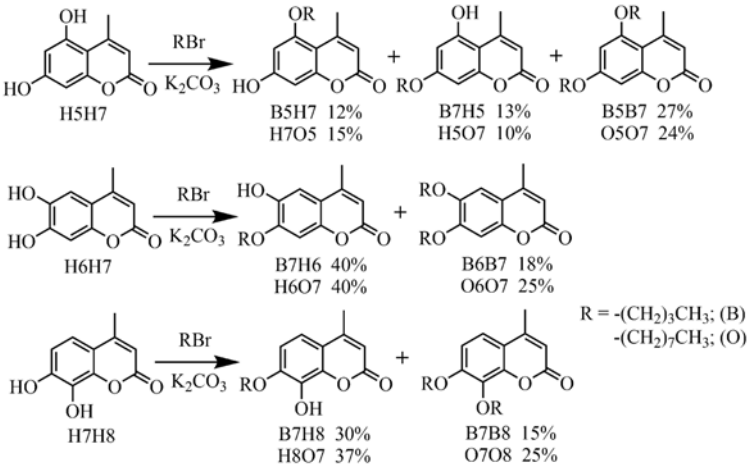
Scheme 1. Syntheses of two dihydroxy-4-methylcoumarins.

3.2 Syntheses of Alkyloxycoumarins

The alkyloxy coumarins were synthesized via an alkylation reaction. Two kinds of alkyl bromide, butyl bromide, and octyl bromide, were employed. One of these alkyl bromides was separately reacted with each of three dihydroxycoumarins (H5H7, H7H8 and H6H7) in the presence of potassium carbonate. A 1:1 molar ratio of a dihydroxycoumarin and alkyl bromide was used in order to obtain the monoalkyloxy products. The reaction was carried out overnight and monitored by TLC which showed some remaining dihydroxycoumarin in every case. The results, however, showed two mono- and one dialkyloxy products from

the reactions with H5H7, while one mono- and one dialkyloxy products were obtained in the case of H6H7 and H7H8, as shown in Scheme 2. These products are clearly identified by their ^{1}H NMR spectra. Figure 1 exhibited the typical ^{1}H NMR spectra of the dihydroxy-4-methylcoumarin and their alkyloxy products. The formation of the dialkyloxycoumarins, 5,7-dibutyloxy-4-methylcoumarin (B5B7) (Figure 1b) was evident from the vanishing of two signals at δ 10.52 and 10.29 ppm of the two hydroxyl protons of H5H7 (Figure 1a).

The ^{1}H NMR spectra of the other two products (Figure 1c and 1d), which had monoalkyloxy substitution at either the 5 or 7 position, were similar and the substituted position could not be clearly identified. The NOE difference technique was thus applied. As shown in Figure 2, the significant enhancement of the signal at δ 4.00 ppm (red circle in Structure I) was observed upon saturation of H_6 at δ 6.32 ppm and H_8 at δ 6.42 ppm (black arrowed). This observation indicated that the spectrum corresponded to Structure I, which was 7-butyloxy-5-hydroxy-4-methylcoumarin (H5B7). In the other case, the positive NOE at δ 3.97 ppm (red circle in Structure II) from saturation of H_6 at δ 6.30 ppm (black arrow) and no NOE observed from saturation of H_8 at δ 6.27 ppm indicated it was belonged to Structure II in Figure 2, which was 5-butyloxy-7-hydroxy-4-methylcoumarin (B5H7).



Scheme 2. Syntheses of alkyloxycoumarins.

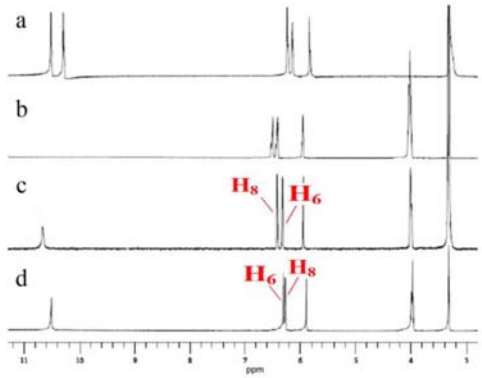


Figure 1. ^{1}H NMR spectra of (a) H5H7, (b) B5H7, (c) B7H5, (d) B5H7.

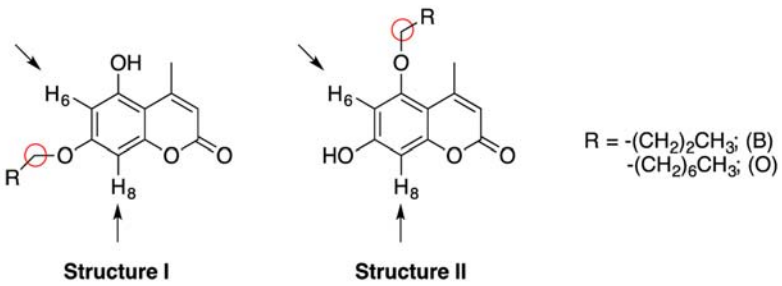
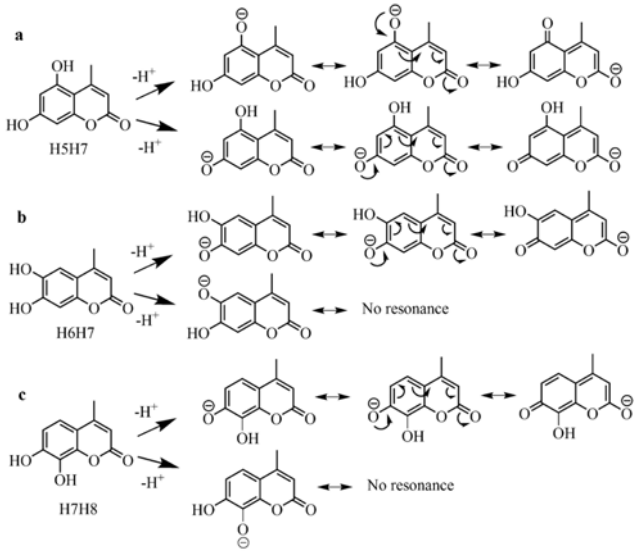


Figure 2. Proposed structure of 5- and 7-monoalkyloxy products from the reaction H5H7: arrows indicated where the protons were saturated, red circles indicated where the signals were enhanced.

Similarly, 5,7-dioctyloxy-4-methylcoumarin (O5O7) and two monooctyloxy products were obtained when H5H7 reacted with octyl bromide. In the same manner, NOE difference experiment was used to differentiate the two octyloxy products, 5-hydroxy-4-methyl-7-octyloxycoumarin (H5O7) and 7-hydroxy-4-methyl-5-octyloxy-coumarin (H7O5).

The formation of two monoalkyloxy products from H5H7 showed that there was no significant influence on the regioselectivity of the alkylation at 5 and 7 positions. This could be due to the existence of two anionic stabilized resonance structures as shown in Scheme 3a. Then the second alkylation could occur at the available 5 or 7 position of each monoalkyloxy product to yield the 5,7-dialkyloxycoumarins.

The other two dihydroxy coumarins, H6H7 and H7H8, were chosen for this study, as both of them could have only one anionic stabilized resonance structure, as shown in Scheme 3b and 3c. Indeed, the alkylation reaction of both compounds occurred preferentially at only the 7 position, to yield the corresponding monoalkyloxy products. The second alkylation at the other available hydroxyl group of each compound thus led to the dialkyloxy product. All these products were well characterized by their ^{1}H NMR spectra.

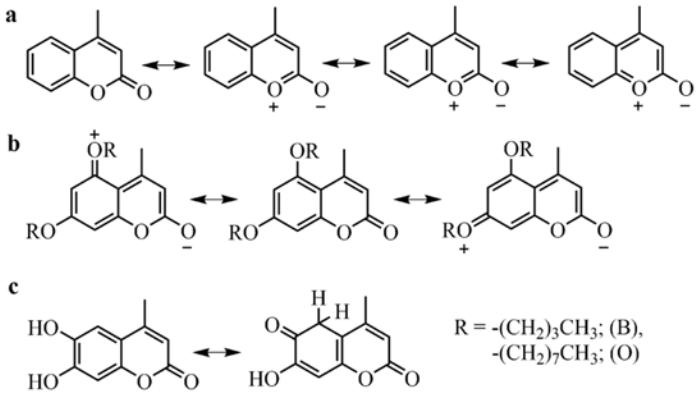


Scheme 3. Anionic resonance structures of (a) H5H7, (b) H6H7, and (c) H7H8.

It should be pointed out that the yield of all the products listed in Table 1 was the actual yield isolated by the column chromatography. Each reaction gave the total yield of all the products in the range of 45-65%. However, it could be stated that the alkylation of H5H7 with butyl bromide and octyl bromide afforded two monoalkyloxy products (B5H7, B7H5, and H7O5, H5O7) and one dialkyloxy product (B5B7 and O5O7) approximately at the ratio of 1:1. For H6H7 and H7H8, the alkylation with either butyl bromide or octyl bromide gave one monoalkyloxy product (B7H6 and H6O7, and B7H8 and H8O7) and one diakyloxy product B6B7 and O6O7, and B7B8 and O7O8) approximately at the ratio of 2:1. The resulting yields were consistent with the aforementioned explanation about the attribution of the anionic stabilized resonance structures of coumarin derivatives in the alkylation reaction.

3.2 UV Absorption Properties and Dimerization Degrees of Mono- and Dialkyloxy-coumarins

The UV absorption spectra of the dihydroxy-4-methylcoumarins and their mono- and dialkyloxy products showed a red shift of the maximum absorption wavelengths compared to 4-methylcoumarin as revealed in Table 1. This is due to the introduction of the hydroxy or alkyloxy groups at 5 and 7 positions. Generally, the parent coumarin is stabilized by the dipolar resonance structures as shown in Scheme 4a. The participation of the hydroxy and alkyloxy substituents leads to additional resonance structures (Scheme 4b) which cause the red shift [27]. In the case of the substitutions at 7 and 8 positions, there is only one additional resonance structure at the 7 position and so the maximum absorption appeared at wavelength 317-321 nm. For the substitution at 5 and 7 positions, two additional resonance structures gave a further red shift to 320-324 nm. The substitution at the 6 position does not give such additional resonance structures but instead, tautomerism can occur (Scheme 4c). Therefore, five coumarin derivatives, including H6H7, B7H6, B6B7, H6O7, O6O7, gave the further red shift to 339-347 nm, presumably due to the attribution of the ketonic tautomers.



Scheme 4. Resonance structures of (a) 4-methylcoumarin, (b) additional resonance structures of 5,7-disubstituted coumarin derivatives, and (c) tautomerism of H6H7.

After the UV irradiation by time, the decreasing absorbance of the coumarin unit at its maximum wavelength is directly proportional to the formation of the dimer. Then, this concept can be applied for the calculation of dimerization degree as other research groups also reported [28, 29]. All the measurements in this dimerization study were made in dimethyl sulfoxide (DMSO) to ensure full solubility of all of the coumarin derivatives. The dimerization of each coumarin derivative was monitored by UV-vis spectroscopic technique and the UV-vis spectra at various irradiation times were recorded. Figure 3 shows the UV-vis spectra of the B5B7 at various given irradiation times. The absorption of B5B7 at wavelength 324 nm decreased over time. From the UV-vis spectra, the DD of the coumarin derivatives could be calculated. The DD of each coumarin derivative was determined during irradiation until no more change in UV-vis absorption measurement. Table 1 listed the highest DD at certain irradiation time of each coumarin derivative. The addition of a hydroxyl or alkyloxy group to the 5-position increases the DD. Changing the -OH to an -OR at both the 5- and 7- positions appears to enhance the DD. This indicates that the symmetry of the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) is changed which lets the energy gap of those two orbitals becomes smaller in the case of either short or long alkoxy substituents at 5,7-position comparable with H5H7. As discussed earlier, substitutions at the 5- and 7-positions allow for an additional two resonance structures compared to the parent 4-methylcoumarin. Substitution of an alkyl group of any length in place of hydrogen appears to assist in overall stabilization, which is expected to enhance the DD. In comparison, the substitution patterns of the 6,7-moieties indicate that an additional hydroxy or alkyloxy group enhances the overall DD, but it is not affected by changing from an -OH to an -OR group. On the other hand, this implies that alkoxy substituents at 6,7-position do not change the symmetry of LUMO and HOMO of the H6H7 molecule which lets the electronic transition is not disturbed. As shown in Figure 4, the plot of the increase in DD with irradiation time for coumarin derivatives with substitution at 5- and 7- positions (Figure 4a) and 6- and 7-positions (Figure 4b). The results show that the 5,7-dibutyloxy-4-methylcoumarin (B5B7) had the highest DD at 86% after 50 minutes of irradiation time.

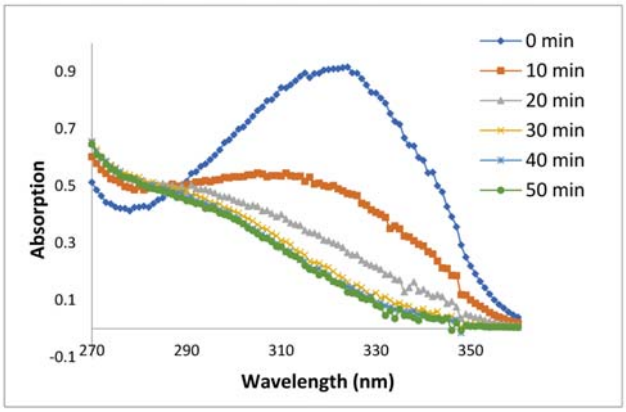


Figure 3. UV absorption spectra of B5B7 after irradiation for a given time.

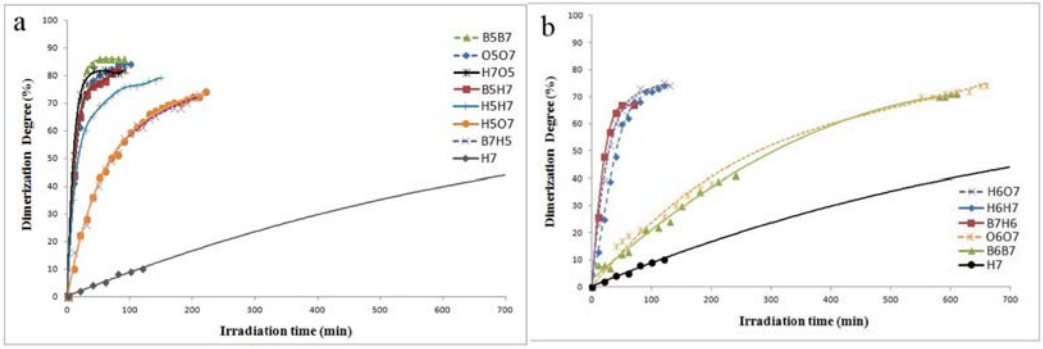


Figure 4. Relationship of dimerization degree of coumarin derivatives and irradiation times: (a) substitution at 5- and 7-position, (b) substitution at 6- and 7-position.

4. CONCLUSIONS

An alkylation reaction using a 1:1 molar ratio of the dihydroxy coumarin and an alkyl bromide afforded the corresponding monoalkyloxy product, together with the dialkyloxy product in reasonable yields. The alkylation was favored by the anionic stabilized resonance structures of the coumarin derivatives. The type of substituents at the same position of coumarins had no significant effect on the maximum absorption wavelength. However, the substitution positions had pronounced influence on the DD. The results indicated that a higher DD was favored with an alkyloxy substitution at the 5-position, comparing to the 7- or the 8-position. While there does not appear to be a distinct trend between the hydroxyl, butyloxy, or octyloxy substitutents at the 5-position, these results indicate that having an alkyloxy group of any length at the 5-position is important for the dimerization reaction.

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