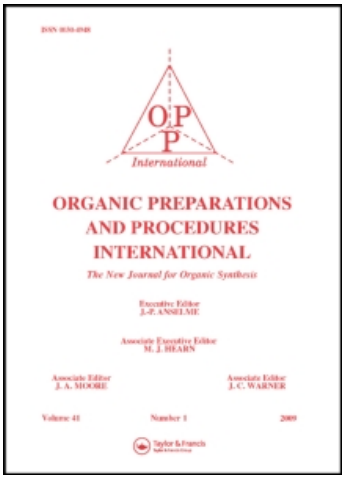

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 7-HYDROXY-4-(ω-CARBOXYALKYL)COUMARINS AND 7-(DIMETHYLAMINO)-4-(ω-CARBOXYALKYL)COUMARINS

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To cite this Article Adamczyk, Maciej , Mattingly, Phillip G. , Pan, You and Rege, Sushil(1996) 'SYNTHESIS OF 7-HYDROXY-4-(ω-CARBOXYALKYL)COUMARINS AND 7-(DIMETHYLAMINO)-4-(ω-CARBOXYALKYL)COUMARINS', Organic Preparations and Procedures International, 28: 5, 627 — 634
To link to this Article: DOI: 10.1080/00304949609458577
URL: http://dx.doi.org/10.1080/00304949609458577

10. R. Y. Yang and L. X. Dai, *J. Org. Chem.*, **58**, 3381 (1993).

11. A. R. Katritzky, P. A. Harris and A. Kotali, *ibid.*, **56**, 5049 (1991).

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SYNTHESIS OF 7-HYDROXY-4-(ω-CARBOXYALKYL)COUMARINS AND 7-(DIMETHYLAMINO)-4-(ω-CARBOXYALKYL)COUMARINS

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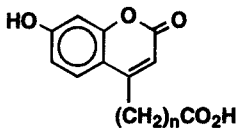
Although coumarin itself has a very low fluorescence quantum yield, its 7-hydroxy and 7-dimethylamino derivatives (**1** and **2**) are highly fluorescent and have been widely used as molecular probes[1,2] and enzyme substrates.[3] Additionally, fluorescent coumarins have been used to prepare bioconjugates of proteins[4] and nucleic acids.[5] We were interested in exploring the impact of the linker used in such bioconjugations on the performance of these two classes of compounds with particular attention to the solubility and quantum yield of the derived bioconjugates. Thus, we required a series of 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins in which the linker varied in length. Commercially available 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins were limited to



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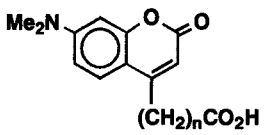

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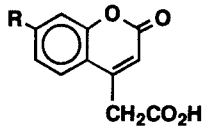


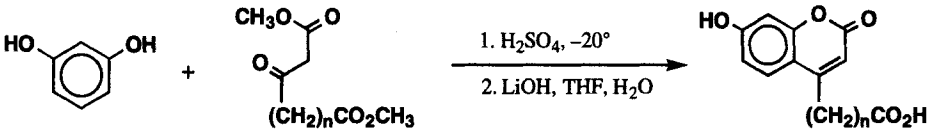
3

a) n = 2 b) n = 3 c) n = 4 d) n = 5 e) n = 6 f) n = 7 g) n = 8 a) R = OH b) R = NMe_2

the acetic acid congeners (**3a** and **3b**). The literature revealed few additional examples. Chaterjee[6] reported the preparation of 7-methoxy-4-(3-carboxypropyl)coumarin *via* a modified Pechman condensation. 7-Hydroxy-4-(2-carboxyethyl)coumarin was prepared by alkylation of ethyl malonate with 7-methoxy-4-(bromomethyl)coumarin, followed by decarboxylation and 7-demethylation.[7] 7-Hydroxy-4-(2-carboethoxyethyl)coumarin was prepared by the direct condensation of ethyl 5-oxo-4-oxaspiro[2,3]hexane-1-carboxylate with resorcinol in ethanolic HCl.[8] The latter method proceeded by the *in situ* generation of the diethyl β-oxoadipate required for the Pechman condensation.[9,10] Indeed, the Pechman condensation seemed to be the most general method for the

preparation of the homologous series of the required 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins.

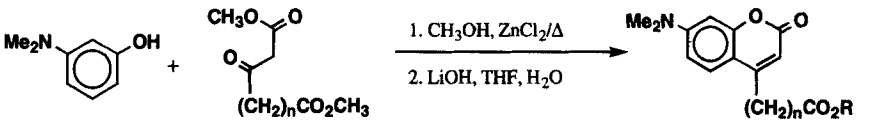
Thus, the β-ketoesters (**4a–g**) were condensed with *o*-resorcinol in concentrated sulfuric acid at –20° to give the 7-hydroxy-4-(ω-carboxyalkyl)coumarins as shown below. The reaction was quenched in ice and the resulting precipitated mixture of methyl ester and free acid was saponified to give the acids (**1a–g**).



4a-g **1a-g**

a) n = 2 b) n = 3 c) n = 4 d) n = 5 e) n = 6 f) n = 7 g) n = 8

Since the application of the same reaction conditions for the preparation of 7-(dimethylamino)-4-(ω-carboxyalkyl)coumarins failed, compounds **2a–g** were prepared as shown in the scheme below. Thus, *o*-(dimethylamino)phenol was condensed with the β-ketoesters (**4a–g**) in refluxing methanol in the presence of zinc chloride[11] to give the corresponding 7-dimethylamino-4-(ω-carbomethoxyalkyl)coumarins (**5a-g**). The esters were hydrolyzed with lithium hydroxide to the corresponding acids (**2a-g**). 7-Hydroxy-4-(ω-carboxyalkyl)coumarins (**1a–g**) and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins (**2a-g**) could be conjugated to proteins directly using any of the existing coupling methodologies.[12-14]



4a-g **5a-g** R = CH_3

a) n = 2 b) n = 3 c) n = 4 d) n = 5 e) n = 6 f) n = 7 g) n = 8 **2a-g** R = H

In conclusion, we have developed a simple method for the synthesis of 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins. We believe that these compounds will find widespread applications as fluorescent probes, as an attractive alternative to the existing compounds.

EXPERIMENTAL SECTION

All reagents were purchased from Aldrich Chemical Co. and used without further purification. The β-ketoesters: dimethyl 3-oxohexanedioate (**4a**),[15] dimethyl 3-oxoheptanedioate (**4b**),[16,17] dimethyl 3-oxooctanedioate (**4c**),[16] dimethyl 3-oxononanedioate (**4d**),[18] dimethyl 3-oxodecanedioate (**4e**),[19] dimethyl 3-oxoundecanedioate (**4f**),[20] dimethyl 3-oxododecanedioate (**4g**), were prepared by the acylation of Meldrum's acid with the appropriate acid chloride[21] or acid.[22] Solvents used were of HPLC grade and used without further purification. Preparative HPLC was performed under the following conditions: column, μBondapak C18, 40x100 mm (Waters); flow rate: 45 mL/min; UV

TABLE 1. Preparation of Coumarin Compounds **1a–g**

Compd	Yield (%)	mp. (°C)	ESI-MS	Elemental Analysis (Found) C	H
1a	67	248–250	234 $(M)^+$	61.48 (61.48)	4.27 (4.28)
1b	45	232–234	249 $(M+H)^+$	62.90 (63.15)	4.83 (5.18)
1c	86	208–210	262 $(M)^+$	64.06 (64.18)	5.34 (5.32)
1d	61	175–177	277 $(M+H)^+$	65.15 (65.23)	5.79 (5.87)
1e	68	158–160	290 $(M)^+$	66.14 (66.18)	6.20 (6.17)
1f	60	75	305 $(M+H)^+$	67.03 (66.98)	6.57 (6.69)
1g	75	210	318 $(M)^+$	67.85 (68.22)	6.91 (7.25)

TABLE 2. Spectral Data for Coumarin Compounds **1a–g**

Compd	^{1}H NMR (solvent) (δ: ppm, J: Hz)	^{13}C NMR (solvent) (δ: ppm)
1a	(CD_3OD): 7.56 (1H, d, J = 9), 6.74 (1H, dd, J = 9, 4), 6.61 (1H, d, J = 2), 6.0 (1H, s), 2.99 (2H, t, J = 4), 2.61 (2H, t, J = 4)	(CD_3OD): 175.59, 163.75, 162.95, 157.82, 156.78, 126.95, 114.43, 112.82, 110.39, 103.71, 30.09, 27.65
1b	($CDCl_3$): 7.70 (1H, br), 7.58 (1H, d, J = 9), 7.0 (1H, s), 6.90 (1H, d, J = 9), 6.14 (1H, s), 2.80 (2H, t, J = 7), 2.48 (2H, t, J = 7), 2.03 (2H, m)	($CDCl_3$): 173.67, 162.48, 160.21, 156.06, 155.35, 125.84, 113.61, 112.43, 110.42, 103.62, 33.21, 31.26, 23.53
1c	($CDCl_3$): 7.65 (1H, d, J = 9), 6.70 (1H, dd, J = 9, 2), 6.72 (1H, d, J = 2), 6.1 (1H, s), 2.65 (2H, t, J = 8), 2.25 (2H, t, J = 8), 1.50 (2H, m), 1.65 (2H, m)	(DMSO-d_6): 174.38, 160.91, 160.32, 158.31, 156.74, 126.22, 112.84, 111.12, 109.23, 102.35, 33.21, 30.54, 27.31, 24.14
1d	(CD_3OD): 7.57 (1H, d, J = 9), 6.80 (1H, d, J = 2), 6.68 (1H, s), 6.05 (1H, s), 2.75 (2H, t, J = 7), 2.29 (2H, t, J = 7), 1.65 (4H, m), 1.45 (2H, m)	(CD_3OD): 177.70, 164.02, 162.83, 159.63, 156.79, 127.24, 114.38, 113.05, 110.28, 103.66, 34.82, 32.58, 29.99, 29.41, 25.23
1e	(CD_3OD): 7.51 (1H, d, J = 9), 6.76 (1H, dd, J = 9, 2), 6.63 (1H, s), 6.01 (1H, s), 2.71 (2H, t, J = 7), 2.22 (2H, t, J = 7), 1.60 (4H, m), 1.40 (4H, m)	(CD_3OD): 178.95, 164.08, 162.82, 159.76, 156.68, 127.13, 114.43, 113.03, 110.17, 103.69, 35.54, 32.65, 30.22, 29.99, 29.47, 26.16
1f	(CD_3OD): 8.80 (1H, br), 7.49 (1H, d, J = 8), 6.97 (1H, s), 6.88 (1H, d, J = 8), 6.10 (1H, s), 2.68 (2H, t, J = 7), 2.31 (2H, t, J = 7), 1.61 (4H, m), 1.33 (6H, m)	($CDCl_3$): 174.89, 163.14, 160.51, 158.19, 155.26, 125.72, 113.69, 112.45, 109.77, 107.73, 103.55, 34.09, 31.92, 29.42, 28.96, 28.30, 24.84
1g	(CD_3OD): 7.61 (1H d, J = 9) 6.81 (1H, dd, J = 9, 2), 6.69 (1H, d, J = 2), 6.05 (1H, s), 2.75 (2H, t, J = 7), 2.26 (2H, t, J = 7), 1.60 (3H, m), 1.35 (9H, m)	(CD_3OD): 177.73, 164.03, 162.65, 159.84, 156.84, 127.26, 114.37, 110.24, 110.15, 103.71, 34.94, 32.76, 30.46, 30.29, 30.16, 29.78, 26.06

detection: 240 nm. Analytical HPLC was performed under the following conditions: column, μBondapak C18, 8x100 mm (Waters); flow rate: 2 mL/min; UV detection: 240 nm. ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, on a Varian Gemini 300 spectrometer. Electrospray ionization mass spectra were recorded on a PE Sciex API 100 instrument. Melting points were taken on an Electrothermal capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

General Method for the Synthesis of Coumarins 1a-g.- β-Ketoester (1 mmol) and resorcinol (1.5 mmol) were added to a flame–dried, round bottom flask. The flask was cooled to –20° in a dry ice–acetone bath under a dry nitrogen atmosphere. Concentrated sulfuric acid (2 mL/mmol) was added dropwise under nitrogen *via* a dropping funnel. The rate of addition was adjusted such that the inside temperature in the flask did not exceed 0°. After the complete addition of sulfuric acid, the reaction was further stirred at –20° for 1 hr, then 14 hrs at 2–8°. The reaction was poured on crushed ice. The precipitated solid was collected by filtration. The crude compound was hydrolyzed with LiOH (3.5 mmol) in water/THF (1:1, 2 mL). THF was removed under vacuum. The aqueous solution was neutralized with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). After drying over anhydrous sodium sulfate the solution was concentrated to give the corresponding acids **1a–g**. The compounds were purified by column chromatography (SiO_2, 50 g, 10% CH_3OH in CH_2Cl_2). Fractions containing the desired compounds were pooled and evaporated to dryness *in vacuo*. The chromatographically pure compounds were recrystallized from water (**Tables 1** and **2**).

TABLE 3. Preparation of Coumarin Compounds **5a–g**

Compd	Yield (%)	mp (°C)	HPLC (solvent[a]) retention time (min)	ESI-MS	Elemental Analysis (Found)		
					C	H	N
5a	36	91–92	(43:67:0.05) 8.6	276 $(M+H)^+$	65.38 (65.01)	6.17 (6.02)	5.13 (4.90)
5b	63	88–89	(50:50:0.05) 6.3	290 $(M+H)^+$	66.36 (66.02)	6.56 (6.67)	4.83 (4.71)
5c	38	99–100	(50:50:0.05) 6.5	304 $(M+H)^+$	67.25 (67.02)	6.92 (6.82)	4.61 (4.52)
5d	21	97–98	(55:45:0.05) 8.16	318 $(M+H)^+$	68.05 (67.95)	7.24 (7.29)	4.41 (4.12)
5e	21	99–100	(60:40:0.05) 6.5	332 $(M+H)^+$	68.79 (68.58)	7.54 (7.70)	4.22 (3.97)
5f	39	88–90	(65:35:0.05) 6.5	346 $(M+H)^+$	69.48 (69.25)	7.81 (7.80)	4.05 (3.70)
5g	29	81–82	(65:35:0.05) 9.4	360 $(M+H)^+$	70.10 (70.20)	8.06 (8.10)	3.89 (3.56)

a) CH_3CN/H_2O/TFA

General Method for the Synthesis of 7-(Dimethylamino)coumarins 5a–g.- A solution of the β-ketoester (4 mmol), 3-dimethylaminophenol (4.4 mmol, 110 mol%) and $ZnCl_2$ (5.3 mmol, 120 mol%) in MeOH (1.5 mL) was heated to reflux for 8–18 hrs. After cooling to ambient temperature, the reaction was acidified with 1 N HCl (20 mL), then extracted with CH_2Cl_2 (3 x 50 mL). The extract was dried over anhydrous sodium sulfate filtered and concentrated to give a brown oil. Polar impurities were removed by column chromatography (SiO_2, 30 g, 25% EtOAc in hexane) before final purification by preparative HPLC. Fractions containing the desired product were combined and lyophilized to give the analytically pure 7-dimethylamino-4-(ω-carbomethoxyalkyl)-coumarins, **5a-g** (**Tables 3** and **4**).

TABLE 4. Spectral Data for Coumarin Compounds **5a–g**

Compd	^{1}H NMR ($CDCl_3$) (δ: ppm, J: Hz)	^{13}C NMR ($CDCl_3$) (δ: ppm)
5a	7.43 (1H, d, J = 9), 6.63 (1H, d, J = 9), 6.53 (1H, s), 5.97 (1H, s), 3.73 (3H, s), 3.06 (6H, s), 2.92 (2H, t, J = 8), 2.70 (2H, t, J = 8)	172.53, 162.08, 155.93, 154.64, 152.89, 124.79, 108.96, 108.41, 108.03, 98.49, 52.05, 40.13, 32.36, 26.53
5b	7.50 (1H, d, J = 9), 6.63 (1H, d, J = 9), 6.52 (1H, s), 5.96 (1H, s), 3.70 (3H, s), 3.05 (6H, s), 2.73 (2H, t, J = 8), 2.44 (2H, t, J = 7), 2.00 (2H, m)	173.42, 161.01, 155.79, 155.65, 125.15, 108.93, 108.48, 98.47, 51.71, 40.13, 33.23, 31.08, 23.72
5c	7.42 (1H, d, J = 9), 6.61 (1H, d, J = 9), 6.50 (1H, s), 5.95 (1H, s), 3.67 (3H, s), 3.04 (6H, s), 2.69 (2H, t, J = 7), 2.36 (2H, t, J = 7), 1.73 (4H, m)	172.95, 162.24, 156.26, 155.97, 152.76, 124.99, 108.85, 108.22, 98.48, 51.63, 40.13, 33.73, 31.42, 27.94, 24.75
5d	7.40 (1H, d, J = 9), 6.61 (1H, d, J = 9), 6.53 (1H, s), 5.96 (1H, s), 3.67 (3H, s), 3 .05 (6H, s), 2.69 (2H, t, J = 7), 2.33 (2H, t, J = 7), 1.69 (6H, m)	172.00, 162.31, 156.60, 155.98, 152.76, 125.03, 108.84, 108.21, 98.53, 51.58, 40.15, 33.89, 31.57, 28.96, 28.19, 24.67
5e	7.41 (1H, d, J = 9), 6.62 (1H, d, J = 9), 6.53 (1H, s), 5.97 (1H, s), 3.67 (3H, s), 3.06 (6H, s), 2.68 (2H, t, J = 7), 2.32 (2H, t, J = 7), 1.64 (4H, m), 1.41 (4H, m)	172.05, 162.36, 156.81, 155.99, 152.75, 125.07, 108.82, 108.25, 98.52, 51.50, 40.14, 34.01, 31.71, 29.15, 28.90, 28.38, 24.80
5f	7.40 (1H, d, J = 9), 6.62 (1H, d, J = 9), 6.50 (1H, s), 5.95 (1H, s), 3.66 (3H, s), 3.04 (6H, s), 2.66 (2H, t, J = 7), 2.30 (2H, t, J = 7), 1.62 (4H, m), 1.34 (6H, m)	174.20, 162.33, 156.92, 155.93, 152.70, 125.06, 108.81, 108.06, 98.40, 51.46, 40.10, 34.02, 31.73, 29.20, 28.50, 24.88
5g	(7.41 (1H, d, J = 9), 6.63 (1H, d, J = 9), 6.52 (1H, s), 5.97 (1H, s), 3.67 (3H, s), 3.05 (6H, s), 2.67 (2H, t, J = 7), 2.31 (2H, t, J = 7), 1.61 (4H, m), 1.31 (8H, m)	174.27, 162.36, 156.96, 155.95, 152.71, 125.08, 108.80, 108.14, 98.47, 51.48, 40.12, 34.08, 31.77, 29.42, 29.19, 29.09, 28.53, 24.91

TABLE 5. Preparation of Coumarin Compounds **2a–g**

Compd	Yield (%)	mp (°C)	HPLC (solvent[a]) retention time (min)	ESI-MS	Elemental Analysis (Found)		
					C	H	N
2a	52	195–197	(33/67/0.05) 6.9	262 $(M+H)^+$	64.30 (64.33)	5.74 (5.80)	5.36 (5.36)
2b	61	211–213	(40/60/0.05) 4.6	276 $(M+H)^+$	65.38 (65.32)	6.17 (6.13)	5.13 (4.95)
2c	60	172–174	(40/60/0.05) 6.1	290 $(M+H)^+$	66.36 (66.49)	6.56 (6.55)	4.83 (4.43)
2d	59	182–183	(42/58/0.05) 7.4	304 $(M+H)^+$	67.25 (67.33)	6.92 (6.90)	4.61 (4.30)
2e	57	131–132	(48/52/0.05) 6.5	318 $(M+H)^+$	68.05 (68.05)	7.24 (7.28)	4.41 (4.04)
2f	56	117–118	(52/48/0.05) 7.7	332 $(M+H)^+$	68.79 (68.77)	7.54 (7.62)	4.22 (3.95)
2g	53	123–125	(60/40/0.05) 5.4	346 $(M+H)^+$	69.48 (69.49)	7.81(7.90)	4.05 (4.10)

a) CH_3CN/H_2O/TFA

TABLE 6. Spectral Data for Coumarin Compounds **2a–g**

Compd	^1H NMR (DMSO-d_6) (δ: ppm, J: Hz)	^{13}C NMR (DMSO-d_6) (δ: ppm)
2a	7.52 (1H, d, J = 9), 6.70 (1H, d, J = 9), 6.50 (1H, s), 5.88 (1H, s), 2.99 (6H, s), 2.96 (2H, t, J = 8), 2.60 (2H, t, J = 8)	172.58, 160.21, 155.0, 154.65, 152.05, 124.60, 108.28, 107.02, 106.17, 96.85, 31.15, 25.23
2b	7.57 (1H, d, J = 9), 6.70 (1H, d, J = 9), 6.53 (1H, s), 5.90 (1H, s), 3.00 (6H, s), 2.70 (2H, t, J = 8), 2.33 (2H, t, J = 7), 1.81 (2H, m)	174.07, 160.76, 156.59, 155.46, 152.67, 125.56, 109.01, 108.48, 107.21, 97.58, 32.95, 30.25, 23.68
2c	7.53 (1H, d, J = 9), 6.69 (1H, d, J = 9), 6.53 (1H, s), 5.92 (1H, s), 3.00 (6H, s), 2.69 (2H, t, J = 8), 2.26 (2H, t, J = 7), 1.59 (4H, m)	175.22, 161.69, 157.88, 156.32, 153.52, 126.48, 109.86, 108.71, 107.88, 98.46, 34.20, 31.39, 28.52, 25.09
2d	7.50 (1H, d, J = 9), 6.70 (1H, d, J = 9), 6.50 (1H, s), 5.90 (1H, s), 3.00 (6H, s), 2.66 (2H, t, J = 8), 2.20 (2H, t, J = 7), 1.54 (4H, m), 1.36 (2H, m)	174.44, 160.87, 157.24, 155.32, 152.65, 125.56, 109.03, 107.86, 106.94, 97.56, 33.51, 30.70, 28.29, 27.95, 24.20
2e	7.45 (1H, d, J = 9), 6.64 (1H, d, J = 9), 6.41 (1H, s), 5.81 (1H, s), 2.93 (6H, s), 2.57 (2H, t, J = 8), 2.14 (2H, t, J = 7), 1.45 (4H, m), 1.25 (4H, m)	175.87, 162.36, 158.65, 156.13, 153.50, 126.39, 109.97, 108.57, 107.49, 98.13, 34.40, 31.60, 29.15, 28.95, 28.86, 24.20
2f	7.51 (1H, d, J = 9), 6.71 (1H, d, J = 9), 6.52 (1H, s), 5.90 (1H, s), 3.00 (6H, s), 2.66 (2H, t, J = 8), 2.18 (2H, t, J = 7), 1.56–1.47 (4H, m), 1.28 (6H, m)	175.35, 161.72, 158.16, 156.31, 153.52, 126.44, 109.88, 108.74, 107.93, 98.45, 34.47, 31.70, 29.53, 29.31, 29.11, 25.31
2g	7.49 (1H, d, J = 9), 6.70 (1H, d, J = 9), 6.51 (1H, s), 5.89 (1H, s), 2.99 (6H, s), 2.65 (2H, t, J = 8), 2.17 (2H, t, J = 7), 1.55–1.44 (4H, m), 1.23 (8H, m)	175.36, 161.72, 158.14, 156.31, 153.50, 126.41, 109.86, 108.72, 107.92,98.42, 34.50, 31.73, 29.63, 29.51, 29.83, 29.12, 25.33

Hydrolysis of 7-(Dimethylamino)-4-(ω-carbomethoxyalkyl)coumarin Esters. A solution of the ester **5a–g** (2 mmol) and LiOH (12 mmol, 600 mol%) in water/THF (1:1, 20 mL) was stirred at ambient temperature for 2–18 hrs (monitored by TLC). The reaction mixture was acidified with concentrated HCl to pH 2, then extracted with EtOAc (5 x 20 mL). The extract was dried over anhydrous sodium sulfate, filtered, then concentrated to give the crude acid which was purified by preparative HPLC. Fractions containing the product were combined and lyophilized to give analytically pure 7-dimethylamino-4-(ω-carboxyalkyl)coumarins, **2a–g** (**Tables 5** and **6.**)

REFERENCES

1. Y. Forster and E. Haas, *Anal. Biochem.*, **209**, 9 (1993).
2. J. E. T. Corrie, *J. Chem. Soc. Perkin Trans. I*, 2975 (**1994**).
3. M. Zimmerman, E. Yurewice and G. Patel, *Anal. Biochem.*, **70**, 258 (1976).
4. M. Pitschke, A. Fels, B. Schmidt, L. Heiliger, E. Kuckert and D. Riesner, *Colloid Polym. Sci.*, **273**, 740 (1995).
5. a) T. G. Laffler and S. R. Bouma. *Eur. Pat. Appl.* EP 357011 A2; *CA* **113**;187586; b) J. Engels, M. Herrlein, R. Konrad and M. Mag, *Eur. Pat. Appl.* EP 390281 A1; *CA* **117**:192263; c) P. Houston and T. Kodadek, *Proc. Natl. Acad. Sci. USA*, **91**, 5471 (1994); d) J.-L. Mergny, A. S. Boutorine, T. Garestier, F. Belloc, M. Rougee, N. V. Bulychev, A. A. Koshkin, J. Bourson and A. V. Lebedev, *Nucleic Acids Res.*, **22**, 920 (1994).
6. A. Chaterjee and R. Mallik, *Synthesis*, 715 (**1980**).
7. S. R. Bouma and J. E. Celebuski. *Eur. Pat. Appl.* EP 413152 A1 910220; *CA* **115**:49407.
8. T. Kato, N. Katagiri and R. Sato, *J. Chem. Soc., Perkin Trans. 1*, 525 (**1979**).
9. S. Sethna, *Chem. Rev.*, **36**, 10 (1945).
10. H. v. Pechman and C. Duisberg, *Ber.*, **16**, 2119 (1883).
11. J. Dey, *J. Chem. Soc.*, **107**, 1606 (1915).
12. A. Williams and I. T. Ibrahim, *Chem. Rev.*, **81**, 589 (1981).
13. M. Mikolajczyk and P. Kiebalsinski, *Tetrahedron*, **37**, 233 (1981).
14. F. Kurzer and D. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
15. J. Korman, *J. Org. Chem.*, **22**, 848 (1957).
16. J. P. Celerier, E. Marx and G. Lhommet, *J. Heterocycl. Chem.*, **25**, 1275 (1988).

17. L. Liu, R. S. Tanke and M. J. Miller, *J. Org. Chem.*, **51**, 5332 (1986).

18. A. Kondo, T. Ochi, H. Iio, T. Tokoroyama and M. Siro, *Chemistry Lett.*, 1491 (**1987**).

19. H. Thoma and G. Spiteller, *Ann.*, 1237 (**1983**).

20. U. Valcavi, P. Farina, S. Innocenti and V. Marotta, *Synthesis*, 124 (**1983**).

21. Y. Oikawa, K. Sugano and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).

22. Y. Hamada, Y. Kondo, M. Shibata and T. Shioiri, *J. Am. Chem. Soc.*, **111**, 669 (1989).

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ISOMER DISTRIBUTION IN THE METHYLATION OF [1]-BENZOTHIENO[2,3-d]TRIAZOLE UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

Submitted by
(04/10/96)

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We have been interested in specific regioselectivity effects of the nature of the phase-transfer catalyst (PTC) on the course of various reactions. As a continuation of our investigations on the alkylation of ambident anions,[1] under phase-transfer catalysis, we devoted our attention to the N-alkylation of the title compound **1**. The synthesis of **1** and of its N-methylated products (**2a-2c**) as well