Some 7-Substituted 4-(Trifluoromethyl)coumarins

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Preparation and spectral properties are given for 13 substituted 4-(trifluoromethyl)coumarins (7-hydroxy, 7,8-dihydroxy, 6-ethyl-7-hydroxy, 6-benzyl-7-hydroxy, 7-methoxy, 7-methyl, 7-amino, 7-(ethylamino), 7-(benzylamino), 7-anilino, 7-[(trifluoroethyl)amino], 7-[(pentadecafluorooctyl)amino], and 2(1*H*)-isoindolyl). Three 7-(acylamido)-4-(trifluoromethyl)coumarins (acetyl, benzoyl, and bromoacetyl) were also prepared as well as two new phenol precursors, 3-[(pentadecafluorooctyl)amino]phenol and 2-(3-hydroxyphenyl)-1*H*-isoindole.

Results and Discussion

Because of their widespread occurrence in nature (*1-3*), their medicinal properties (*4-10*), and their use as optical brighteners (*11-17*), coumarins have long occupied the interest of synthetic chemists (*18-20*). In the last few years 7-hydroxy- and 7-aminocoumarins have received increased attention because of their applications as laser dyes (*21-24*). Even more recently their fluorescence properties have been used to advantage in substrates for the biochemical assay of enzymes (*25-29*).

In many of these uses it is often advantageous to be able to control optical properties such as ultraviolet absorption maxima or fluorescence excitation and emission maxima of the dyes by suitable alterations in their structures. This paper reports some of our observations on a study of several such alterations using 7-substituted 4-(trifluoromethyl)coumarin as the base structure. These compounds are readily prepared by the von Pechmann reaction using zinc chloride as the condensing agent (*30*, *31*).

The compounds prepared with their yields and physical properties are listed in Table I. The zinc chloride-catalyzed von Pechmann reaction is limited to those phenols that carry a strong electron-donating group in the 3 position; this group appears in the 7 position of the coumarin. Phenols with electron-withdrawing groups in the 3 position (e.g., 3-bromophenol) or unsubstituted phenols (e.g., 2-naphthol) or phenols with strong electron donators in other than the 3 position (e.g., 2-aminophenol) failed. Phloroglucinol also failed. 3-Cresol did react, but the yield was very low; 2,3-dimethylphenol failed. The 7-(acylamido)coumarins studied were prepared by acylation of 7-amino-4-(trifluoromethyl)coumarin. UV absorption and fluorescence spectral data are presented in Table II.

Two of the phenols used as starting materials are new compounds, and their preparation is described. 3-[(Pentadecafluorooctyl)amino]phenol was prepared by diborane reduction of pentadecafluoro-*N*-(3-hydroxyphenyl)octanamide in tetrahydrofuran (*32*), and 2-(3-hydroxyphenyl)-1*H*-isoindole was prepared by similar reduction of 2-(3-hydroxyphenyl)-1*H*-isoindole-1,3(2*H*)-dione. 3-(Ethylamino)phenol and 3-[(trifluoroethyl)amino]phenol (*32*, *33*) were also prepared by diborane reduction. 3-(Benzylamino)phenol was prepared either by diborane reduction of *N*-(3-hydroxyphenyl)benzamide or by the reaction of benzylamine with resorcinol (*34*). 3-Anilinophenol was prepared by the latter route (*35*).

Experimental Section

Melting points, taken on a Mettler Model FP1 apparatus at a heating rate of 2 °C/min, are corrected; boiling points are uncorrected. NMR spectra, in Me_2SO-d_6 solvent except as noted, were taken on a Varian EM-360 spectrometer; shifts (δ) are given in parts per million relative to internal Me_4Si; s = singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet; coupling constants (J) are given in Hertz. Infrared absorption spectra (in cm^{-1}, KBr pellets) were taken on a Perkin-Elmer Model 457 spectrometer. Fluorescence spectra were measured on an Aminco-Bowman spectrometer using an ellipsoidal condensing system and standardized with a glass reference standard. Satisfactory elemental analyses for all new compounds were submitted for review.

Pentadecafluoro-N-(3-hydroxyphenyl)octanamide. To a solution of 56.3 g (0.52 mol) of 3-aminophenol in 300 mL of tetrahydrofuran was added 112.5 g (0.26 mol) of perfluorooctanoyl chloride (*36*). After being stirred for ~18 h, the mixture was poured into 3 L of water. This solution was extracted with three 500-mL portions of ether. The combined extracts were washed successively with 500 mL of 1 N hydrochloric acid, 500 mL of dilute sodium bicarbonate solution, and 500 mL of water. Drying over magnesium sulfate, filtering, and evaporating left 121.3 g (92%) of crude product melting at 131 °C. Several recrystallizations from aqueous ethanol raised that to 149.7 °C. An analytical sample was sublimed at 130 °C and 1 Pa: mp 150.0 °C; NMR (in acetone-d_6) δ 3.0 (s, 2, OH + NH), 6.8 (m, 1, ArH), and 7.3 (m, 3, ArH); IR 1700 cm^{-1} (carbonyl).

3-[(Pentadecafluorooctyl)amino]phenol. A solution of 25.26 g (50 mmol) of pentadecafluoro-*N*-(3-hydroxyphenyl)octanamide in 50 mL of dried (NaPb alloy) tetrahydrofuran was added under argon over a 20-min period to a stirred, 1 M solution of diborane in tetrahydrofuran (200 mL). The reaction mixture was stirred at room temperature for 2 h, then refluxed for 21 h, and finally cooled to room temperature. Excess diborane was destroyed by cautious addition of 5 mL of absolute ethanol followed by 1 mL of water. Concentrated aqueous hydrochloric acid (15 mL) was added, and ~180 mL of the tetrahydrofuran was distilled off. The residue was poured into 100 mL of water. This solution was extracted with three 50-mL portions of ether. The combined ether extracts were washed with 25 mL of water, and then with two 50-mL portions of 0.8 N aqueous sodium hydroxide solution. The sodium hydroxide extracts were washed with 25 mL of ether, then acidified to a pH of less than 2 with concentrated hydrochloric acid, and reextracted 3 times with 50-mL portions of ether. These were dried over anhydrous magnesium sulfate, filtered, and evaporated to leave 13.3 g (54%) of solid product, which was recrystallized from benzene: mp 94.9 °C; NMR δ 3.92 (a triplet of doublets, 2, $J(CF_2)$ = 17.8 Hz, J(NH) = 7.2 Hz, CH_2), 6.2 (m, 4, ArH), 6.97 (t, 1, NH), 9.15 (s, 1, OH).

2-(3-Hydroxyphenyl)-1H-isoindole. To a suspension of 15.90 g (67 mmol) of 2-(3-hydroxyphenyl)-1*H*-isoindole-1,3-(2*H*)-dione (*37*) in 100 mL of dried (NaPb alloy) tetrahydrofuran was added, over 90 min, 200 mL of 1 M diborane in tetrahydrofuran. After 2 h at room temperature, the reaction mixture was refluxed for 20 h, then cooled to room temperature, and worked up as in the previous case except that addition to the 100 mL of water resulted in precipitation of a white solid, which was filtered off and washed with water. The filtrate was extracted 3 times with 50-mL portions of ether. Evaporation of the ether left a gummy brown solid, which was dissolved in 200 mL of 0.5 N aqueous sodium hydroxide. This solution was washed 3 times with 100-mL portions of ether. The aqueous solution was acidified to pH 1.4 by addition of concentrated

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Table I. 7-Substituted 4-(Trifluoromethyl)coumarins

no.	substituent 7-	substituent other	yield, %	mp, °C	recryn solvent	δ(CH_3)	δ(CH_2)	δ(3-H)	δ(ArH)	δ(other)
1	OH		34	186.7	aq EtOH			6.78 (s, 1)	7.1 (m, 3)	
2	OH	8-OH	4	224.1	aq EtOH			6.68 (s, 1)	6.9 (m, 2)	
3	OH	6-C_2H_5	47	181.3	aq EtOH	1.14 (t, 3, J = 7 Hz)	2.60 (q, 2)	6.68 (s, 1)	6.80 (s, 1), 7.33 (s, 1)	
4	OH	6-$C_6H_5CH_2$	42	224.3	aq EtOH		3.93 (s, 2)	6.68 (s, 1)	7.0 (m, 7)	
5	OCH_3		24	113.9	aq EtOH	3.90 (s, 3)		6.87 (s, 1)	7.2 (m, 3)	
6	CH_3		5	102.0	aq EtOH	2.45 (s, 3)		6.98 (s, 1)	7.4 (m, 3)	
7	NH_2		69		aq EtOH			6.48 (s, 1)	7.0 (m, 5)[a]	
8	$NHCH_2CH_3$		58	161.7	95% EtOH	1.20 (t, 3, J = 7 Hz)	3.2 (m)[b]		6.8 (m, 4)	
9	$NHCH_2C_6H_5$		66	145.2	aq EtOH		4.39 (d, 2, J = 6 Hz)		6.7 (m, 4)	phenyl, 7.32 (s, 5); NH, 7.70 (d, 1)
10	NHC_6H_5		89	161.0	aq EtOH			6.78 (s, 1)	7.3 (m, 8)	
11	$NHCH_2CF_3$		81	190.4	abs EtOH		4.12 (m, 2)	6.57 (s, 1)	7.2 (m, 4)[c]	
12	$NHCH_2(CF_2)_6CF_3$		94	166.9	abs EtOH		4.28 (m, 2)	6.62 (s, 1)	7.1 (m, 4)[c]	
13	2(1*H*)-isoindolyl		81	249.7	*n*-BuOH		3.33 (s)[b]	6.60 (s)	7.0 (m)	
14	$NHCOCH_3$		80	184.0	MeOH/Et_2O	2.13 (s, 3)		6.90 (s, 1)	7.8 (m, 3)	NH, 3.38 (s, 1)
15	$NHCOC_6H_5$		100	229.9	EtOAc					
16	$NHCOCH_2Br$		100	200.7	EtOAc					

[a] Includes the NH_2. [b] The signal was too weak to obtain a useable integration. [c] Includes the NH.

Table II. Spectral Data for 7-Substituted 4-(Trifluoromethyl)coumarins[a]

no.	ultraviolet absn λ_{max}	ultraviolet absn $10^{-4}\epsilon$	fluorescence maxima excitation	fluorescence maxima emission	rel fluorescence intensity
1	338	1.26	407	502	1.00
2	341	0.99			nil
3	340	1.12	414	510	0.52
4	345	1.29	419	512	1.46
5	332	1.91	354	415	0.22
6	290	0.81	343	421	*b*
7	382	1.70	409	480	2.72
8	390	1.07	423	498	0.93
9	390	1.97	395	493	2.76
10	400	2.19	436[c]	512[c]	*b*
11	370	1.86	397	475	3.02
12	371	1.58	390	470	3.04
13			420	503	1.22
14			351	433	2.50
15			350	440	2.72
16			353	430	0.95

[a] In absolute ethanol except as noted. [b] Saturated solution of unknown concentration. [c] In 1/1 ethanol/dimethylformamide.

hydrochloric acid. The precipitated product was filtered off, washed with water, and dried overnight at room temperature and 3 Pa. The yield was 6.68 g (47%) and the melting point was 116 °C. After several recrystallizations from aqueous ethanol and sublimation at 150 °C and 1 Pa, it melted at 165.7 °C: NMR δ 4.60 (s, 4, CH_2), 6.2 (m, 4, ArH), 7.48 (s, 4, ArH), 9.17 (s, 1, OH). Elemental analysis indicated that it was still contaminated with some 2-(3-hydroxyphenyl)-1*H*-isoindole-1-(2*H*)-one, but it was sufficiently pure for preparation of the desired coumarin.

7-Substituted 4-(Trifluoromethyl)coumarins. The phenol (10 mmol), ethyl trifluoroacetoacetate (1.94 g, 11 mmol), anhydrous zinc chloride (1.70 g, 12 mmol), and ethanol (6 mL) were refluxed for 12 h. The cooled reaction mixture was poured into 100 mL of 0.1 N aqueous hydrochloric acid. The precipitated product was filtered, washed with water, and dried overnight at room temperature and 3 Pa. The yield and the solvent used for recrystallization are listed in Table I. Analytical samples of the new compounds were sublimed at 100–150 °C and 0.1–1 Pa as a final purification step.

7-Acetamido-4-(trifluoromethyl)coumarin. Ketene (245 mL at 60 kPa and 22.7 °C, 6 mmol) was condensed by means of liquid nitrogen into a 25-mL stainless-steel vessel containing 1.15 g (5 mmol) of 7-amino-4-(trifluoromethyl)coumarin and 5 mL of chloroform. After 20 h at room temperature, the crude product was washed from the vessel with chloroform, centrifuged, and dried overnight at room temperature and 5 Pa: weight, 1.08 g (80%); mp 180 °C. It was purified by chromatography on silica gel using methylene chloride containing progressively larger amounts of methanol until the product eluted. The fraction containing the acetoxy compound was evaporated, and the residue was recrystallized from either ethanol or methanol/ether (mp 184.0 °C).

7-Benzamido-4-(trifluoromethyl)coumarin. A mixture of 0.4 g (1.75 mmol) of 7-amino-4-(trifluoromethyl)coumarin, 0.25 mL (2.15 mmol) of benzoyl chloride, and 1 mL of dry pyridine was heated for 5 min on a steam bath and then poured into 10 mL of water. The product precipitated in essentially quantitative yield and was recrystallized from ethyl acetate (mp 229.9 °C).

7-(Bromoacetamido)-4-(trifluoromethyl)coumarin. 7-Amino-4-(trifluoromethyl)coumarin (0.42 g, 1.0 mmol) was added to an ice-cold solution of 0.2 mL (2.3 mmol) of bromoacetyl bromide in 1 mL of tetrahydrofuran. After 30 min at room temperature, 10 mL of ice water was added. The product was separated, washed with water, dried, and recrystallized from ethyl acetate. An analytical sample was sublimed at 140 °C and 0.1 Pa (mp 200.7 °C).

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