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Synthesis of furanochromones: a new step in improvement of fluorescence properties

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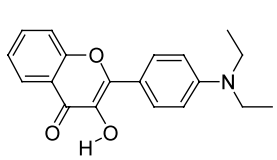
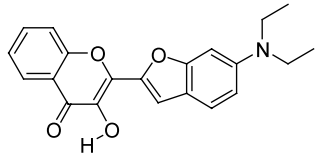
Abstract—New 3-hydroxychromone derivatives with a fused furan heterocycle (2-aryl-3-hydroxyfurano[3,2-*g*]chromones) have been synthesized. This was achieved by an important improvement in the synthetic procedure. Like their parent analogs, these new compounds exhibit two intensive fluorescence emission bands belonging to normal (N*) and tautomer (T*) excited-state forms. While the spectral position of the N* band remains unchanged, the T* band is shifted to longer wavelengths, providing larger separation between the two bands. The new compounds exhibit increased molecular extinction and, more importantly, have about twice as high fluorescence quantum yields. These properties make them very promising for designing new two-band fluorescence sensors.

3-Hydroxyflavones have recently attracted the attention of researchers due to their interesting photochemical behavior and as prospective two-band fluorescence sensors. This is a unique organic dye family that undergoes an excited state intramolecular proton transfer (ESIPT) reaction resulting in two highly intensive, well separated and solvent-dependent emission bands originating from the normal excited form (N*) and the phototautomer (T*).[1,2] The introduction of an electron donor, a dialkylamino group, to the 4′-position of **1** increased the charge-transfer character of the N* form, which made the relative intensity of the N* band much higher and strongly dependent on solvent polarity.[3–5] This property resulted in a variety of applications for substituted 3-hydroxyflavones as ion sensors[6] and as probes in the studies of organized systems such as micelles[7,8] and phospholipid vesicles.[9–12] Attempts to provide further improvements to these valuable properties resulted in the synthesis of 2-benzo/naphthofuryl-3-hydroxychromone derivatives.[13] They showed increased fluorescence quantum yields and strong red shifts in absorption and fluorescence spectra. Finally, the introduction of a dialkylamino group to the 6′-position of 2-(2-benzo[*b*]furanyl)-3-hydroxychromone (**2**) resulted in the longest wavelengths in absorption and fluorescence reported for 3-hydroxychromone derivatives to date.[14] However, in order to serve better as fluorescence sensors for biological systems, some fluorescence properties of 3-hydroxychromones still have to be improved. It is favorable to increase the fluorescence quantum yield, which is normally lower than 30%, and the extinction coefficient, usually about 35,000.[5,14] Furthermore, for dual color measurements and imaging in microscopy, it is desirable to apply the probes having high separation between fluorescence maxima, which appears to be insufficient for 3-hydroxychromone probes exposed to highly polar and non-homogeneous



1



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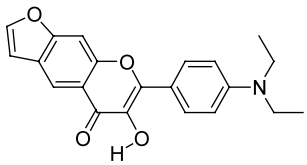
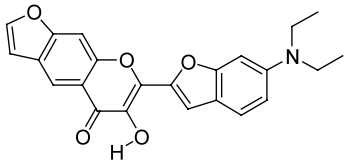


1a



2a

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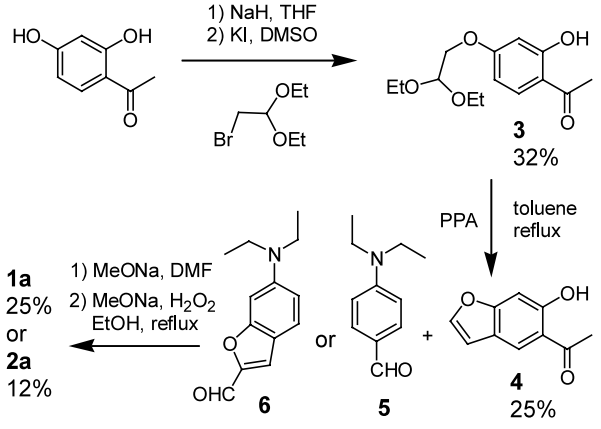
environments. This problem is particularly important for 4′-dialkylamino-substituted 3-hydroxyflavones, the strongly solvatochromic N* band of which shifts to the red and overlaps with the T* band.[10,14] In this letter we report two 2-aryl-3-hydroxyfurano[3,2-*g*]chromone derivatives **1a** and **2a**, in which the fused furan heterocycle provides a 3-hydroxychromone chromophore with improved fluorescence properties. Moreover, we suggest a modified procedure for the synthesis of 3-hydroxychromone derivatives, which is essential for obtaining the reported compounds.

4′-Diethylamino-3-hydroxy-furano[3,2-*g*]flavone (**1a**) and 2-(6-diethylaminobenzo[*b*]furan-2-yl)-3-hydroxyfurano[3,2-*g*]chromone (**2a**) were synthesized in four steps starting from 2′,4′-dihydroxyacetophenone (Scheme 1). The latter was transformed to its sodium salt with sodium hydride, and then reacted with bromoacetaldehyde diethylacetal in DMSO at 50°C, using KI as a catalyst. The product **3**[15] was refluxed in toluene in the presence of polyphosphoric acid (PPA) for 2 h. The resulting benzofuran derivative **4**[16] was isolated after silica gel column chromatography (hexane/ethyl acetate, 8/1, v/v). An attempt to convert **4** into the corresponding 3-hydroxychromones by a general two-step procedure[17,18] failed. Therefore, the conditions for both of the steps were modified. For condensation of **4** with aldehydes **5** and **6**, we applied sodium methoxide in DMF instead of the commonly used sodium hydroxide in aqueous water. The reaction was completed in 1 h, while with the common method it took several weeks. The mixture was diluted with ethanol, then, subsequently, a 20 molar excess of sodium methoxide and a 15 molar excess of 30% hydrogen peroxide were added. It was then refluxed for less than 1 min, cooled to room temperature and poured into water. After neutralization, the resultant precipitate was filtered. The target chromones were purified by crystallization from butanol.[19] The yields of **1a** and **2a** for the last two steps were found to be 25 and 12%, respectively. The failure of the general procedure[17,18] in this case could be due to the effect of π-electron donation by the dialkylamino group and the fused furan heterocycle. Considering the complicated structural nature of the 3-hydroxychromones synthesized via the modified procedure, this could be a breakthrough in the synthesis of advanced chromones.

Absorption and fluorescence properties of 3-hydroxyfurano[3,2-*g*]chromones **1a** and **2a** were studied with respect to the parent 3-hydroxychromones **1** and **2** in six solvents of different polarity: hexane, toluene, ethyl acetate, chloroform, acetonitrile and ethanol.[20] In all the solvents the furanochromones show absorption spectra shifted to longer wavelengths by 4–5 nm (210–300 cm^{-1}), which is, for **1a**, accompanied by increased extinction coefficients, ca. 5,000 $l \times mol^{-1} \times cm^{-1}$ (Fig. 1 and Table 1). Thus, the introduction of a furan heterocycle at different sites of the chromone chromophore results in different spectral effects. The fused furan in the case of **1a** favors significant growth of molecular extinction, without a strong red shift, while the introduced furan in the case of **2** results in the strong red shift accompanied by a relatively small increase in molecular extinction. In fluorescence spectra furanochromones **1a** and **2a** exhibit two bands, the intensity ratio (I_{N*}/I_{T*}) of which is highly sensitive to solvent polarity. This behavior is typical for 3-hydroxychromone derivatives.[4,5] The observed effects on the positions of the fluorescence bands are very interesting. Introduction of the furan heterocycle to chromones **1** and **2** results in a red shift of the T* emission band, while the N* band remains at almost the same position (see Figs. 2 and 3 and Table 1). This is very unusual, since all the modifications provided previously on modulation of the donor properties of the 2-aryl substituent in 3-hydroxychromones affected both of the bands with stronger shifts of the N* band.[5,14] The red shift of the T* band, which appears to be stronger in less polar solvents (Table 1), increases band separation for furanochromones **1a** and **2a** by 12–17 nm (360–520 cm^{-1}) and 7–13 nm (180–320 cm^{-1}), respectively (Figs. 2 and 3). The other prominent feature of furanochromones is their high fluorescence quantum yield. It is approximately twice that of the parent chromones and reaches record values compared to all the reported 3-hydroxychromones, 70% for **1a** in ethanol and 61% for **2a** in chloroform (Table 1).



Scheme 1. Synthesis of chromones **1a** and **2a**.

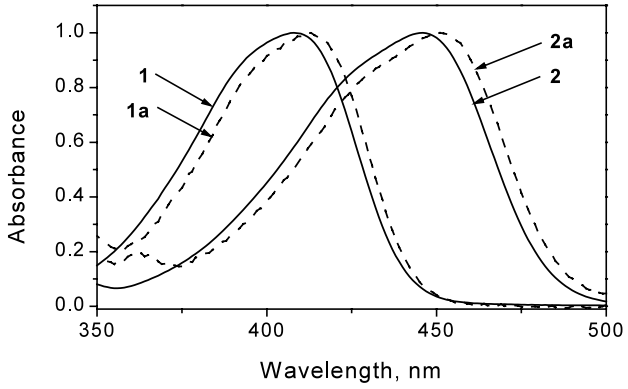


Figure 1. Normalized absorption spectra of the studied chromones in toluene.

Table 1. Spectral properties of the studied chromones[a]

Solvent		λ_{max} abs (nm)	λ_{max} fl N* (nm)	λ_{max} fl T* (nm)	I_{N^*}/I_{T^*}	ε ($l \times mol^{-1} \times cm^{-1}$)	φ
Hexane	**1**	403	425	553	0.010	37000	0.14
	1a	407	426	571	0.0077	42000	0.26
	2	439	457	583	0.078	44800	0.20
	2a	445	460	599	0.088	47000	0.23
Toluene							
	1	408	456	566	0.044	35000	0.14
	1a	413	458	581	0.0313	40000	0.29
	2	446	508	613	0.55	37600	0.26
	2a	451	508	623	0.601	39000	0.36
EtOAc	**1**	401	475	570	0.253	35000	0.05
	1a	406	476	584	0.133	41000	0.13
	2	436	537	618	1.93	37000	0.26
	2a	440	538	626	2.24	38000	0.40
$CHCl_3$	**1**	413	481	560	0.669	35000	0.19
	1a	418	482	573	0.422	41000	0.34
	2	453	545	621[b]	4.21[b]	37000	0.46
	2a	458	546	629[b]	4.07[b]	38000	0.61
CH_3CN	**1**	404	509	571	1.30	35000	0.09
	1a	408	510	586	1.01	38000	0.18
	2	437	582	–	–	36000	0.25
	2a	441	582	–	–	37000	0.37
EtOH	**1**	412	523	–	–	35000	0.52
	1a	418	523	–	–	38000	0.70
	2	444	600	–	–	36000	0.09
	2a	449	600	–	–	37000	0.18

[a] λ_{max} abs: positions of absorption maxima; λ_{max} fl N* and λ_{max} fl T*: positions of fluorescence maxima of N* and T* forms (dashes signify that the corresponding maxima are not resolved). φ is the fluorescence quantum yield determined with **1** as the reference ($\varphi = 0.52$ in ethanol, see Ref. 3), and ε-molar extinction coefficient. All the data for compounds **1** and **2**, reported in Ref. 14, were reproduced and corrected.

[b] The values were evaluated from results on deconvolution of the spectra to two bands approximated by log-normal function using the Siano program kindly provided by the author (A. O. Doroshenko from the Karazin University, Kharkov, Ukraine).

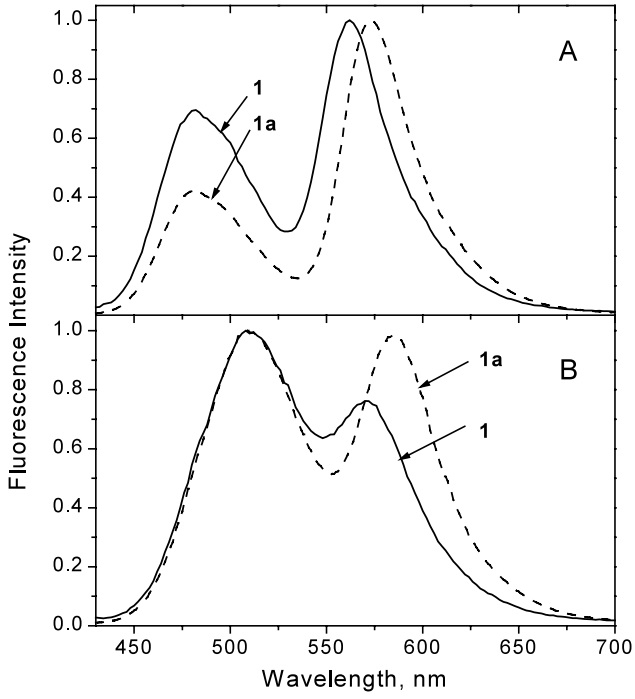


Figure 2. Normalized fluorescence spectra of **1** and **1a** in chloroform (A) and acetonitrile (B).

It is essential that the introduction of the furan heterocycle does not change the basic fluorescence property of 3-hydroxychromones—their dual emission. Furthermore, the strong sensitivity of the intensity ratio between emission bands (I_{N^*}/I_{T^*}) to solvent polarity is also preserved. Thus, an increase in solvent polarity from hexane to acetonitrile results in a strong growth of I_{N^*}/I_{T^*} for both furanochromones (Table 1), which is similar to that for the parent chromones. This is a very important fact, because it allows further modifications of the chromone system to be suggested to design new dual emission dyes.

In conclusion, a new modification of the procedure for the preparation of 3-hydroxychromones allowed the synthesis of new 2-aryl-3-hydroxyfurano[3,2-*g*]chromones in a short time and with relatively high yields.The highly polarizable π-electron abundant furan heterocycle provides a 3-hydroxychromone chromophore with substantially improved fluorescence properties, the most significant of which are a dramatic increase in the fluorescence quantum yield and larger separation between two emission maxima. Finally, it should be noted that the target furanochromones, due to the high reactivity of the furan heterocycle, can be very promising for further derivatization with the purpose of designing new molecular sensors.

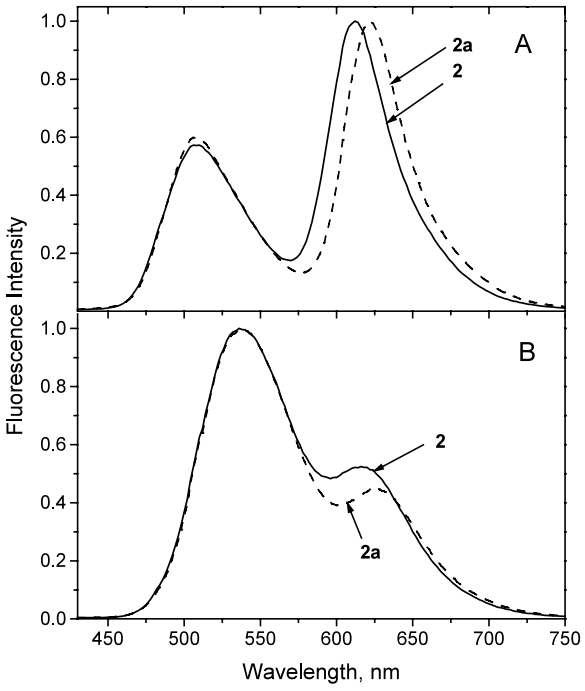


Figure 3. Normalized fluorescence spectra of furanochromones **2** and **2a** in toluene (A) and ethyl acetate (B).

Acknowledgements

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15. **1-[4-(2,2-Diethoxyethoxy)-2-hydroxyphenyl]ethan-1-one** isolated by silica gel column chromatography (hexane/ethyl acetate, 3:1, v/v), yield 32%, mp 50°C, was used in the next step without characterization.
16. **1-(6-Hydroxybenzo[*b*]furan-5-yl)ethan-1-one**, yield 25%, mp 101°C, ^{1}H NMR (200 MHz, $CDCl_3$) 2.70 (3H, s), 6.73 (1H, d, *J* 2.2 Hz), 7.04 (1H, s), 7.56 (1H, d, *J* 2.2 Hz), 8.00 (1H, s), 12.43 (1H, s), EI *m*/*z* 176.0 (M^+), 161.0, 149.1, 133.0, 121.0, 105.0, 85.1, 77.0, 71.1, 57.0.
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19. **4′-Diethylamino-3-hydroxy-furano[3,2-*g*]flavone** (**1a**): yield 25%, mp 155°C, ^{1}H NMR (200 MHz, $CDCl_3$) 1.24 (6H, t, *J* 7.1 Hz), 3.46 (4H, q, *J* 7.1 Hz), 6.79 (2H, d, *J* 9.2 Hz), 6.87 (1H, s), 6.91 (1H, d, *J* 2.1 Hz) 7.66 (1H, s), 7.72 (1H, d, *J* 2.1), 8.19 (2H, d, *J* 9.2 Hz), 8.46 (1H, s), EI *m*/*z* 349.1 (M^+), 334.1, 305.0. **2-(6-Diethylaminobenzo[*b*]furan-2-yl)-3-hydroxyfurano [3,2-*g*]chromone** (**2a**): yield 12%, mp 228°C, ^{1}H NMR (200 MHz, $CDCl_3$) 1.25 (6H, t, *J* 7.1 Hz), 3.46 (4H, q, *J* 7.1 Hz), 6.76 (1H, dd, *J* 8.8, 2.1 Hz), 6.88 (1H, d, *J* 2.1 Hz), 6.93 (1H, d, *J* 2.1 Hz), 7.49 (1H, d, *J* 8.8 Hz), 7.64 (1H, s), 7.75 (1H, d, *J* 2.1 Hz), 7.78 (1H, s), 8.49 (1H, s), EI *m*/*z* 389.1 (M^+), 374.1, 345.1, 209.0, 161.0.
20. All the solvents were of spectroscopic grade. Absorption and fluorescence spectra were recorded on a Cary 3 Bio spectrophotometer (Varian) and Quanta Master spectrofluorometer (Photon Technology International), respectively. Excitation wavelength for the fluorescence measurements was 410 nm.