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Synthesis and physical properties of various organic dyes derived from a single core skeleton, 1,2-dihydroindol-3-one

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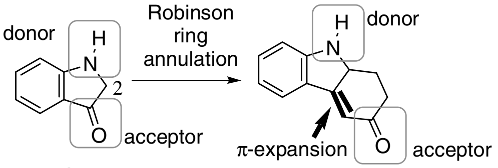
ABSTRACT

Various organic dyes were synthesized from 1,2-dihydroindol-3-one analogue via Robinson ring annulation, which proceeded efficiently using DBU as a base to give the π-expanded compounds. These compounds exhibited longer Stokes shifts (over 100 nm) than the 1,2-dihydroindol-3-ones (50–80 nm). Emission peaks of the obtained materials covered the 440–640 nm range.

The importance of organic light-emitting materials has increased greatly in recent years. They can be used in electroluminescent[1] and electrogenerated chemiluminescent[2] materials, chemosensors,[3] environmental sensors (temperature,[4] pH,[5] solvent,[6] and viscosity[7]), metal ion sensors,[8] etc.[9] Recently, these types of materials have received much attention for potential biological applications in fluorescence imaging and bio-labeling.[10–16] We are interested in compact structures with luminescence properties that can be introduced into various compounds causing little structural change.[16] Efficient fluorophores require the following characteristics: (1) a good donor–acceptor relationship and (2) a rigid structure to prevent nonradiative decay. In this context, coumarin derivatives bearing a donor–acceptor system are thought to have an enhanced fluorescence quantum yield by introducing a donating amino moiety into the cyclic system.[17] Consequently, we focused on a 1,2-dihydroindol-3-one structure (**1**). It consists of the donor (amino group) and acceptor (carbonyl group) parts connected by a π-system (benzene ring); it also has a ring structure that will enhance the fluorescence quantum yield. Structure (**1**) possesses an α-proton activated by a carbonyl group, which can facilitate the expansion of the π-system via a Robinson ring annulation at the 2-position of **1** (Eq. 1). The synthesis of 1,2-dihydroindol-3-one derivatives has been examined for use as intermediates in the synthesis of alkaloids, pharmaceutical agents, and insecticides.[18] Surprisingly, however, few reports describe the optical properties of derivatives of **1**.[18d,19] Herein, we report the synthesis and optical properties of 1,2-dihydroindol-3-one derivatives with various ranges of emission peaks by a simple reaction of the original 1,2-dihydroindol-3-one structure.



1 **2** (1)

Synthesis of the basic compound, *N*-acetyl-1,2-dihydroindol-3-one (**3**), was based on a procedure reported in a related patent[20] (Scheme 1). The reaction of **3** with NaOH was examined to remove the acetyl group, but the desired compound (**4**) was not obtained. However, the enol form (**4′**) was observed in the ^{1}H NMR spectrum (solvent: $CDCl_3$). Therefore, we protected the 2-position using a methyl group. The dimethylated derivative (**5a**) was obtained by the reaction of **3** with methyl iodide, with subsequent removal of the acetyl group. The monomethylated compound (**6**) was also formed by the reaction with methyl iodide by judicious choice of a base ($KOBu^t$) and its equivalent (1.05 equiv) in comparable yield. After the investigation of various bases for the Robinson ring annulation, we found that DBU was the best base for the reaction of **6** with methyl vinyl ketone to give **7a**. The one-pot synthesis of **7a** could be achieved by the reaction of **6** with DBU, followed by reaction with aq NaOH under reflux in EtOH.[21]

To investigate comprehensive changes by an expansion of the π-system, methyl and phenyl substituents on nitrogen atoms as well as a dicyanomethylene group at the carbonyl moiety were introduced into **5a** and **7a** (Scheme 2).

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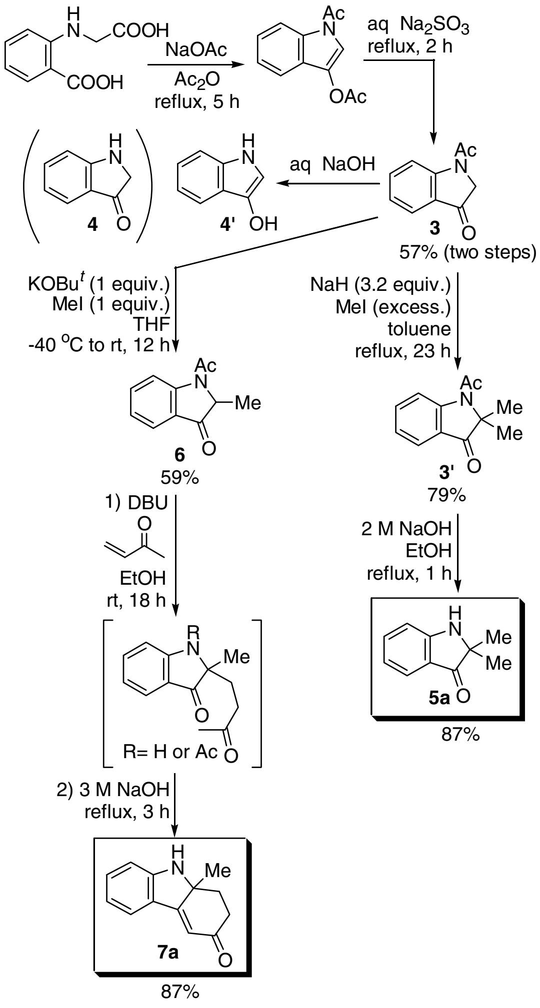
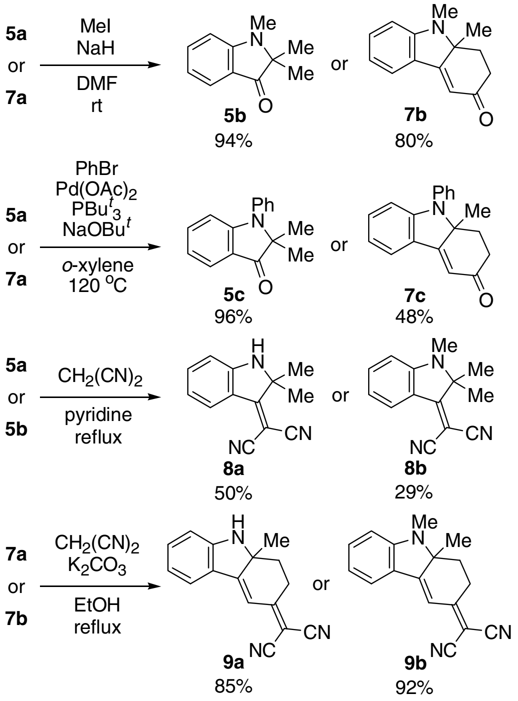


Scheme 1. Synthesis of **5a** and **7a**.



Scheme 2. Derivatization of **5a** and **7a**.

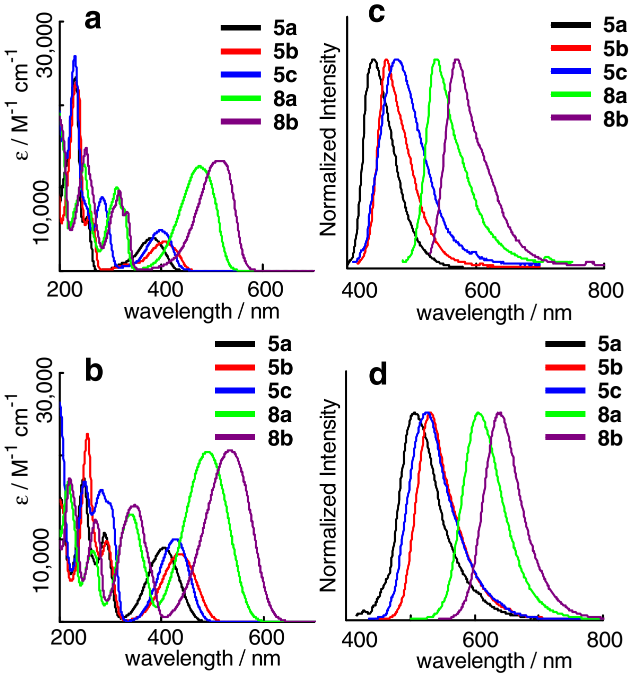


Figure 1. UV–vis absorption spectra of (a) **5** and **8**, (b) **7** and **9** in CH_3CN (3.0×10^{-5} M), and FL spectra of (c) **5** and **8**, (d) **7** and **9** in CH_3CN (3.0×10^{-7} M) excited at λ_{max}. Black line, **5a** and **7a**; red line, **5b** and **7b**; blue line, **5c** and **7c**; green line, **8a** and **9a**; purple line, **8b** and **9b**.

The UV–vis absorption and fluorescence spectra of the obtained compounds were measured in CH_3CN (Fig. 1). The optical data are presented in Table 1. The compounds bearing methyl (**5b** and **7b**) and phenyl (**5c** and **7c**) substituents on the nitrogen atom showed longer absorption and emission peaks than **5a** and **7a**, indicating that these groups enhanced the electron-donating ability of the amino group. To obtain longer absorption and emission peaks, it was efficient to change the carbonyl group to the stronger electron-withdrawing dicyanomethylene moiety. Large bathochromic shifts were obtained in the absorption and emission spectra of **5a** versus **8a** and **5b** versus **8b**. Enhancement of the molecular absorption coefficients (ε_{max}) was also observed.

Regarding UV–vis absorption spectra, a bathochromic shift between **5a** and **7a** was observed. This result is consistent with those of various substituted compounds (**5b** vs **7b**, **5c** vs **7c**, **8a** vs **9a**, and **8b** vs **9b**) accompanied by ca. 14–30 nm change. The red shift of 30 nm in the absorption peaks by the introduction of another C–C double bond is well known in the estimation of α,β-unsaturated ketones.[22] Khodorkovsky and co-workers reported the introduction of two vinyl tethers in their donor–acceptor system in which a bathochromic shift of ca. 80 nm (40 nm/one vinyl component) was observed.[23] Therefore, our system is slightly defective in the π-expansion in relation to absorption, possibly a result from the torsion of the fused π-conjugated ring system.

Specific changes of the emission characters were observed. The emission peak shifted to longer wavelength (about 49–70 nm) between **5** and **7** or **8** and **9**. It is noteworthy to maintain the full width at half maximum (fwhm) in a range of 55–80 nm even in the bathochromic shift of the emission peaks.[16c,24] Quantum yields (Φ_F) of the carbonyl derivatives were maintained or decreased by the change in the π-system (**5** vs **7**). Interestingly, the quantum yield increased in compounds having a dicyanomethylene moiety

Table 1
Physical properties of **5**, **7**, **8**, and **9** from UV–vis absorption and FL spectra

Compound	λ_{max} (nm) [ε_{max} (M^{-1} cm^{-1})][a]	λ_{em} (nm)[b] [fwhm (nm)]	Φ_F	Stokes shift[c] (nm)
5a	382.5 [4,000]	442 [54]	0.31[d]	59.5
7a	405 [8,900]	507 [70]	0.06[d]	102
5b	406.5 [3,500]	461 [55]	0.24[d]	54.5
7b	436 [8,200]	531 [65]	0.18[d]	95
5c	399 [4,900]	476 [80]	0.10[d]	77
7c	426.5 [10,000]	525 [77]	0.12[d]	98.5
8a	476 [12,500]	540 [61]	0.05[e]	64
9a	490 [20,500]	606 [72]	0.16[e]	116
8b	518 [13,300]	571 [66]	0.09[e]	53
9b	535 [20,700]	639 [68]	0.15[e]	104

[a] Measured in CH_3CN (3.0×10^{-5} M).

[b] Measured in CH_3CN (3.0×10^{-7} M). Excited at λ_{max}.

[c] Stokes shift = $\lambda_{em} - \lambda_{max}$.

[d] Determined with quinine sulfate ($\Phi_F = 0.55$) as a standard (3.0×10^{-7} M in 0.l M aq H_2SO_4).

[e] Determined with fluorescein ($\Phi_F = 0.90$) as a standard (3.0×10^{-7} M in 0.1 M aq NaOH).

as the electron-withdrawing group (**8** vs **9**). Although we have no clear explanation for this phenomenon, one of the possibilities can be mentioned. From investigation of the solvent effects in comparison to cyclohexane, THF, and acetonitrile, the bathochromic shifts were observed in the UV–vis absorption and fluorescence spectra (See Supplementary data; Fig. S1 and Table S1). Compounds having dicyanomethylene moiety (**8b** and **9b**) showed a considerable red shift in both absorption and emission peaks, which suggests that the excited state has a polar structure or a charge-transfer character. The polar excited state is stabilized, and emission occurs efficiently when the donor and acceptor parts are separated. This trend might be enhanced in a stronger donor–acceptor relationship, and is a good reason to increase the quantum yield of **8** versus **9**.

We found that enhancement of the Stokes shift was observed in the π-expanded compounds. Stokes shifts around 50–80 nm were observed in the spectra of **5** and **8**. On the other hand, larger Stokes shifts over 100 nm were obtained in **7** and **9**. Consequently, these materials can cover the 440–640 nm range in emission bands (Fig. 2).

Finally, we preliminary investigated the fluorescent character in water for biological applications. Compounds discussed in this Letter were dissolved in H_2O/CH_3CN (49:1) except for **9b**. Fluorescence spectra are presented in Figure 3 (also see Supplementary data; Fig. S3 and Table S2). They covered the 480–630 nm range in emission bands. The relations between the structures and the emission characters observed in CH_3CN (vide supra) were varied, that would be caused by a protic character in H_2O/CH_3CN conditions.

In summary, we reported the synthesis and photophysical properties of 1,2-dihydroindol-3-one derivatives obtained by the simple reactions. The π-system is easily expanded using a Robinson ring annulation. Their emission peaks ranged from 440 nm to 640 nm, which largely covers the visible region (Fig. 2). Our results show that compounds based on 1,2-dihydroindol-3-one unit are useful for various fluorophores. Some of them were dissolved in H_2O/CH_3CN and emitted under such conditions. And it will be possible that, for the biological application, a water solubilizing moiety and/or a bioconjugatable reactive group is introduced onto the indolic nitrogen in these compounds using 'post-synthetic derivatization' strategy.[25] Investigation of further π-expansion using Robinson ring annulation is underway to ensure the longer emission peaks.

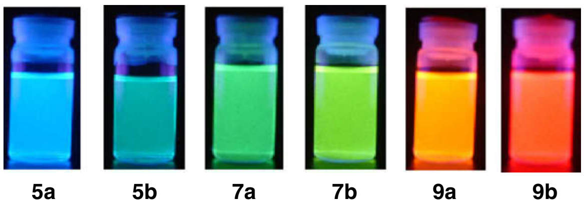


Figure 2. Photographs of **5a**, **5b**, **7a**, **7b**, **9a**, and **9b** in CH_3CN under 365 nm irradiation.

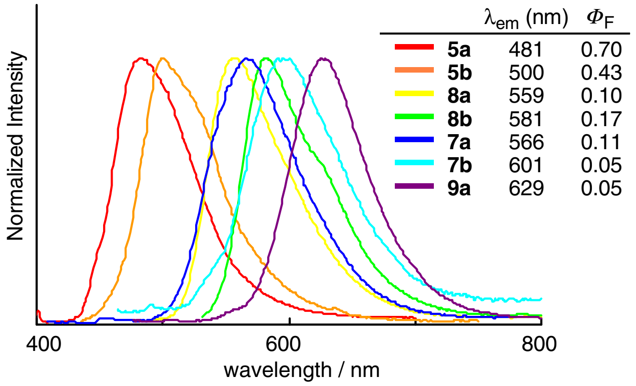


Figure 3. FL spectra of **5a**, **5b**, **8a**, **8b**, **7a**, **7b**, and **9a** in H_2O/CH_3CN (49:1) excited at λ_{max}. Quantum yields (Φ_F) were determined with fluorescein ($\Phi_F = 0.90$) as a standard (3.0×10^{-7} M in 0.1 M aq NaOH).

Supplementary data

Supplementary data (experimental procedures, spectroscopic data for all new compounds, UV–vis absorption and FL spectra in cyclohexane, THF, CH_3CN, and H_2O/CH_3CN (49:1), and photographs of all compounds discussed in this manuscript under 365 nm irradiation) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.098.

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21. *Preparation of* **7a**: To a solution of **6** (0.910 g, 4.81 mmol) in EtOH (25 mL) were added methyl vinyl ketone (0.41 mL, 5.1 mmol) and DBU (71.9 μL, 0.481 mmol) at room temperature. The mixture was refluxed for 18 h. To the reaction mixture was added a solution of NaOH (0.595 g, 14.9 mmol) in H_2O (5 mL). After being stirred for additional 3 h in refluxing conditions, the mixture was neutralized with 1 M aq HCl (a few drops). To a solution was added brine (50 mL), and the solution was extracted with EtOAc (30 mL × 3). The combined organic layer was dried with $MgSO_4$. After the filtration and evaporation, the residue was subjected to column chromatography on SiO_2 (hexane/EtOAc = 1:1) to give **7a** (0.838 g, 4.21 mmol) in 87% yield as yellow solid. The solid was further purified by reprecipitation from hexane and EtOAc to give orange plate crystals: mp 153.0–154.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3H), 2.15 (dt, 1H, *J* = 6.4 and 12.5 Hz), 2.26 (ddd, 1H, *J* = 2.2, 5.4 and 12.6 Hz), 2.46 (ddd, 1H, *J* = 5.4, 12.5 and 18.3 Hz), 2.57 (ddd, 1H, *J* = 1.5, 6.0 and 18.2 Hz), 4.57 (br s, 1H), 6.14 (s, 1H), 6.80 (d, 1H, *J* = 8.0 Hz), 6.83 (t, 1H, *J* = 7.5 Hz), 7.30 (dt, 1H, *J* = 1.2 and 8.3 Hz), 7.46 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 34.1, 35.2, 63.2, 111.7, 113.8, 119.6, 122.4, 123.8, 133.8, 153.9, 168.2, 197.4; IR (KBr) 3269, 3032, 2968, 1612, 1577, 1469, 1311, 1215, 955, 850, 766, 650 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.00; H, 6.46; N, 7.04.
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