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Synthesis of Coumarin/Phenanthridine-Fused Heterocycles and Their Photochemical and Thermochromic Properties

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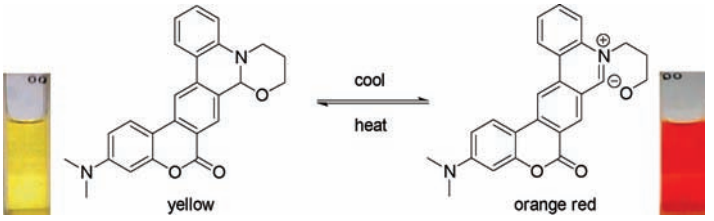
ABSTRACT



Four coumarin and phenanthridine-fused heterocycles were efficiently synthesized using base-mediated annulation of *N*-alkylquinolinium iodide and coumarin as a key step. One compound is found to be sensitive to light and changes color upon UV irradiation; the others are sensitive to heat and possess negative thermochromic properties. A novel light- and heat-sensitive molecular skeleton is introduced.

Heterocyclic rings are one of the fundamental components in the skeleton of the biologically active compounds produced by nature.[1] A facile synthetic route to a new family of heterocycles may not only open the possibility of finding further types of biologically active units for therapeutics but also generate potential functional materials to construct molecular devices. Perhaps because of this, great efforts have been focused on developing new methodologies that increase the structural complexity while decreasing the number of synthetic steps to facilitate the construction of new heterocycles.[2]

In this respect, coumarins and phenanthridines represent two important subsets of heterocycles that have wide applications in various aspects such as drugs,[3] DNA targeting agents,[4] and dyes.[5] While numerous methods for preparations of coumarin[6] and phenanthridine[7] derivatives were developed in the past, the synthesis of compounds with a coumarin and phenanthridine-fused molecular skeleton has never been reported. In light of their potential biological activities and functional properties associated with the coumarin and phenanthridine

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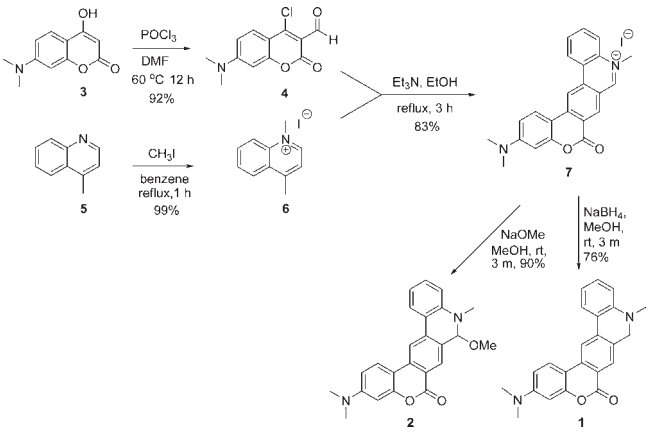
moieties, we envisioned that an efficient preparation of the novel coumarin and phenanthridine-fused heterocycles may generate compounds with unprecedented properties. Here we report our efforts toward the development of a facile scaffold using base-mediated annulation of *N*-alkylquinolinium salt and coumarin. The photochemical behaviors and the thermochromic properties of the synthesized compounds were explored by UV−vis, EPR, and variable temperature proton NMR spectroscopy.

Scheme 1



Scheme 1 shows the preparation of the coumarin and phenanthridine-fused heterocycles **1** and **2**. The starting material 7-dimethylamino-4-hydroxycoumarin (**3**)[8] was first converted to 4-chloro-7-dimethylamino-2-oxo-2*H*-chromene-3-carbaldehyde (**4**) by treating it with phosphorus oxychloride in DMF. The condensation of **4** and *N*-methyl 4-methylquinolinium iodide (**6**) in the presence of triethylamine as a base in ethanol under reflux conditions gave the intermediate iminium iodide **7**, which can be trapped by sodium borohydride or sodium methoxide in methanol to afford the target compounds **1** and **2**, respectively. Compound **6** was prepared by refluxing the commercially available 4-methylquinoline (**5**) with methyl iodide in benzene. The molecular structures of **7**, **1**, and **2** were elucidated by X-ray crystallography as shown in Figure 1,[9] which all reveal a coumarin and phenanthridine-fused skeleton. The proposed mechanism for the annulation is depicted in Scheme 2. It starts with a triethylamine-mediated deprotonation of the 4-methyl hydrogen on **6** to yield 1,4-dihydro-1-methyl-4-methylenequinoline (**8**). The condensation of **8** and **4** affords the intermediate **9**, which then undergoes intramolecular cyclization to give the alcohol **10**. The final dehydration of **10**

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(9) Crystallographic data (excluding structure factors) for **1**, **2**, **7**, **13**, and **17** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-778474, -778475, -791032, -786005, and -786004, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

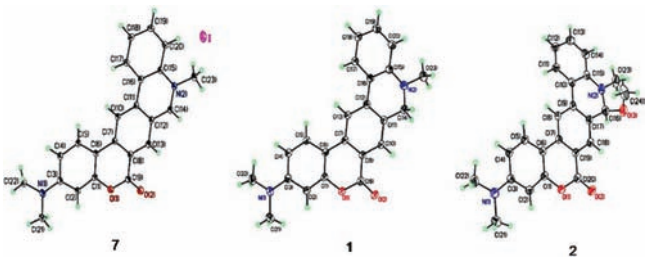
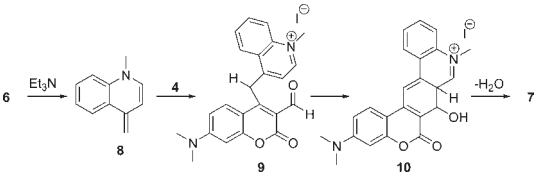


Figure 1. ORTEP crystal structures of heterocycles **7**, **1**, and **2**.

Scheme 2



generates the aromatized iminium iodide **7**. This base-mediated annulation not only provides a quick access to a coumarin and phenanthridine-fused skeleton but also offers the possibility of synthesizing a library of potentially bioactive compounds. Presumably, this annulation methodology can also be extended to the synthesis of other *N*-heterocycles such as naphthalene and phenanthridine-fused derivatives.

Having characterized the structures of heterocycles **1** and **2**, we turned our attention toward their photochemical and thermochromic properties. Compound **1** was found to be highly sensitive to light. Upon UV irradiation (352 nm), the light yellow **1** in methylene chloride turns red within seconds. This light-induced color variation is irreversible even when the photogenerated product is heated. Figure 2 shows the UV−vis absorbance changes of **1** before and after irradiation. With the increase of exposure time, a new absorption band with the peak

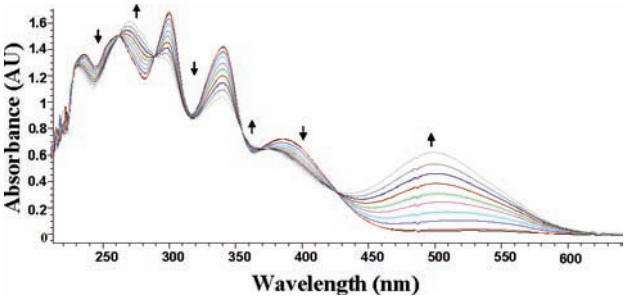
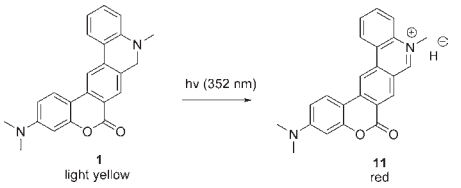


Figure 2. UV−vis spectra of **1** (1.0×10^{-4} M in CH_2Cl_2) obtained with different exposure time (352 nm), 0−4 min with 30 s increments.

wavelength around 499 nm gradually increases, along with the appearance of five isosbestic points at 262, 289, 355, 369, and 425 nm.

Scheme 3



Although the proposed photogenerated product **11** (Scheme 3) is not stable enough to be isolated and characterized, its formation is confirmed by the ^{1}H NMR spectra of compound **1** in deuterated DMSO after irradiation, which clearly indicate the appearance of the characteristic iminium carbon hydrogen, *N*-methyl, and hydride ion absorption signals of the iminium hydride **11** at 10.10, 4.48, and −35.33 ppm, respectively (Supporting Information (SI), Figure S1).[10] The photoreaction presumably involves first a light-induced homolytic C−H bond cleavage to generate a benzylic radical and a hydrogen radical and is followed by an electron transfer from the former to the latter to afford the ion pair **11**. Evidence for the presence of radical species is furnished by EPR-spectral studies. The irradiated solution of **1** in degassed methylene chloride at room temperature exhibits EPR signals around 3500−3550 G (Figure 3), revealing a typical EPR absorption pattern of diradical species.

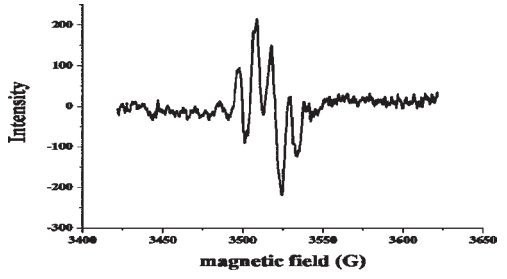


Figure 3. EPR spectra of **1** in degassed CH_2Cl_2 solution at 25 °C, recorded after irradiation with a 360 nm laser source.

Theoretically, this iminium hydride **11** may function as a light-induced hydride source in organocatalytic hydride reductions.[11]

Interestingly, compound **2** was found to exhibit negative thermochromic properties in protic solvents. It is light yellow in methanol at +50 °C and turns orange red as the temperature is decreased. The color reverts swiftly back to yellow when the temperature is increased. Figure 4 shows the UV−vis absorption spectra of **2** in methanol under temperatures between +50 to 0 °C. When the temperature is decreased, the absorption band with the peak wavelength around 485 nm gradually increases, along with the appearance of four isosbestic points at 226, 253, 290, and 412 nm. When the temperature is increased, the red species in methanol quickly decays away with the disappearance, i.e., turning yellow, of the 485 nm band.

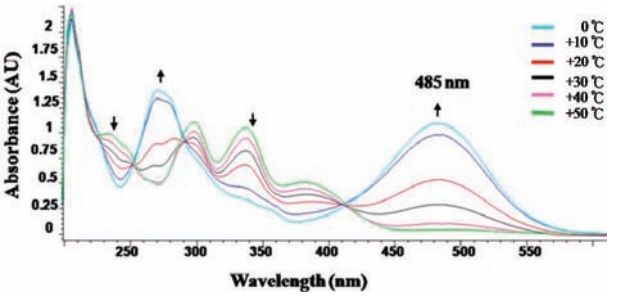
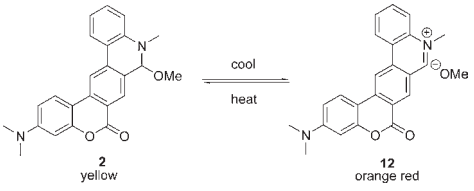


Figure 4. UV−vis spectra of **2** (2.0×10^{-5} M in MeOH) at temperatures between +50 to 0 °C, with decrements of 10 °C.

This reversible thermochromic process is repeated ten times without significant changes in the UV−vis spectra (SI, Figure S3). Scheme 4 shows the proposed negative thermochromic switch between **2** and **12**. While various attempts to isolate the iminium methoxide **12** proved to be futile, variable temperature NMR experiments of **2** in CD_3OD did provide evidence for its emergence, that is, the appearance of three new discernible singlets at around 9.63, 5.19, and 4.36 ppm (with the integration ratio close to 1:3:3), which were assigned to the absorptions of the iminium carbon hydrogen, methoxide hydrogens, and *N*-methyl hydrogens of **12**, respectively (SI, Figure S2).[10]

Scheme 4



The switching between **12** and **2** probably involves a thermally induced nucleophilic attack of the methoxide ion to the iminium carbon of the highly conjugated orange red ion pair **12** to give the less conjugated yellow neutral species **2**. When the temperature is decreased, **2** reverts to **12** via the elimination of the methoxide ion to regain the aromaticity. Although the methoxide ion is far from a good leaving group, we speculate that its elimination from the coumarin/phenanthridine-fused skeleton at lower temperature is

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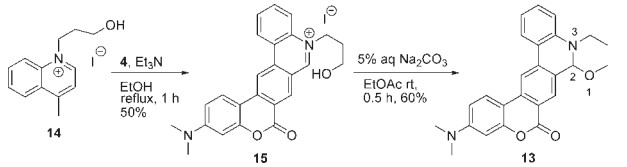
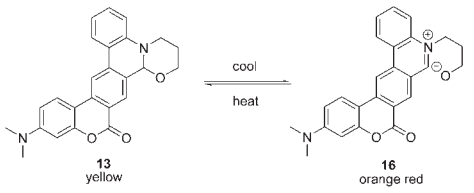
substantially facilitated by adopting an *antiperiplanar* conformation relative to the lone pair electrons on the adjacent nitrogen atom, as indicated in the X-ray crystal structure of **2** (Figure 1). Furthermore, the fact that the OMe group is nearly orthogonal to the coumarin/phenanthridine-fused plane also leads to a decrease of the C−OMe bond strength (the C−OMe bond length reads 1.436 Å, which indeed is longer than the average C−O bond length). To the best of our knowledge, the thermal equilibrium between **2** and **12** represents the first example of organic negative thermochromism that involves the dissociation of an alkoxide (methoxide) ion as a leaving group rather than the commonly seen neutral amines.[12]

Scheme 5



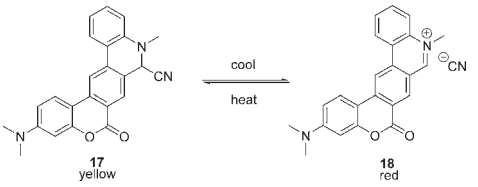
In an effort to alter the thermochromic switch between **2** and **12** from an intermolecular to an intramolecular reaction, the oxazine **13** was designed and prepared by a similar method as described in Scheme 5. The 4-methylquinoline (**5**) was first *N*-alkylated by reacting with 3-iodopropan-1-ol in benzene to give the imminium iodide **14**, which was followed by condensation with **4** in the presence of triethylamine in ethanol under reflux conditions to give the iminium iodide **15**. Final cyclization was realized by treating **15** with aqueous sodium carbonate in ethyl acetate at room temperature to afford **13**. Indeed, **13** was found to exhibit negative thermochromic properties (SI, Figures S5−S7). It is light yellow in methanol at room temperature and turns orange red (zwitterion **16**) as the temperature is decreased (Scheme 6).

Scheme 6



Since cyanide is a better leaving group than methoxide, carbonitrile **17** was also prepared by treating iminium iodide **7** with potassium cyanide in methanol to further explore the scope of this new type of thermochromic reactions. As expected, the carbonitrile **17** was found to possess the negative thermochromic properties similar to that of **2** and **13** (Supporting Information, Figures S9−S11). It is light yellow in methanol at +60 °C and turns red (iminium cyanide **18**) as the temperature is decreased (Scheme 7).

Scheme 7



The observation of light-sensitive and thermochromic properties of these coumarin/phenanthridine-fused heterocycles suggests that light or heat can conceivably serve as a third controllable parameter (stimulus) in addition to pH jump and redox potential for the newly developed phenanthridine-based lockable molecular switch.[13] Moreover, this coumarin and phenanthridine-fused molecular skeleton may also function as a potential photoresponsive chromophore in the design of new photochromic colorants, if an appropriate functional group is introduced onto the phenanthridine moiety. Considering the redox- and light-sensitive properties associated with phenanthridine derivatives along with the intrinsic fluorescence properties of coumarins, we believe that this readily available coumarin and phenanthridine-fused scaffold may have a major influence on the future development of novel coumarin/phenanthridine-based organic functional materials.

In summary, we have developed an efficient route for the construction of a novel coumarin and phenanthridine-fused molecular skeleton via an Et_3N-mediated condensation of *N*-alkylquinolinium salt and coumarin. Four compounds were synthesized as examples for illustration, and their photochemical and thermochromic properties were investigated. Our studies indicate that **1** is sensitive to light, and **2**, **13**, and **17** possess negative thermochromic properties. Further development of related photochromic colorants based on this coumarin and phenanthridine-fused skeleton is currently underway.

Acknowledgment. We thank the National Science Council of the Republic of China, Taiwan, for financially supporting this research under Contract No. NSC 98-2113-M-029-003-MY2.

Supporting Information Available. Synthesis of **1**, **2**, **4**, **6**, **7**, **13**−**15**, and **17**; experimental details; and additional spectra. X-ray structure details for **1**, **2**, **7**, **13**, and **17** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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