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2-Pyridone-based fluorophores containing 4-dialkylamino-phenyl group: Synthesis and fluorescence properties in solutions and in solid state

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ABSTRACT

Novel highly emissive 2-pyridone-based compounds **3a,b** and **4a–d** were synthesized by a convenient one-pot method from 4-(dialkylamino)acetophenones (**1a**,**b**) and cyanoketene dithioacetal (**2a**) or sulfonyl ketene dithioacetals (**2b**,**c**), and their fluorescence properties were investigated. A simple structure modification of 2-pyridones significantly affected their optical properties including the emission wavelength and fluorescence intensity. All the 6-(4-dialkylamino)phenyl-2-pyridones showed positive solvatofluorochromism and intense blue-green fluorescence in nonpolar solvents such as chloroform (Φ: 0.80–0.92) and dichloromethane (Φ: 0.83–0.94). A hypsochromic shift of the fluorescence emission maxima and strong fluorescence in a polar solvent were observed by substituting the dimethylamino group with a diethylamino group. Introduction of a sulfonyl group disturbed the molecular planarity of compounds **4a**, **4b**, and **4d**, resulting in a strong fluorescence in acetone (Φ: 0.86–0.95) and acetonitrile (Φ: 0.59–0.88). These results indicate that 2-pyridone-based compounds have great potential as fluorophores for various practical applications.

1. Introduction

Fluorescence has been applied in the fields of chemical, medical, and material sciences because of its high sensitivity and color tunability. Special attention has been devoted to develop new fluorophores using small organic molecules, fluorescent proteins, and quantum dots, and notable progress has been made in these fields [1–5]. Small organic molecules have great advantages as fluorophores because their fluorescence properties can be easily optimized by synthetic chemical modifications. Particularly, fluorescent heterocyclic compounds have attracted much attention as fluorescent probes for clinical diagnostics and as light-emitting materials for organic electroluminescent devices [6–9].

2-Pyridone is an *N*-heterocyclic compound found in diverse biologically active natural products. Because the 2-pyridone scaffold plays an important role in bioactive substances, several 2-pyridone-based compounds possessing a broad spectrum of

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biological activities such as antibacterial, antifungal, anticancer, antiviral, antianxiety, and antimalarial activities have been reported [10–16]. Recently, we reported the synthesis of fluorescent 2-pyridone derivatives such as 6-aryl-2*H*-pyran-2-ones from ketene dithioacetals [17]. These 2-pyridone derivatives exhibited modest fluorescence in the solid state by aggregation-induced emission enhancement (AIEE) phenomena, whereas fairly weak or no fluorescence was observed in solutions. In some cases such as in visualizing the structure and function of biological substances, the emission of light in solutions is an essential characteristic of fluorophores. To the best of our knowledge, 2-pyridone derivatives that exhibit a strong fluorescence in solutions have not yet been reported. During our search for novel fluorophores, fluorescent dyes based on 2-pyrone, an oxygen analog of 2-pyridone, were also synthesized [18–21]. The electron-donating or -withdrawing substitution pattern at the 2-pyrone ring was necessary for push–pull induced intramolecular charge transfer (ICT) and considerably affected the fluorescence properties. The previously synthesized 2-pyrone derivatives exhibited almost no fluorescence in solutions; however, the 2-pyrone derivatives with appropriate substituents exhibited light emission in both the solid state and solutions. In particular, the 2-pyrone derivative with a (4-diethylamino)phenyl group at the 6-position of the 2-pyrone ring showed intense fluorescence ($\Phi = 0.95$) in chloroform because the molecular aggregation was suppressed by substituting the dimethylamino group with a diethylamino group [21]. Therefore, we envisioned that a strong fluorescence emission in solutions can be obtained by reducing the molecular aggregation of 2-pyridone. Herein, we report the synthesis and characterization of novel 2-pyridone derivatives, 6-(4-dialkylamino)phenyl-2-pyridones, which showed interesting fluorescence properties including the fluorescence intensity, emission wavelength, and solvatofluorochromism that can be attributed to the substitution effect.

2. Experimental

The compounds were identified and the fluorescence properties were measured by following standard procedures using the following equipment. The melting points were determined using a Mitamura Riken Kogyo Mel-Temp apparatus or a Laboratory Devices Mel-Temp II apparatus and were uncorrected. The IR spectra were recorded in KBr pellets using a Jasco 810 or Shimadzu IR-460 spectrometer. The UV absorption spectra were recorded in 95% ethanol using a Hitachi 323 spectrometer. The fluorescence spectra were recorded using a Shimadzu RF-5300pc spectrofluorometer. The NMR spectra were recorded using Gemini 300NMR (300 MHz), and JEOL-GX-400 (400 MHz) spectrometers using tetramethylsilane as the internal standard. The mass spectra were recorded using a JEOL DX-303 mass spectrometer. Elemental microanalyses were performed using a Perkin–Elmer CHN analyzer at Nagasaki University. All the chemicals were reagent grade and used as received without further purification unless otherwise specified.

2.1. Synthesis of 6-(4-(dimethylamino)phenyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(**3a**)

A solution of 4-(dimethylamino)acetophenone (**1a**; 1.63 g, 10.0 mmol) in DMSO (20 mL) was cooled to 10–15 °C. Powdered NaOH (1.60 g, 40 mmol) was added to the solution, and the mixture was stirred for 10 min at the same temperature. Then, methyl 2-cyano-3,3-bis(methylsulfanyl)acrylate (**2a**; 2.03 g, 10.0 mmol) was slowly added to the mixture under stirring at 10–15 °C over a period of 30 min. Stirring was continued for a further 5 h at the same temperature. The reaction mixture was poured into 300 mL ice water, acidified with 10% HCl, and then stand for 30 min. The resulting caramel-colored liquid product was collected by decantation and washed several times with water. A mixture of the residue, water, and morpholine (3.00 g, 34.4 mmol) was heated for 20 min at ~200 °C. After cooling, the residue was collected by filtration and washed with 10 mL methanol to give compound **3a** (0.96 g, 3.37 mmol) as yellow crystals in 34% yield [16]. An analytical sample of compound **3a** was recrystallized from DMF and methanol, affording yellow crystals, mp 329–330 °C. IR (KBr, cm^{-1}) ν: 2922, 2208 (CN), 1607 (CO), 1585, 1534. UV (EtOH) λ_{max} nm (log ε): 410 (4.67). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.62 (3H, s, SMe), 3.08 (6H, s, NMe_2), 6.32 (1H, s, 5-H), 6.77 (2H, d, $J = 9.0$ Hz, 3′, 5′-H), 7.55 (2H, d, $J = 9.0$ Hz, 2′, 6′-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.8, 49.9, 91.8, 98.2, 111.5, 115.9, 118.7, 128.9, 152.2, 160.6, 162.9, 168.6. MS *m*/*z*: 286 ($M^+ + 1$, 45), 285 (M^+, 100), 284 (88), 269 (8), 226 (14), 44 (6). Anal. Calcd. for $C_{15}H_{15}N_3SO$ = 285.0936: C, 63.13; H, 5.30; N, 14.73%. Found: C, 62.85; H, 5.28; N, 14.65%.

2.2. Synthesis of 6-(4-(diethylamino)phenyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**3b**)

Compound **3b** (37.0 mg 0.12 mmol) was prepared in 2.4% yield from compounds **1b** (0.96 g, 5.0 mmol) and **2a** (1.02 g, 5.0 mmol) in a similar manner as described for the synthesis of compound **3a**. An analytical sample of compound **3b** was recrystallized from DMF and methanol, affording yellow crystals, mp 282–284 °C. IR (KBr, cm^{-1}) ν: 2967, 2210, 1603, 1587, 1528, 1221, 1150, 795. ^{1}H NMR (DMSO-d6, 400 MHz) δ: 1.22 (6H, t, $J = 7.1$ Hz, $-CH_2$-Me), 2.61 (3H, s, SMe), 3.43(4H, q, $J = 7.1$ Hz, N–CH_2–), 6.33 (1H, s, 5-H), 6.78 (2H, d, $J = 9.1$ Hz, 3′, 5′-H), 7.62 (2H, d, $J = 9.1$ Hz, 2′, 6′-H), 10.99 (1/2H, brs, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.4, 12.5, 13.7, 43.8, 91.5, 98.0, 111.0, 116.0, 116.6, 129.3, 149.8, 150.5, 160.7, 162.9. Ms *m*/*z*: 314 (M^++1, 12), 313 (M^+, 59), 299 (20), 298 (100), 270 (11). Anal. Calcd for $C_{17}H_{19}N_3SO$ = 313.1249. C, 65.15; H, 6.11; N, 13.41%. Found: C, 65.03; H, 6.13; N, 13.61%.

2.3. Synthesis of 6-(4-(diethylamino)phenyl)-4-(methylsulfanyl)-3-(phenylsulfonyl)pyridin-2(1H)-one (**4a**)

A solution of 4-(dimethylamino)acetophenone (**1a**; 1.63 g, 10.0 mmol) in DMSO (20 mL) was cooled to 10–15 °C. One-half of the powdered NaOH (0.56 g, 14.0 mmol) was added to the solution, and the mixture was stirred at 10–15 °C for 10 min. Then, 3,3-bis(methylsulfanyl)-2-phenylsulfonylacrylonitrile (**2b**; 1.43 g, 5.0 mmol) was slowly added to the mixture under stirring at 10–15 °C over a period of 30 min. Stirring was continued for a further 2 h at the same temperature. The remaining half of the powdered NaOH (0.56 g, 14.0 mmol) was added to the reaction mixture, and the mixture was stirred for 20 min. Then, compound **2b** (1.43 g, 5.0 mmol) was slowly added to the reaction mixture, and the mixture was stirred for 3 h at the same temperature. The reaction mixture was poured into 300 mL ice water, acidified with 10% HCl, and stand for 30 min. The resulting precipitate was collected by filtration and washed several times with water. Water and morpholine (1.5 g, 17.2 mmol) were added to the precipitate, and the mixture was heated for 20 min at ~200 °C. After cooling, the residue was treated with 10 mL methanol, affording compound **4a** (0.96 g, 2.40 mmol) as yellow crystals in 24% yield. An analytical sample of compound **4a** was recrystallized from DMF and methanol, affording orange needles, mp 316–318 °C. IR (KBr, cm^{-1}) ν: 3457 (br, NH or OH), 2923, 2368, 1613, 1531, 1149. UV (EtOH) λ_{max} nm (log ε): 400 (4.41). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.54 (3H, s, Me), 3.05 (6H, s, NMe_2), 6.42 (1H, s, 5-H), 6.88 (2H, d, $J = 8.8$ Hz, 3″, 5″-H), 7.28 (2H, m, 3′,5′-H), 7.44 (1H, m, 4′-H), 7.77 (2H, d, $J = 9.0$ Hz, 2″, 6″-H), 8.05 (2H, d, $J = 8.3$ Hz, 2′, 6′-H), 11.78 (1/2H, br s, NH). ^{13}C