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A new series of 2,5-bis(4-methylphenyl)-1,3,4-oxadiazole derivatives: their synthesis and fluorescence properties for anion sensors

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Abstract—A new series of 2,5-bis(4-methylphenyl)-1,3,4-oxadiazole derivatives containing various substituted groups on the *ortho*-position to oxadiazole ring was synthesized and their fluorescent sensor properties were investigated. The fluorescent sensor molecules showed UV absorption shift as well as fluorescence emission shift upon exposure to fluoride anion in DMF solution, which was considerably dependent on the substituent attached on the phenyl group. The new sensory compound, **1d** can be used as a fluoride anion sensor in terms of naked-eye detection and fluorescent sensing with high selectivity.

Recently, there is a growing interest in the design and synthesis of fluorescent organic compounds for chemical sensors because of their potential active components in environmental and bio-analytical fields.[1] The simple modification of the chemical structure, the solubility, and the optical properties of these organic materials enables us to demonstrate a variety of molecular structures. Among, fluorescent materials, a great deal of attention has been received with heterocyclic ring system due to their interesting properties closely related to optical and optoelectronic properties. The exploration of conjugated 1,3,4-oxadiazole-containing polymers and small molecules offers enhanced thermal and photophysical stability as well as improved electron-transporting property. Considerable research on the synthetic routes for oxadiazole moieties was accomplished as polymer backbone constituents[2] and side-chains,[3] and as small molecules.[4] Since oxadiazole groups are known as one of the most extensively investigated class of electron-accepting species, oxadiazole-based compounds have been used as electron transport materials in organic light emitting diodes (OLEDs).[5] The optical and electrical properties exhibited by such heterocyclic cores are mainly attributed to their electron deficiency, high photoluminescence quantum yields, and good thermal and chemical stability of the oxadiazole ring. It has been reported that introduction of oxadiazole units into the side-chain[6] or main chain[7] of poly(phenylenevinylene)s (PPVs) could significantly improve their LED device efficiency. By utilization of such heterocyclic rings, in which the molecular symmetry of the central core is reduced leading to a less favorable packing in the crystal state.[8] In addition, oxadiazole derivatives were reported as sensitive sensory materials in the forms of polymeric materials[9] and of small molecular materials[10] for fluoride or explosive nitroaromatic compound sensing.

It has been extensively studied on the development of fluorescent and colorimetric sensors for anions, which are both highly sensitive at low analyte concentration and convenient to use.[11] Among chemosensors for anions, phosphate and fluoride ion sensing are of special interest due to their importance in a number of disease states and environmental pollutants.[12] Fluoride has unique chemical properties, and its recognition and detection are of growing interest because it is associated with nerve gas, the analysis of drinking water, and the refinement of uranium used in nuclear weapon manufacture. As a result, there is a need to develop selective methods for fluoride detection in environments that are not easily served by conventional ion selective electrodes. In a previous paper, we reported an oxadiazole

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analogue with *ortho*-hydroxyphenyl group acting as a fluoride-selective sensor.[10b] Addition of fluoride anion into the sensory compound caused a color change as well as blue shift of emission, which was explained by intramolecular hydrogen bond alteration. Herein, we are reporting synthesis of new π-conjugated oxadiazole compounds **1a**–**e** containing blocked *ortho*-hydroxyphenyl units, and this class of compounds was found to exhibit strong fluorescence in their solutions. Moreover, one of these analogues **1d** showed anion recognition event even though the intramolecular hydrogen bond was forbidden.

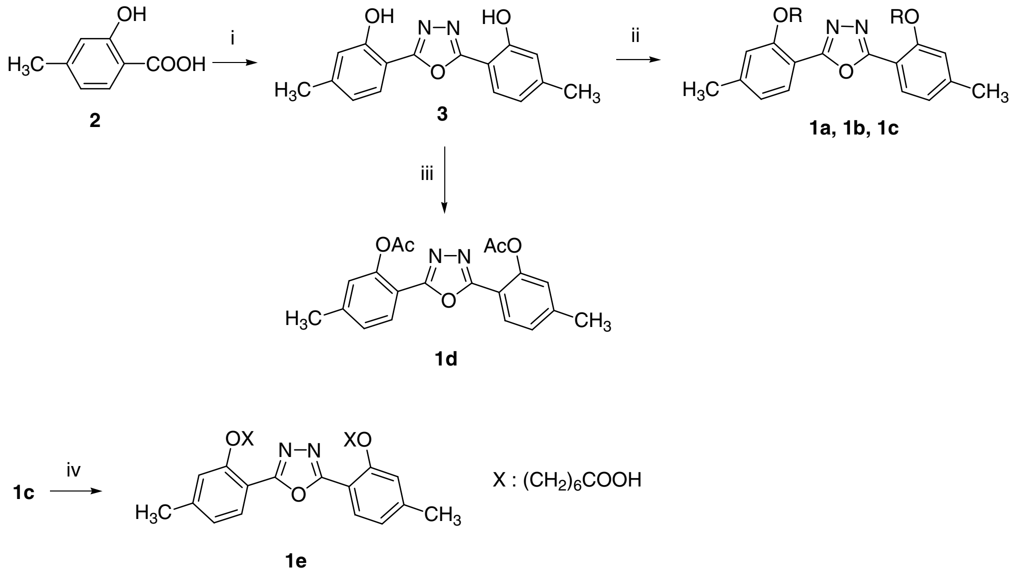
Compound **3**, 2,5-bis(2-hydroxy-4-methylphenyl)-1,3,4-oxadiazole was synthesized in a single step by a reaction with 4-methylsalicylic acid and aminourea in polyphosphoric acid (PPA) at 130 °C according to the reported method (Scheme 1).[13] Compounds **1a**–**c** were synthesized by Williamson ether synthesis with the corresponding halides and **3** with good yields. Compound **1d** was obtained by reaction with **3** and acetic anhydride in methylene chloride in the presence of triethylamine. Compound **1e** was obtained by hydrolysis of **1c** using concentrated hydrochloric acid. All the compounds are readily soluble in organic solvents such as tetrahydrofuran (THF), chloroform, and dichloromethane, and were characterized by ^{1}H NMR spectroscopy and elemental analysis.[14] The spectroscopic results were consistent with the proposed molecular structures. Compounds **1a**–**e** are stable such that they can be stored at ambient temperature for a long period more than three months. Optical characteristics of **1a**–**e** were investigated in DMF solution. Their absorption and fluorescence emission data in DMF are summarized in Table 1. Compounds **1a**–**c** and **1e** show well-resolved vibronic structures with two distinct absorption maxima around 270 and 310 nm, while a single absorption at 286 nm was exhibited by **1d**. It has already been reported that the number of absorption bands depends on the substituent on the hydroxyl group and solvent used.[9c] It is presumed that the conjugated resonance structure of ester bond with benzene ring in **1d** played a major role in the single absorption.

Table 1. UV–vis and photoluminescence data of **1a**–**e**[a] in DMF

Compound	Before addition of F^-		After addition of F^{-b}	
	λ_{max} (nm)	λ_{em} (nm)[c]	λ_{max} (nm)	λ_{em} (nm)[c]
1a	274, 312	366	274, 312	366
1b	274, 314	365	274, 314	365
1c	273, 315	369	273, 315	369
1d	286	359	382	448
1e	274, 312	368	274, 312	368

[a] $[\mathbf{1}] = 1.0 \times 10^{-5}$ M.
[b] $[F^-] = 1.0 \times 10^{-3}$ M.
[c] Excited at 324 nm.

Compounds **1a**–**e** exhibited the fluorescence emission maxima ranging from 359 to 368 nm as shown in Table 1. Since the hydroxyl groups in **1** were blocked with various substituents, the long wavelength emission from keto tautomer was not observed, which was frequently seen in the free hydroxyl group-containing oxadiazole with the excited state intramolecular proton transfer (ESIPT) as reported earlier.[9c,10b] Absorption and fluorescence spectra of **1d** in DMF after addition of fluoride anion (as its tetrabutylammonium counterion) are shown in Figures 1 and 2, respectively, and the related spectra maxima of other compounds are summarized in Table 1. In the cases of **1a**–**c** and **1e**, the absorption and emission spectral maxima remain virtually unchanged. Figure 1 shows absorption changes of **1d** upon addition of F^-, AcO^-, Br^-, Cl^-, and I^-. Only the fluoride anion induces a red shift of the absorption from 286 nm to 382 nm with a color change from colorless to yellow. The color change of **1d** upon exposure to



Scheme 1. Synthesis of 2,5-bis(4-methylphenyl)-1,3,4-oxadiazole derivatives. Reagents and conditions: (i) aminourea hydrochloride, PPA, 130 °C; (ii) NaH, DMF, 130 °C (**1a**: R = CH_3, **1b**: R = 2-hydroxy(2-ethoxy)ethoxy, **1c**: R = 6-cyanohexyl); (iii) $(CH_3CO)_2$, Et_3N, CH_2Cl_2, room temperature; (iv) concentrated HCl, 90 °C.

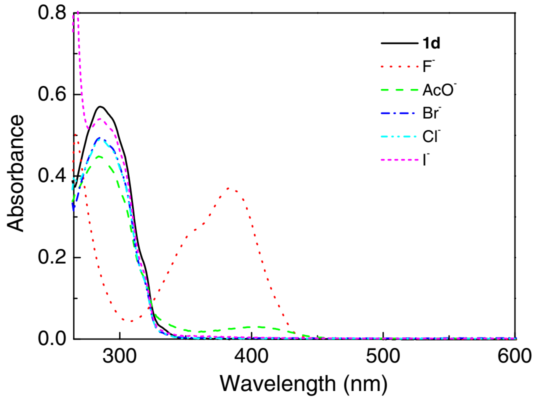


Figure 1. UV–vis absorption spectra of **1d** (1×10^{-5} M) in DMF upon titration with tetrabutylammonium fluoride (TBAF, 100 equiv).

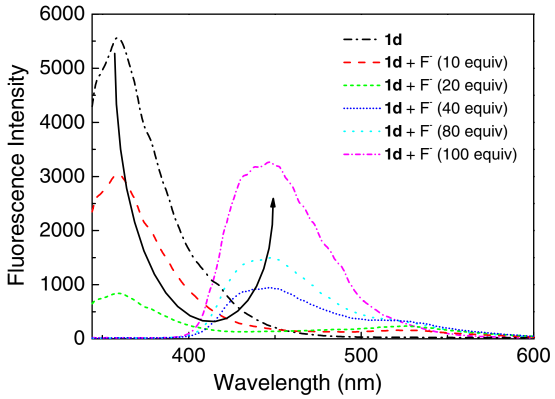


Figure 2. Emission spectra of **1d** (1×10^{-5} M) in DMF upon titration with TBAF.

fluoride anion can be used for naked-eye detection of F^-. Similar results on the possible naked-eye detection with oxadiazole analogues with adjacent hydroxyl group were drawn by precedent experiments accomplished by Wang et al. and by our group, which resulted from the strong intramolecular charge transfer effect.[10a,b] Though **1d** has acetyl-protected hydroxyl groups adjacent to oxadiazole ring, that is, in the absence of intramolecular hydrogen bonding, it is believed that the electron-withdrawing effect was facilitated by acetyl group and this leaded to higher anion binding affinities.[15] New emission maximum can be observed upon addition of excess fluoride anion to **1d** as shown in Figure 2. Initially, upon exposure to fluoride anion, original emission band at 359 nm decreased dramatically with appearance of small emission band at 530 nm. As the concentration of fluoride anion increased more than 40 equiv, a new and broad emission band at 448 nm was newly formed and the fluorescence intensity was gradually enhanced, of which the new emission maximum appeared at the wavelength of the absorption band edge of fluoride-added solution. Demonstration of dual fluorescence colors depending on the analyte concentration is rare in the sensory system. Though the long wavelength emission appeared by addition of anion, it did not result from the ESIPT tautomer, because long wavelength emission (keto form emission) generally centered above 500 nm as reported earlier.[16] The ^{1}H NMR F^- titration experiment in **1d** did not exhibit a formation of new peak, especially free hydroxyl group at 9–10 ppm, responsible for cleavage of acetyl group from **1d** (Fig. 3). However it is clearly seen the considerable up-field shifts of three benzene protons. For the up-field shifts in NMR spectra, strong electron-donating effect through anion to benzene ring is responsible for the spectral changes, which affects the electron distribution of benzene group.[17] Thus it is presumed that the structural variation by addition of fluoride anion was not expected for the new emission at 448 nm, presumed that significant electron or energy transfer occurred in the presence of fluoride anion. Fluorescence emission shift as well as absorption changes upon addition of fluoride originate from the enhanced electron density on oxygen atom, which strengthens the intramolecular charge transfer (ICT) effect between the electron-withdrawing oxadiazole and electron-donating fluoride anion.[18]

As a concluding remark, we have presented a facile synthetic procedure for the preparation of 2,5-bis(4-methylphenyl)-1,3,4-oxadiazole derivatives with various substituents in the *ortho*-position to oxadiazole ring. These compounds are highly blue-luminescent and,

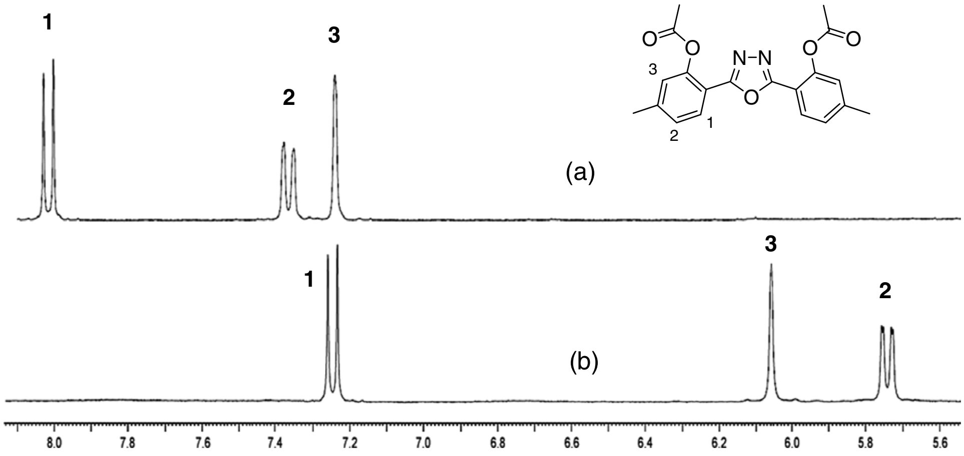


Figure 3. Partial ^{1}H NMR spectra of **1d** in DMSO-d_6 in the absence (a) and in the presence (b) of 100 equiv of TBAF.

especially, **1d** showed fluoride anion sensing behavior in DMF solution in terms of both absorption and fluorescence emission changes, demonstrating naked-eye detection is possible. At the low concentration of fluoride anion (less than 20 equiv), green emission was exhibited from **1d** solution, while blue fluorescence emission was developed in the excess of the anion (more than 40 equiv). The oxadiazole derivative **1d** exhibits colorimetric and fluorometric sensing ability and should be promising for selective sensory molecule with dual fluorescence colors dependent on the anion concentration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.008.

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14. All new compounds showed satisfactory spectroscopic and analytical data (Also see Supplementary data).

    Typical procedure for product **1a**: To a mixture of NaH (320 mg, 8.0 mmol) in DMF (50 mL) was slowly added 2,5-bis[2-hydroxy-4-methylphenyl]-1,3,4-oxadiazole **3** (0.99 g, 3.5 mmol) at room temperature, the mixture was stirred for 30 min at 50 °C. Iodomethane (1.14 g, 8.0 mmol) in DMF (2 mL) was added to this solution, and the mixture was refluxed for 18 h. After cooling to room temperature, this reaction mixture was poured into ethanol and then filtered. The filtered compounds were washed with ethanol. The product was purified by recrystallization in ethanol to afford white powder of pure **1a** in 1.0 g (92%) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.88 (d, 2H, Ar-H), 6.87 (d, 2H, Ar-H), 6.85 (s, 2H, Ar-H), 3.97 (s, 6H, OCH_3), 2.41 (s, 6H, Ar-CH_3). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.81; N, 9.03. Found: C, 69.51; H, 5.60; N, 9.00.

    Typical procedure for product **1d**: To a mixture of **2** (1.41 g, 5.0 mmol) in CH_2Cl_2 (25 mL) was slowly added triethylamine (16 mL) at room temperature, the mixture was stirred for 30 min at 0 °C. Acetic anhydride (16 mL) was slowly added to this solution, and the mixture was stirred for 4 h at room temperature. After the reaction, the reaction mixture was poured into water and then extracted with chloroform. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated. The product was purified by flash column chromatography (ethyl acetate–hexane = 1:1) to afford white powder of pure **1d** in 1.41 g (77%) yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.94 (d, 2H, Ar-H), 7.21 (d, 2H, Ar-H), 7.07 (s, 2H, Ar-H), 2.46 (s, 6H, CH_3), 2.43 (s, 6H, $COCH_3$). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.70; H, 4.99; N 7.65.
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