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Research Article

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The Design, Synthesis and Spectroscopic/Photophysical Characterization of Phosphonate-substituted BODIPY

Fosfonat-substitüye BODIPY Tasarımı, Sentezi ve Spektroskopik/Fotofiziksel Karakterizasyonu

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ABSTRACT

BODIPY compounds continue to attract the attention of scientists from multidisciplinary areas because of the wide range applications and excellent photophysical properties as fluorescent sensors or dyes. In this study, a new phosphonate-substituted BODIPY dye was synthesized by classical condensation-oxidation-complexation method from pyrrolic compounds and aldehyde. The structure and photophysical properties of the synthesized BODIPY compound were determined by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, UV-Vis absorption and fluorescence spectroscopic techniques.

Key Words

BODIPY, fluorescent dyes, phosphonate, pyrrole.

ÖZ

BODIPY bileşikleri floresan sensör veya boya olarak geniş kullanım alanına sahip olması ve üstün fotofiziksel özelliklerinden dolayı multidisipliner alanlardaki bilim insanlarının ilgisini çekmeye devam etmektedir. Bu çalışmada, yeni bir fosfonat-substitüye BODIPY boyası, pirol ve aldehitten kondenzasyon-yükseltgenme-kompleksleşme metodu kullanılarak sentezlenmiştir. Sentezlenen BODIPY bileşiğinin yapısı ve fotofiziksel özellikleri ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, UV-Vis absorpsiyon ve floresans spektroskopi teknikleriyle tanımlanmıştır.

Anahtar Kelimeler

BODIPY, floresan boyalar, fosfonat, pirol.

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INTRODUCTION

Fluorescent dyes draw the attention of scientists from multidisciplinary areas, which includes clinical diagnostics, biotechnology, molecular biology and biochemistry, materials science, and analytical and environmental chemistry. Among the various highly fluorescent dyes, the family of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (abbreviated as BODIPY, Fig. 1) has gained popularity [1-4]. The first member of this dye was reported in 1968 by Treibs and Kreuzer [5] but the usage of BODIPY-based dyes for biological labeling, for electroluminescent devices, as tunable laser dyes, as fluorescent switches and fluorophores in sensors and labels were recognized in the mid 1990's. The use of BODIPY in different areas due to its excellent properties such as insensitivity to the polarity and pH, high molar absorption coefficients, sharp fluorescence peaks with high quantum yields, stability under physiological conditions; has earned great interest in last decades [6,7]. Moreover, their spectroscopic and photo physical properties can be tuned by small structural modifications.

BODIPY compounds could be obtained from the condensation reaction of pyrrolic compounds with aldehydes, acid chlorides or anhydrides and the following oxidation and complexation reactions. In the above context, the design of functionalized BODIPY structures for applications in different areas is especial interest. To the best of our knowledge there is a few examples for phosphonate including BODIPYs in literature. [8,9]. Ziessel et al. introduced the phosphonate fragments either on the boron or on the side chain of the BODIPY dyes for water solubility and hydrolysis of the phosphonate allowed easy isolation of the target molecules [8]. In another work, peptidic phosphonates were employed for the labeling of human leukocyte elastase. These compounds were obtained by clicking a BODIPY fluorophore to phosphono peptide [9].

In this study, novel phosphonate-substituted BODIPY at the *meso* position was synthesized and its structure and photophysical properties was determined by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, UV-Vis absorption and fluorescence spectroscopic techniques.

MATERIALS and METHODS

Chemicals and Instrument

Chemicals and solvents were purchased from Acros Organics, J.T. Baker, Fisher Scientific, Lab-Scan, Riedel-de Haën and were used without further purification. Technical grade hexane and ethyl acetate were obtained from Birpa and purified by fractional distillation. Reactions were monitored by TLC using precoated silica plates (Kieselgel 60, F254, E.Merck), visualized with UV light. Flash column chromatography was performed by using silica gel (0.05-0.63 mm, 230-400 mesh ASTM, E.Merck). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 MHz)and ^{31}P NMR (162 MHz) spectra were

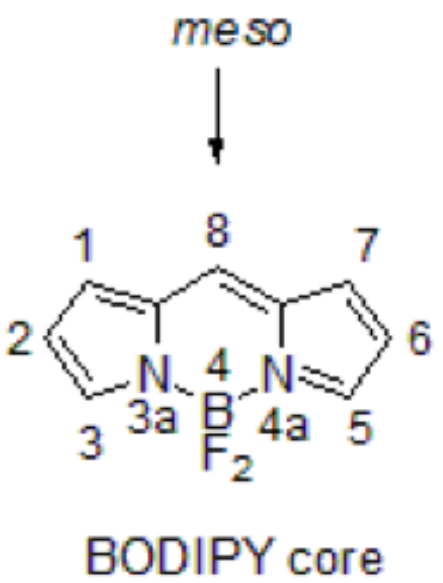
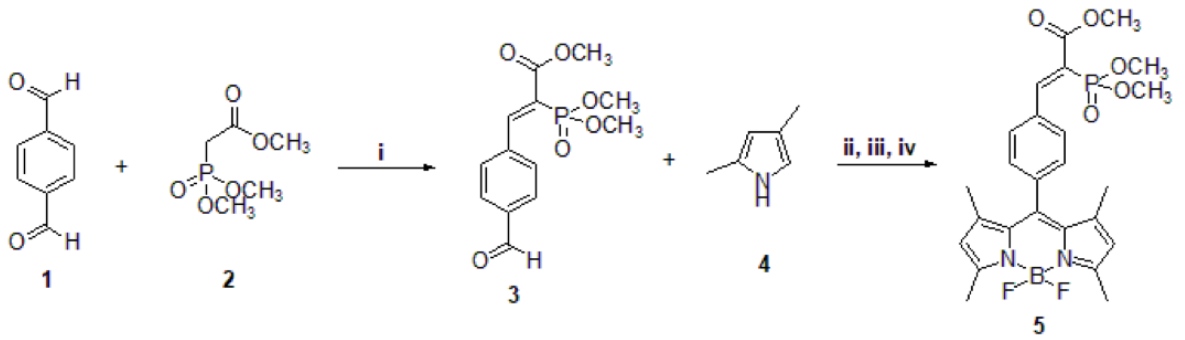


Figure 1. Representation of the BODIPY framework.



Scheme 1. Synthesis of phosphonate-substituted BODIPY. Reagents and Conditions: i) piperidine, acetic acid, toluene, reflux, 8 h; ii) TFA, DCM, rt, 2 h; iii) DDQ, 0.5 h; iv) Et_3N, 15 min, $BF_3.OEt_2$, 2 h.

recorded using $SiMe_4$ and H_3PO_4 as an internal reference with Bruker DPX-400 FT NMR spectrometer. Chemical shifts (δ) were given as ppm and coupling constants (*J*) as Hz. High resolution mass spectra were recorded on an Agilent (1200/6210) TOF LC/MS spectrometer. UV-Vis spectra were recorded on MAPADA Instruments, UV-3100PC Spectrophotometer. Fluorescence spectra were recorded on Thermo Scientific, Lumina Fluorescence Spectrometer.

Synthesis of (*E*)-methyl 2-(dimethoxyphosphoryl)-3-(4-formylphenyl)acrylate (3)

Trimethylphosphonoacetate (**2**) (1.26 g, 6.94 mmol) and terephthalaldehyde (**1**) (0.93 g, 6.94 mmol) were dissolved in toluene and piperidine (0.0178 g, 0.21 mmol) and acetic acid (0.0067 g, 0.111 mmol) were added to this solution. The resulting mixture was refluxed under a Dean-Stark trap for 8 h (TLC monitoring). After the completion of the reaction the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc-Hexane, 1:2). The compound was obtained as colorless viscous oil (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OC***H***$_3$), 3.77 (s, 3H, OC***H***$_3$), 3.80 (s, 3H, OC***H***$_3$), 7.48 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, Ar***H***), 7.67 (d, $^3J_{P,H}$ = 24.0 Hz, 1H, C***H***=C), 7.83 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, Ar***H***), 9.97 (s, 1H, CO***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 53.4, 53.4, 126.1 (d, $^1J_{P,C}$ = 179.1 Hz), 129.0, 129.9, 137.1, 139.2 (d, $^3J_{P,C}$ = 20.0 Hz), 147.8 (d, $^2J_{P,C}$ = 7.3 Hz), 166.1 (d, $^2J_{P,C}$ = 12.3 Hz), 191.4.

Synthesis of phosphonate-substituted BODIPY (5)

2,4-dimethylpyrrole (**4**) (0.060 g, 0.737 mmol) and (*E*)-methyl 2-(dimethoxyphosphoryl)-3-(4-formylphenyl) acrylate (**3**) (0.100 g, 0.335 mmol) were dissolved in dichloromethane. Catalytic amount of trifluoroacetic acid (TFA) (0.00382g, 0.0335 mmol) was added and the mixture was stirred at room temperature for 2 h under a N_2 atmosphere. Subsequently, the reaction mixture was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.056 g, 0.335 mmol) and stirred for additional 0.5 h, followed by the addition of Et_3N (0.335 mL). After 15 min, $BF_3.OEt_2$ (0.335 mL) was added and the mixture was stirred at ambient temperature for additional 2 h. The reaction mixture was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc-Hexane, 4:1). The compound was obtained as red solid (25% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 6H, CH_3), 2.49 (s, 6H, CH_3), 3.72 (s, 3H, OC***H***$_3$), 3.78 (s, 3H, OC***H***$_3$), 3.81 (s, 3H, OC***H***$_3$), 5.92 (s, 2H, pyrrole-H), 7.26 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, Ar***H***), 7.46 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, Ar***H***), 7.70 (d, $^3J_{P,H}$ = 24.0 Hz, 1H, C***H***=C). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 13.6, 51.7, 52.3, 52.4, 120.5, 123.4 (d, $^1J_{P,C}$ = 180.2 Hz), 127.6, 128.7, 130.0, 133.4 (d, $^3J_{P,C}$ = 20.1 Hz), 136.3, 139.2, 141.8, 147.5 (d, $^2J_{P,C}$ = 6.3 Hz), 154.9, 165.4 (d, $^2J_{P,C}$ = 13.0 Hz). ^{19}F NMR (376 MHz): δ = -146.2 (dd, 2F, *J* = 40.6, 82.1, BF_2). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 16.3).

RESULTS and DISCUSSION

The synthesis of phosphonate-substituted BODIPY (**5**) were performed in two steps according to the reported methods (Scheme 1) [10,11]. Firstly, methyl 2-(dimethoxyphosphoryl)-3-(4-formylphenyl)acrylate (**3**) was synthesized by the Knoevenagel condensation reaction of trimethylphosphonoacetate (**2**) and terephthalaldehyde (**1**). In the second step, **3** was reacted with 2,4-dimethylpyrrole (**4**) to give the corresponding dipyrromethane and subsequent oxidation and complexation of the reaction mixture formed phosphonate-substituted BODIPY compound **5** in 25% yield. The structure of the BODIPY **5** was identified by NMR spectroscopy.

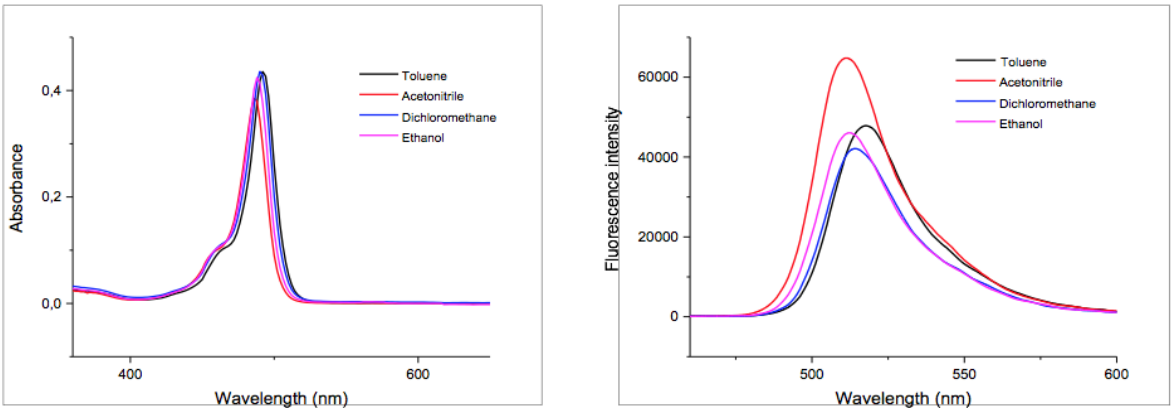


Figure 2. Absorption (left) and emission (right) spectra of phosphonate-substituted BODIPY in different solvents.

The aromatic region of the ^{1}H NMR spectrum shows two pyrrole protons at 5.92 ppm and the peaks at 7.26 ppm and 7.46 ppm belong to the phenyl ring protons. In the aliphatic region of the spectrum two peaks at 1.31 ppm and 2.49 ppm for four methyl protons and three peaks at 3.72 ppm, 3.78 ppm and 3.81 ppm for three methoxy protons were observed. The peak at 7.70 ppm belongs to double bond proton. ^{13}C NMR, ^{19}F NMR and ^{31}P NMR also confirms the suggested structure.

Photophysical properties of the phosphonate-substituted BODIPY were investigated in toluene, acetonitrile, dichloromethane and ethanol (Figure 2). The collected photophysical data are summarized in Table 1 (see Figure 2 for the spectra). As given in the table, maximum absorption wavelengths of the phosphonate-substituted BODIPY lay between 486 and 492 nm. In all solvents, absorption spectra and the absorption intensities of the compound 5 were similar. Fluorescence intensity of the BODIPY was higher in acetonitrile compared to toluene, ethanol and dichloromethane. Maximum fluorescence wavelength was obtained in toluene (Table 1).

As a result; a new phosphonate-substituted BODIPY compound was synthesized by using 2,4-dimethylpyrrole and aldehyde and its spectroscopic and photophysical properties were determined. It is worthy of note that; this BODIPY compound could be a candidate as a fluorescent sensor. As a continuation of the study, we will search the sensor properties of this compound.

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Table 1. Absorption and emission wavelengths of the BODIPY in different solvents.

Solvent	λ max,abs (nm)	λ max,em (nm)[a]
Toluene	492	518
Acetonitrile	486	511
Ethanol	488	513
Dichloromethane	490	514

a Excited at 460 nm.

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