Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2016, **26**, 196–198
Mendeleev Communications

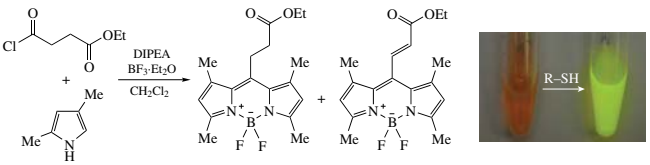
Synthesis, crystal structure and optical properties of a new *meso*-acrylate BODIPY dye

Alexey A. Pakhomov,*[a] Yuriy N. Kononevich,[b] Alexander A. Korlyukov,[b] Vladimir I. Martynov[a] and Aziz M. Muzafarov[b,c]

[a] *M. M. Shemyakin–Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 117997 Moscow, Russian Federation. Fax: +7 495 336 6166; e-mail: alpah@mail.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*
[c] *N. S. Enikolopov Institute of Synthetic Polymeric Materials, Russian Academy of Sciences, 117393 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2016.04.005

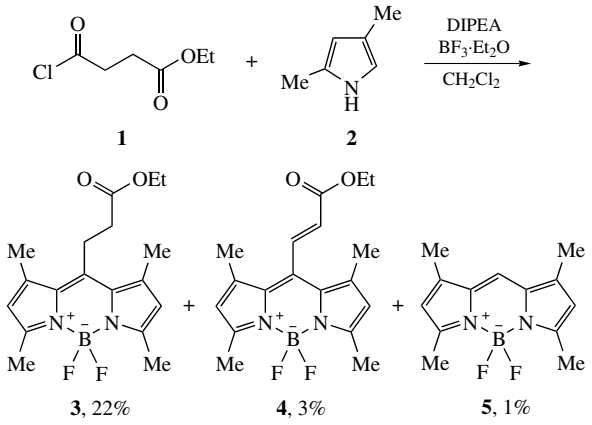
The *meso*-acrylic 1,3,5,7-tetramethyl-BODIPY derivative was obtained from 2,4-dimethylpyrrole and ethyl 4-chloro-4-oxobutanoate and its crystal structure was characterized by X-ray diffraction. This 8-alkenyl-BODIPY dye is originally nonfluorescent, but turns-on fluorescence upon the double bond reduction.



Borondipyrromethene (BODIPY) and its derivatives are photostable fluorescent dyes with high extinction coefficient and remarkable quantum yield.[1] Outstanding photophysical properties of these dyes open new avenues to the state-of-the-art materials such as fluorescent labels, sensors, solar collectors, lasers *etc*.[2–7] Recently, much effort has been aimed at the synthesis of BODIPY derivatives with fluorescence emission up to near-IR range.[8] A considerable bathochromic shift is provided by π-system extention of BODIPY core with unsaturated/polyaromatic substituents. At the same time, additional substituents in most cases lead to extra vibrational modes of the compound and eventually to the quantum yield drop. Quantum yield decrease has also been observed in a fairly compact compounds, for instance, almost a complete fluorescence quenching occurs in C8 (*meso*) vinyl-substituted BODIPY derivatives.[9,10] In contrast, *meso*-substituted BODIPY derivatives with alkyl or aromatic substituents do not display quantum yield drop.[1] Quantum mechanical calculations showed that the quantum yield drop in the case of *meso*-vinyl-substituted BODIPY is due to structure distortion in the excited state followed by its thermal deactivation.[11]

In this work we have found that the synthesis of 1,3,5,7-tetramethyl-BODIPY derivative from ethyl 4-chloro-4-oxobutanoate **1** and 2,4-dimethylpyrrole **2** in contact with air resulted in the main product **3** as well as byproduct **4** with a double C=C bond at the *meso*-position in the BODIPY core and byproduct **5** without any substituent at the *meso*-position (Scheme 1).†

Compounds **3**, **4** and **5** were separated by column chromatography on silica gel using toluene as the eluent. Structures of synthesized compounds were confirmed by NMR spectroscopy. Compounds **3** and **5** were described earlier.[12–14] The new compound **4** was intensely colored but nonfluorescent. Previously,



Scheme 1

† Dichloromethane was distilled over phosphorus pentoxide. 2,4-Dimethylpyrrole, DIPEA and boron trifluoride diethyl etherate were purchased from Acros Organics. The reactions were monitored by TLC using Fluka silica gel (60 F 254) plates (0.25 mm). Column chromatography was carried out using Merck 60 (230–400 mesh) silica gel. Visualization was made with UV light. ^{1}H NMR spectra were recorded on a Bruker Avance II spectrometer (300 MHz). Chemical shifts are reported relative to chloroform (δ = 7.25 ppm).

Synthesis of the BODIPY derivatives **3**–**5**. Ethyl 4-chloro-4-oxobutanoate **1** (1.65 g, 0.01 mol) was added to a solution of 2,4-dimethylpyrrole **2** (1.2 g, 0.013 mol) in dry dichloromethane (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 24 h. Then DIPEA (2.85 g, 0.022 mol) was added followed after 15 min by boron trifluoride diethyl etherate (4.7 g, 0.033 mol). The reaction mixture was stirred at room temperature for 2 h in a closed vessel. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica (eluent, toluene). Yield: 22% of compound **3**, 3% of compound **4** and <1% of compound **5**.

For **3**: ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, Et), 2.43 (s, 6H, Me), 2.51 (s, 6H, Me), 2.58 (t, 2H, CH_2), 3.30 (t, 2H, CH_2), 4.18 (q, 2H, Et), 6.06 (s, 2H, Pyr).

For **4**: ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 3H, Et), 2.16 (s, 6H, Me), 2.52 (s, 6H, Me), 4.28 (q, 2H, Et), 6.04 (s, 2H, Pyr), 6.20 (d, 1H, CH), 7.74 (d, 1H, CH).

For **5**: ^{1}H NMR ($CDCl_3$) δ: 2.24 (s, 6H, Me), 2.53 (s, 6H, Me), 6.04 (s, 2H, Pyr), 7.03 (s, 1H, *meso*-CH).

the synthesis of BODIPY derivatives with double bond at *meso*-position (C8) was accomplished by derivatization of C8 methyl, thioester or halogen groups.[9,10,15] In our work *meso*-acrylic BODIPY derivative was obtained directly in the course of synthesis of the BODIPY moiety. The content of side product **4** was 14% relative to the main product **3**.

Evaporation of the solvent from toluene solution of compound **4** led to the formation of large red crystals suitable for X-ray diffraction study.‡ The geometry of the BODIPY moiety of **4** is not planar and the fused cyclic system is bent over the C(8)···B(4) line, so that the angle between pyrrole fragments planes is 6.84(5)° (Figure 1). The crystal packing of **4** is characterized by the formation of infinite stacks between fused cyclic systems. In this packing, pyrrole cycle participates in the stacking interaction with a diazaborine cycle [the corresponding interplanar distance is 3.30(4) Å, the centroid–centroid distance is 3.8238(7) Å]. In addition, the stacking interaction between two pyrrole cycles N(1)C(9)C(1)C(2)C(3) is also observed [interplanar and centroid–centroid distances are 3.5955(17) and 4.3922(10) Å]. The length of C(8)–C(11) bond clearly indicates the absence of a conjugation between the C(11)–C(12) vinyl group and BODIPY moiety, and the dihedral angle C(10)C(8)C(11)C(12) value of 54.96(13)° is close to the most energetically favorable one.[11] When the *meso*-position is occupied by a bulky aromatic group, it is oriented perpendicular to the plane of the BODIPY core-structure due to steric hindrances. In this case, there is no conjugation between π-systems of BODIPY and *meso*-substituent, consequently the latter does not show a considerable influence upon the compound spectral properties.[1] In compound **4** more compact vinyl group is oriented at a dihedral angle of 54.96(13)° and tends to be conjugated to the core-structure after the light energy absorption owing to BODIPY core bending in the excited state;[11] transition to the ground state in this case occurs mostly by thermal deactivation. Visually, *meso*-acrylic BODIPY **4** is a red colored nonfluorescent dye, in contrast to the saturated derivative **3**, which is a bright green fluorescent compound.[12]

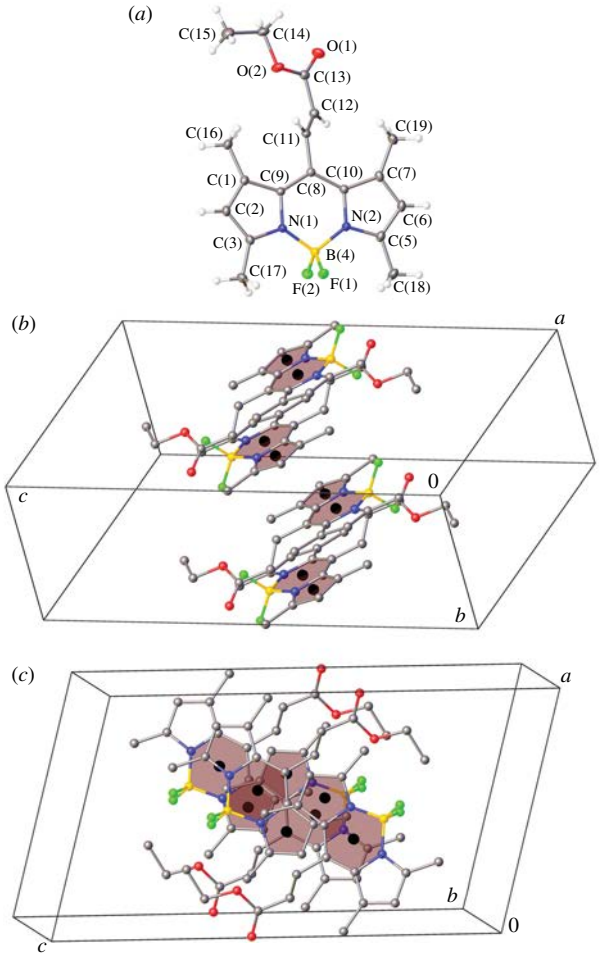


Figure 1 X-ray crystal structure of **4**. (*a*) Molecular structure presented as ADP ellipsoids at 50% probability. Infinite stacks in crystal packing [(*b*) side view and (*c*) top view]. The overlapping of pyrrol and diazaborine cycles is highlighted, the centroids of cycles are shown by black spheres.

‡ *Crystal data for* **4**. $C_{18}H_{21}BF_2N_2O_2$ (M = 346.18 g mol^{-1}), monoclinic, space group $P2_1/n$, a = 10.9471(5), b = 7.8452(4) and c = 19.8761(9) Å, β = 103.0270(10)°, V = 1663.07(14) Å^3, Z = 4, T = 120 K, μ(MoKα) = = 0.104 mm^{-1}, d_{calc} = 1.383 g cm^{-3}, 21549 reflections measured (3.922° ⩽ ⩽ 2θ ⩽ 61.012°) using a Bruker APEX II diffractometer at 120 K, 5071 unique (R_{int} = 0.0325, R_σ = 0.0282) which were used in all calculations. The final R_1 was 0.0405 [for 4184 reflection with $I > 2\sigma(I)$] and wR_2 was 0.1070 (all data). The structure was solved with the ShelXT[18] structure solution program using Direct Methods and Olex2 program[19] and refined with the ShelXL refinement package[20] using Least Squares minimization.

CCDC 1471447 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

We studied spectral properties of acrylate **4**. In absorbance spectra, a peak in the visible range with the maximum at 505 nm was detected. This peak was considerably broadened as compared to that of compound **3** at 500 nm (Figure 2). This circumstance may argue in favor of vibrational sublevels multitude. Compound **3** is bright fluorescent with maximum at 508 nm. Meanwhile, compound **4** was practically nonfluorescent, that is in line with properties of the *meso*-vinyl BODIPY derivatives reported earlier.[9–11]

The double C=C bond at a *meso*-position of BODIPY **4** should be reactive in Michael-type nucleophilic addition,[10] *e.g.,* with thiols. In fact, when an excess of glutathione was added to compound **4** dissolved in the alkaline (0.1 M NaOH) ethanol–H_2O solution, the reaction mixture gradually became bright-green fluorescent when observed under the UV light (Figure 2, insert). Obviously, the double bond was transformed into single one upon thiol addition. On the one hand, this distinctive feature of compound **4** can be used for the detection of thiols and other nucleophilic agents. On the other hand, fluorogenic behavior of compound **4** upon conjugation with the target object may be applicable in bioimaging.[16,17] In contrast to the earlier described analogues, compound **4** can be saponified to the carboxylic derivative[12,13] which can be further ligated to a desirable functional group. The resultant compound can be conjugated to cysteine residues of target protein analogously to maleimide. However, due to *trans* configuration of the C=C bond of acrylate-BODIPY, the reaction with compound **4** should be slower than with maleimide, which contains *cis*-C=C bond. Nevertheless, compound **4** becomes brightly fluorescent only after conjugation,

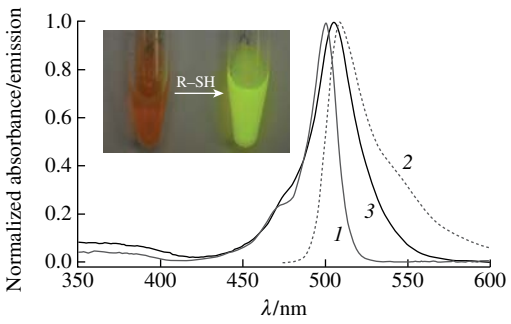


Figure 2 Normalized (*1*) absorption and (*2*) fluorescence emission spectra of compound **3** and (*3*) absorption spectrum of compound **4** in ethanol. Insert: sample of **4** before and after thiole induced 'switching-on' (image was taken at weak day light, test-tubes were highlighted by UV light from below).

that eliminates or minimizes the washing off the unbound fluorophore.

In conclusion, during the synthesis of *meso*-substituted 1,3,5,7-tetramethyl-BODIPY we obtained and separated several derivatives including one with the unsaturated ethyl acrylate moiety at the *meso*-position. Crystal structure and photophysical properties of the *meso*-acrylate BODIPY dye were studied. This compound can be readily converted to the carboxylic derivative suitable for the subsequent functionalization. Due to the location of a double bond at the *meso*-position of BODIPY this compound can be used in bioorthogonal reactions with the following conversion from nonfluorescent to the bright fluorescent state.

This work was in part supported by the Russian Science Foundation (project no. 14-13-01478).

References

1 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891.
2 T. Papalia, G. Siracusano, I. Colao, A. Barattucci, M. C. Aversa, S. Serroni, G. Zappalà, S. Campagna, M. T. Sciortino, F. Puntoriero and P. Bonaccorsi, *Dyes Pigments*, 2014, **110**, 67.
3 F. Sozmen, S. Kolemen, H.-O. Kumada, M. Ono, H. Saji and E. U. Akkaya, *RSC Adv*., 2014, **4**, 51032.
4 S. P. Singh and T. Gayathri, *Eur. J. Org. Chem.*, 2014, 4689.
5 T. V. Ovchinnikova, A. V. Pshezhetsky, A. B. Tuzikov and N. V. Bovin, *Mendeleev Commun.*, 2015, **25**, 422.
6 E. V. Ilnitskaya, Y. N. Kononevich, A. M. Muzafarov, S. A. Rzhevskiy, I. A. Shadrin, E. V. Babaev, V. I. Martynov and A. A. Pakhomov, *Russ. J. Bioorg. Chem*., 2015, **41**, 451 (*Bioorg. Khim*., 2015, **41**, 505).
7 M. Liras, M. Pintado-Sierra, F. Amat-Guerri and R. Sastre, *J. Mater. Chem*., 2011, **21**, 12803.
8 Y. Ni and J. Wu, *Org. Biomol. Chem*., 2014, **12**, 3774.
9 M. P. Shandura, V. P. Yakubovskyi, Y. V. Zatsikha, O. D. Kachkovsky, Y. M. Poronik and Y. P. Kovtun, *Dyes Pigments*, 2013, **98**, 113.
10 I. J. Arroyo, R. Hu, B. Z. Tang, F. I. López and E. Peña-Cabrera, *Tetrahedron*, 2011, **67**, 7244.
11 R. Lincoln, L. E. Greene, C. Bain, J. O. Flores-Rizo, D. S. Bohle and G. Cosa, *J. Phys. Chem. B*, 2015, **119**, 4758.
12 A. A. Pakhomov, Y. N. Kononevich, M. V. Stukalova, E. A. Svidchenko, N. M. Surin, G. V. Cherkaev, O. I. Shchegolikhina, V. I. Martynov and A. M. Muzafarov, *Tetrahedron Lett*., 2016, **57**, 979.
13 I. A. Boldyrev, X. Zhai, M. M. Momsen, H. L. Brockman, R. E. Brown and J. G. Molotkovsky, *J. Lipid Res*., 2007, **48**, 1518.
14 L. Wu and K. Burgess, *Chem. Commun.*, 2008, 4933.
15 B. Dhokale, T. Jadhav, S. M. Mobin and R. Misra, *Chem. Commun*., 2014, **50**, 9119.
16 D. P. Chauhan, T. Saha, M. Lahiri and P. Talukdar, *Tetrahedron Lett.*, 2014, **55**, 244.
17 J. C. T. Carlson, L. G. Meimetis, S. A. Hilderbrand and R. Weissleder, *Angew. Chem. Int. Ed.*, 2013, **52**, 6917.
18 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3.
19 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr*., 2009, **42**, 339.
20 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3.

Received: 11th December 2015; Com. 15/4796