1078 Russian Chemical Bulletin, International Edition, Vol. 67, No. 6, pp. 1078—1082, June, 2018

9-Ethyl-3-{6-(het)aryl-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl}-9*H*-carbazoles: synthesis and study of sensitivity to nitroaromatic compounds

E. V. Verbitskiy,[a,b]★ Yu. A. Kvashnin,[a] A. A. Baranova,[b] Yu. A. Yakovleva,[b]
K. O. Khokhlov,[b] G. L. Rusinov,[a,b] and V. N. Charushin[a,b]

[a]*I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,*
22 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation.
E-mail: Verbitsky@ios.uran.ru
[b]*Ural Federal University named after the first President of Russia B. N. Yeltsin,*
19 ul. Mira, 620002 Ekaterinburg, Russian Federation

5-(9-Ethyl-9*H*-carbazol-3-yl)-substituted 6-(het)aryl[1,2,5]oxadiazolo[3,4-*b*]pyrazines were synthesized by direct transition metal-free C—H functionalization in the pyrazine ring. Their photophysical and sensory properties with respect to nitrobenzene and 2,4-dinitrotoluene vapors were studied using a Nitroscan portable detector of nitro-explosive substances (Ekaterinburg, Russia).

Key words: furazano[3,4-*b*]pyrazines, carbazoles, C—H functionalization, chemosensors, fluorescence quenching.

The development of new chemosensors for determination of nitro-containing aliphatic and aromatic compounds as dangerous ecotoxicants and explosives is an actual trend in analytical and organic chemistry in connection with the growing ecological problems and the terrorist threat.[1—5] Existing methods for detecting nitroaromatic explosives are based on the use of living beings as bio-detectors (most often dogs, less often rats or pigs, and even rarer bees or wasps),[6] X-ray devices or other analyzers using such complex methods as chromatography-mass spectrometry, ion mobility spectrometry in an alternating electric field, detection of microscopic particles by infrared radiation.[7,8] All of them are not readily available and require substantial preparation of the sample being analyzed.

The method based on fluorescence quenching is one of the simplest and highly sensitive for detection of nitro compounds. In this case, the main working elements are fluorophores, planar polyaromatic electron-donating structures capable of reversibly forming π-complexes with nitroaromatic compounds. In the literature, there are many examples of highly efficient fluorophores on the basis of both electron-rich conjugated polymers[9] and "small" molecules.[10] Nevertheless, when polymers are compared with small conjugated molecules, the latter have significant advantages due to their easier synthesis and purification, as well as a clearly determined individual structure and reproducibility of properties from batch to batch.[6,10]

Fluorescent organic molecules and polymers containing a conjugated carbazole moiety are successfully used as promising chemosensors of nitroaromatic compounds.[10—12] In addition, the push-pull systems with an acceptor fragment represented by an azaheterocycle (*e.g.*, pyridine[13,14] or pyrimidine[15—19] derivatives) are very promising sensory materials for determination of various nitroaromatic compounds using the principle of fluorescence quenching.

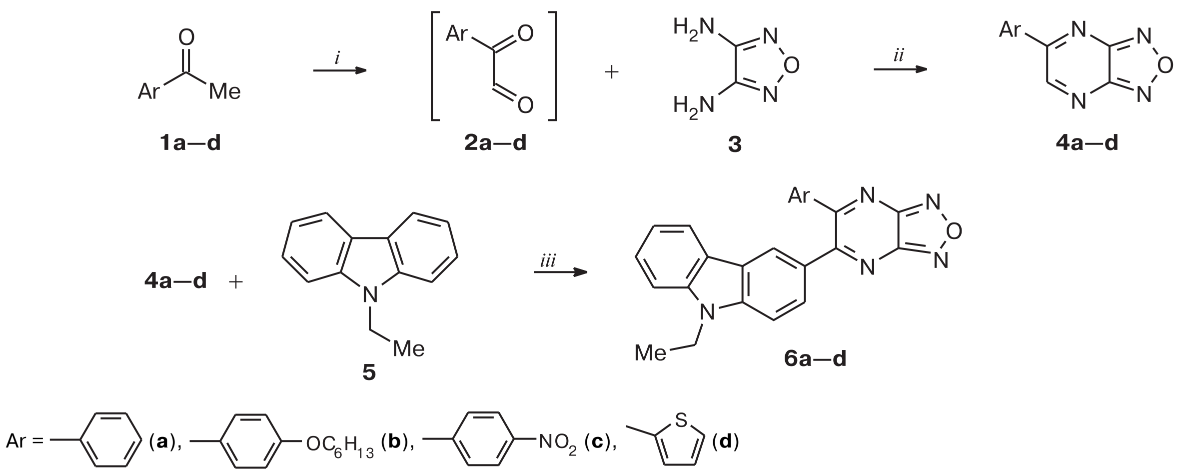
Thus, the search for new sensors for determination of nitroaromatic compounds based on the push-pull D—π—A-type systems with an azine acceptor fragment is an actual synthetic problem.

The purpose of the present study is the synthesis of new push-pull systems based on 6-(het)aryl-[1,2,5]-oxadiazolo[3,4-*b*]pyrazines with 9-ethyl-9*H*-carbazole substituent as a donor fragment and also the study of the photophysical and sensory properties of these compounds for the detection of nitroaromatic substances in the vapor phase. The choice of [1,2,5]oxadiazolo[3,4-*b*]pyrazine derivatives as objects of investigation is due to the presence of pronounced fluorescence in the solid state, which is a necessary condition for the detection of vapors of nitro compounds.[20]

The target fluorophores were synthesized by sequences of reaction given in Scheme 1. Acetophenones **1a—c** or 2-acetylthiophene (**1d**) were oxidized with selenium(IV) oxide to the corresponding (het)arylglyoxals **2a—d**, which underwent condensation with 3,4-diaminofurazan (**3**) to give 5-(het)aryl-[1,2,5]oxadiazolo[3,4-*b*]pyrazines **4a—d** in up to 75% yields. In the last step, furazanopyrazines **4a—d** were involved into the transition-metal free oxidative coupling with 9-ethyl-9*H*-carbazole (**5**). This reaction is

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1078—1082, June, 2018.

Scheme 1



Reagents and conditions: *i*. SeO_2, reflux, 1,4-dioxane; *ii*. reflux, 1 h, EtOH—AcOH (1 : 1); *iii*. 1) $BF_3 \cdot Et_2O$, MeCN, 2) oxidation in air.

an example of nucleophilic substitution of hydrogen (S_N^H) in the π-deficient pyrazine ring under the action of C-nucleophilic *N*-ethylcarbazole as an analog of *N,N*-disubstituted aniline.[21,22] The yield of the target 9-ethyl-3-{6-(het)aryl-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl}-9*H*-carbazoles (**6a—d**) in the last step ranged within 42—68%. The structure of the products was confirmed by ^{1}H and ^{13}C NMR spectra, as well as by X-ray diffraction data on the example of 9-ethyl-3-[6-(4-hexyloxyphenyl-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl}-9*H*-carbazole (**6b**) (Fig. 1).

We studied the photophysical properties of fluorophores **6a—d** (Figs 2 and 3, Table 1). All pyrazines **6a—d** have absorption maxima in the "blue" region (435—466 nm) of visible spectrum, which is due to the intramolecular charge transfer in the excited state from the electron-donating fragment (carbazole) to the electron-withdrawing pyrazine ring. Compounds **6a—d** visually have fluorescence in acetonitrile solution, but the relative fluorescence quantum yields of these compounds are below 1.00% (quinine sulfate solution in 0.1 *N* sulfuric acid, for which Φ = 0.55, was used as the standard). The sharp increase in the fluorescence intensity of a solution of compound **6b** having a long alkyl substituent, in comparison with other fluorophores **6a,c,d**, is apparently due to a decrease in the contribution of aggregation processes facilitating fluorescence quenching as a result of nonradiative intermolecular transitions from the excited state.

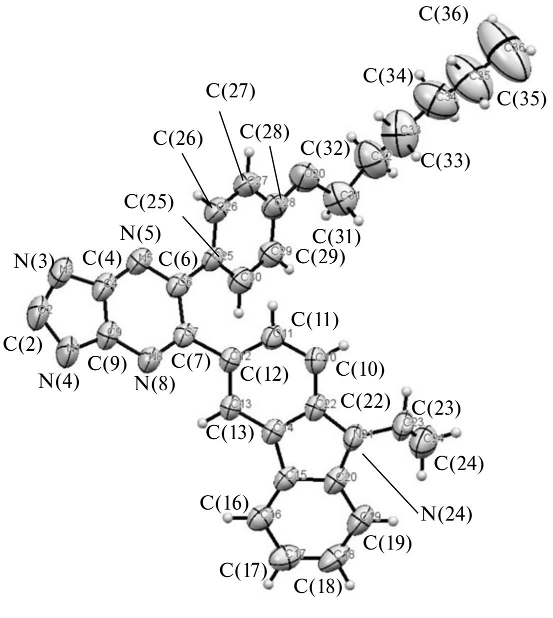


Fig. 1. Geometry of compound **6b** in crystal.

Nitrobenzene (NB) and 2,4-dinitrotoluene (DNT) were chosen as model nitroaromatic explosives. Since compounds **6a—d** weakly fluoresce in acetonitrile solution, fluorescent titration for nitroaromatic compounds and

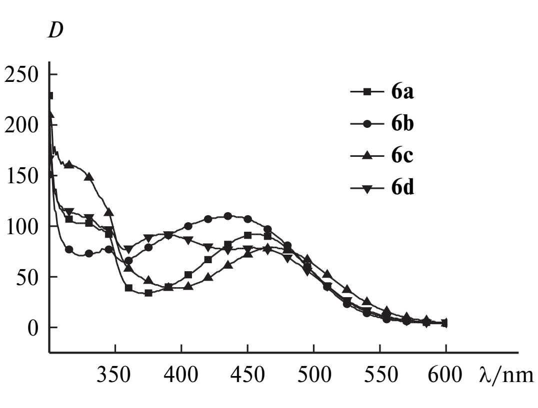


Fig. 2. UV spectra of fluorophores **6a—d** in CH_3CN (C = 10^{-5} mol L^{-1}).

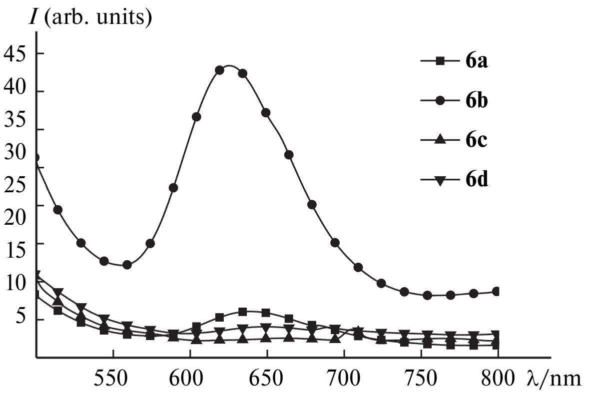


Fig. 3. Fluorescence spectra of compounds **6a—d** in the solid state.

Table 1. Optical properties of compounds **6a—d**

Compound	Absorption		Fluorescence in the solid state	
	λ_{max} /nm	ε /L mol^{-1} cm^{-1}	λ_{ex}	λ_{fl}
			nm	
6a	453	9200	453	638
6b	435	11000	435	625
6c	466	7900	466	705
6d	455	7900	455	650

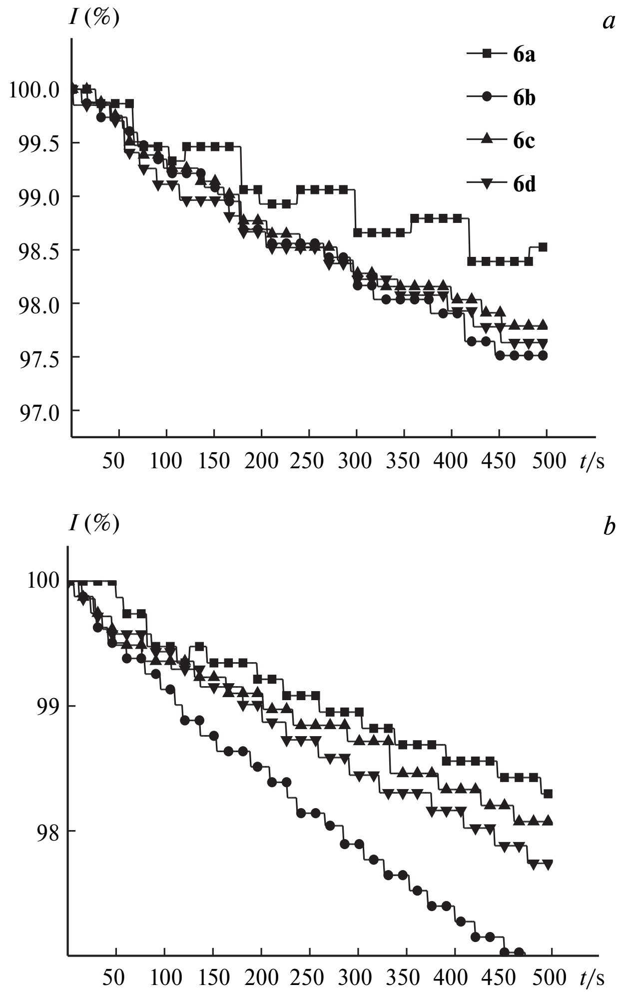


Fig. 4. Fluorescence quenching graph of the sensor based on fluorophores **6a—d** in a Nitroscan portable detector of nitro-explosives when exposed to saturated vapors of NB (*a*) and DNT (*b*).

determination of their detection limits in solutions failed. However, we carried out the tests for the detection of nitrobenzene and 2,4-dinitrotoluene saturated vapors using an original portable detector of nitro-explosives (Nitroscan[23] produced by the Intermolecular Security Systems research-and-production association, Ekaterinburg, Russia). The nitroaromatic compound (50 g) was left in a sealed glovebox (0.8 m×0.6 m×0.4 m) for one day (DNT was used instead of TNT because of the high risk of using large amounts of the latter). After that, a Nitroscan portable detector of nitro-explosives with a sensor on the basis of each of the fluorophores **6a—d** was placed in the glovebox containing saturated vapors of the nitro compounds. The maximum decrease in the sensor fluorescence intensity took place within 50 s, after which the Nitroscan detector was removed from the glovebox and purged with air. The detection process was repeated 5—10 times. The results are shown in Fig. 4.

As it is seen from Fig. 4, the luminescence intensity decreased with each cycle. However, it should be noted that for the first five cycles its value dropped only by ~1—2%. In addition, there was an irreversible quenching with each cycle, which indicates the impossibility to reuse the obtained sensors. It also follows from Fig. 4 that the most sensitive fluorophore, for which the fastest fluorescence quenching occurs, is compound **6b** having the highest fluorescence in the solid state. Note also that the sensitivity of all fluorophores to DNT was significantly higher than to NB. The observed picture correlates with the increase in electrostatic interactions between the analyte and the sensor due to the growth of the electron-deficiency of the π-system of nitro compounds as the number of nitro groups increases.

Thus, we proposed a convenient method for the synthesis of new fluorophores based on carbazolyl-substituted furazanopyrazines using the $S_N{}^H$ methodology, which allows direct transition metal-free oxidative C—C cross-coupling of two aryl fragments. It was established that the obtained fluorophores have a relatively weak response in the form of fluorescence quenching on nitrobenzene and dinitrotoluene, but we plan to continue to work in this direction with the aim of finding more efficient push-pull systems based on the pyrazine core, which can be used as sensory elements for nitroaromatic compounds.

Experimental

Compounds **6a** and **6d** were synthesized earlier according to a similar procedure in 44 and 56% yields, respectively.[19]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE^{III}-500 spectrometer (500 and 126 MHz) in $CDCl_3$ or DMSO-d$_6$, using TMS as an internal standard. Elemental analysis was carried out on a Perkin—Elmer PE-2400 automated analyzer. Melting points were determined on a Boetius hot-stage and were not corrected.

Reaction progress and purity of products were monitored by TLC on Sorbfil plates, visualizing under UV light.

UV spectra were recorded on a UV-2401 PC spectrometer (Shimadzu) for solutions of compounds in acetonitrile with a concentration of 10^{-5} mol L^{-1}. Excitation and emission spectra were recorded on a Hitachi F-7000 spectrofluorimeter at room temperature.

To measure emission in the solid state, the sample of the test compound (~1 mg) was dissolved in acetone (1 mL). The resulting suspension was applied to quartz glass in the form of a thinnest film. Then, the sample was placed in a cuvette compartment to record the fluorescence spectrum.

X-ray diffraction studies were performed on a Xcalibur 3 automatic four-circle diffractometer with a CCD detector using the standard procedure (λMoK, graphite monochromator, ω/2θ-scan technique in 1° steps, 295(2) K). The structure was solved and refined using the SHELXTL24 software package by the full-matrix least squares method with respect to F^2. Nonhydrogen atoms were included in the model in the anisotropic approximation. Hydrogen atoms were localized using the electron density distribution maps and included in the refinement in the isotropic approximation by the riding model with dependent thermal parameters. The results of X-ray diffraction studies were deposited with the Cambridge Crystallographic Data Center as cif-files (CCDC 1581898 for compound **6b**). These materials are available free of charge and can be requested at www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 5-(4-R-phenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazines (4b and 4c) (general procedure). A mixture of 4-substituted acetophenone **1b** (or **1c**) (10 mmol) and selenium dioxide (1.1 g, 10 mmol) in a solution of 1,4-dioxane (15 mL) and water (1 mL) was refluxed for 12 h. Selenium was filtered off, washed with 1,4-dioxane (5 mL). The solvent was evaporated at reduced pressure. The residue was dissolved in a mixture of ethanol (5 mL) and acetic acid (5 mL), 3,4-diaminofurazan (**3**) (1.0 g, 10 mmol) was added, and the resulting mixture was refluxed for 1 h and cooled to room temperature. A precipitate formed was filtered, washed with ethanol, and dried in air. Compounds **4b** (**4c**) were obtained as crystalline powders.

5-(4-Hexyloxyphenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (4b). The yield was 1.29 g (62%), a yellow powder. M.p. 75 °C. ^{1}H NMR ($CDCl_3$), δ: 9.39 (s, 1 H, H^{pyrazine}); 8.25 (d, 2 H, H^{arom}, J = 8.8 Hz); 7.08 (d, 2 H, H^{arom}, J = 8.8 Hz); 4.08 (t, 2 H, CH_2, J = 6.5 Hz); 1.87—1.82 (m, 2 H, CH_2); 1.50—1.36 (m, 2 H, CH_2); 1.37 (d, 4 H, $(CH_2)_2$, J = 3.2 Hz); 0.93 (m, 3 H, CH_3). ^{13}C NMR (DMSO-d$_6$), δ: 163.6, 158.0, 153.0, 152.3, 151.2, 130.7, 126.4, 115.6, 68.5, 31.5, 29.0, 25.6, 22.6, 14.0. Found (%): C, 64.29; H, 6.20; N, 18.63. $C_{16}H_{18}N_4O_2$ (298.35). Calculated (%): C, 64.41; H, 6.08; N, 18.78.

5-(4-Nitrophenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (4c). The yield was 1.57 g (75%), a yellow powder. M.p. 151—152 °C. ^{1}H NMR (DMSO-d$_6$), δ: 9.87 (s, 1 H, H^{pyrazine}); 8.64 (d, 2 H, H^{arom}, J = 8.9 Hz); 8.47 (d, 2 H, H^{arom}, J = 8.9 Hz). ^{13}C NMR (DMSO-d$_6$), δ: 158.3, 155.8, 152.2, 151.6, 149.7, 139.8, 130.4, 124.2. Found (%): C, 49.53; H, 2.04; N, 28.84. $C_{10}H_5N_5O_3$ (243.18). Calculated (%): C, 49.39; H, 2.07; N, 28.80.

Synthesis of 9-ethyl-3-{6-aryl-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl}-9*H*-carbazole derivatives (6b,c) (general procedure). The reagent $BF_3 \cdot Et_2O$ (62 μL, 0.5 mmol) was added to a mixture of 5-aryl-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**4b** or **4c**) (0.5 mmol) and 9-ethyl-9*H*-carbazole (98 mg, 0.5 mmol) in acetonitrile (4 mL) with stirring. The mixture was stirred for 12 h at room temperature. The solvent was evaporated at reduced pressure, the residue was treated with aqueous Na_2CO_3, filtered, washed with H_2O, and dried in air. Recrystallization of the resulting powder gave the target $S_N{}^H$-products **6b** or **6c**.

9-Ethyl-3-[6-(4-hexyloxyphenyl-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-9*H*-carbazole (6b). The yield was 103 mg (42%), a red powder. M.p. 155 °C. ^{1}H NMR (DMSO-d$_6$), δ: 8.45 (d, 1 H, H^{arom}, J = 1.3 Hz); 8.11 (d, 1 H, H^{arom}, J = 7.7 Hz); 7.67 (d, 1 H, H^{arom}, J = 8.2 Hz); 7.59 (d, 1 H, H^{arom}, J = 8.7 Hz); 7.51 (dd, 2 H, H^{arom}, J = 11.0 Hz, J = 4.7 Hz); 7.47 (d, 2 H, H^{arom}, J = 8.7 Hz); 7.25 (m, 1 H, H^{arom}); 6.91 (d, 2 H, H^{arom}, J = 8.8 Hz); 4.47 (q, 2 H, CH_2, J = 7.0 Hz); 3.97 (t, 2 H, CH_2, J = 6.5 Hz); 1.71—1.63 (m, 2 H, CH_2); 1.40—1.31 (m, 5 H, H^{aliph}); 1.29—1.22 (m, 4 H, $(CH_2)_2$); 0.85 (t, 3 H, CH_3, J = = 6.7 Hz). ^{13}C NMR (DMSO-d$_6$), δ: 164.5, 164.0, 161.2, 152.0, 141.3, 140.6, 132.4, 130.6, 128.7, 128.6, 126.9, 123.4, 122.6, 122.3, 120.9, 120.2, 114.5, 110.2, 108.9, 68.2, 37.7, 31.4, 28.9, 25.5, 22.4, 14.3, 14.2. Found (%): C, 73.40; H, 5.99; N, 14.03. $C_{30}H_{29}N_5O_2$ (491.60). Calculated (%): C, 73.30; H, 5.95; N, 14.25.

9-Ethyl-3-[6-(4-nitrophenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-9*H*-carbazole (6c). The yield was 148 mg (68%), a dark red powder. M.p. 246—248 °C (decomp.). ^{1}H NMR (DMSO-d$_6$), δ: 8.44 (s, 1 H, H^{arom}); 8.25 (d, 2 H, H^{arom}, J = = 8.5 Hz); 8.11 (d, 1 H, H^{arom}, J = 7.7 Hz); 7.78 (d, 2 H, H^{arom}, J = 8.2 Hz); 7.66 (d, 1 H, H^{arom}, J = 8.1 Hz); 7.57 (d, 1 H, H^{arom}, J = 8.6 Hz); 7.50 (t, 1 H, H^{arom}, J = 7.6 Hz); 7.44 (d, 1 H, H^{arom}, J = 8.4 Hz); 7.24 (t, 1H, H^{arom}, J = 7.4 Hz); 4.44 (q, 2 H, CH_2, J = 6.7 Hz); 1.30 (t, 3 H, CH_3, J = 7.0 Hz). ^{13}C NMR (DMSO-d$_6$), δ: 163.4, 162.9, 151.8, 151.2, 148.1, 144.3, 140.9, 140.1, 131.2, 128.3, 127.0, 126.5, 123.3, 123.2, 122.0, 121.9, 120.4, 119.8, 109.7, 108.6, 37.2, 13.6. Found (%): C, 65.94; H, 3.79; N, 19.20. $C_{24}H_{16}N_6O_3$ (436.43). Calculated (%): C, 66.05; H, 3.70; N, 19.26.

Preparation of a sensor element based on fluorophores 6a—d for Nitroscan instrument. A dry, undyed, nonwoven industrial spunlace fabric (70% wood pulp, 30% polypropylene) manufactured by Kunshan Yichen Clean Material Co. (China) was used as a porous substrate for the sensor. A piece of the nonwoven fabric (50 mm in diameter) was immersed in a solution of each of the fluorophores **6a—d** with a concentration of $1.0 \cdot 10^{-3}$ mol L^{-1} for 5 min. Then, the nonwoven fabric with the immobilized fluorophore was removed from the solution and dried for 30 min at 70—80 °C. The sensory material thus obtained was placed in a cartridge. The assembled sensor was used in the Nitroscan device.[23]

This work was financially supported by the Russian Foundation for Basic Research (Project No. 17-03-00011-A).

References

1. M. E. Germain, M. J. Knapp, *Chem. Soc. Rev.*, 2009, **38**, 2543.
2. M. Krausa, A.A. Reznev, *Vapor and Trace Detection of Explosives for Antiterrorism Purposes*, Boston, Kluwer Academic Publisher, 2004.
3. Y. Salinas, R. Martínez-Máñez, M. D. Marcos, F. Sancenón, A. M. Costero, M. Parra, S. Gil, *Chem. Soc. Rev.*, 2012, **41**, 1261.
4. G. I. Sunahara, G. Lotufo, R. G. Kuperman, J. Hawari, *Ecotoxicology of Explosives*, Boca Raton, London, 2009.
5. A. Hakonen, P. O. Andersson, M. S. Schmidt, T. Rindzevicius, M. Käll, *Anal. Chim. Acta*, 2015, **893**, 1.
6. G. V. Zyryanov, D. S. Kopchuk, I. S. Kovalev, E. V. Nosova, V. L. Rusinov, O. N. Chupakhin, *Russ. Chem. Rev.*, 2014, **83**, 783.
7. D. S. Moore, *Rev. Sci. Instrum.*, 2004, **75**, 2499.
8. S. W. Thomas, G. D. Joly, T. M. Swager, *Chem. Rev.*, 2007, **107**, 1339.
9. S. J. Toal, W. C. Trogler, *J. Mater. Chem.*, 2006, **16**, 2871.
10. S. Shanmugaraju, P. S. Mukherjee, *Chem. Commun.*, 2015, **51**, 16014.
11. K. S. Prakash, R. Nagarajan, *Tetrahedron*, 2013, **69**, 8269.
12. J. Peng, K. Ye, J. Sun, Y. Zhan, J. Jia, P. Xue, G. Zhang, Z. Zhang, R. Lu, *Dyes and Pigments*, 2015, **116**, 36.
13. Y. Peng, A.-J. Zhang, M. Dong, Y.-W. Wang, *Chem. Commun.*, 2011, **47**, 4505.
14. D. C. Santra, M. K. Bera, P. K. Sukul, S. Malik, *Chem. – Eur. J.*, 2016, **22**, 2012.
15. E. V. Verbitskiy, A. A. Baranova, K. I. Lugovik, M. Z. Shafikov, K. O. Khokhlov, E. M. Cheprakova, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *Anal. Bioanal. Chem.*, 2016, **408**, 4093.
16. E. V. Verbitskiy, A. A. Baranova, K. I. Lugovik, K. O. Khokhlov, E. M. Cheprakova, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *ARKIVOC*, 2016, 360—373.
17. E. V. Verbitskiy, E. B. Gorbunov, A. A. Baranova, K. I. Lugovik, K. O. Khokhlov, E. M. Cheprakova, G. A. Kim, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *Tetrahedron*, 2016, **72**, 4954.
18. E. V. Verbitskiy, E. M. Cheprakova, A. A. Baranova, K. O. Khokhlov, K. I. Lugovik, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *Chem. Heterocycl. Compd.*, 2016, **52**, 904.
19. E. V. Verbitskiy, A. A. Baranova, K. I. Lugovik, K. O. Khokhlov, E. M. Cheprakova, M. Z. Shafikov, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *Dyes and Pigments*, 2017, **137**, 360.
20. Y. A. Kvashnin, N. A. Kazin, E. V. Verbitskiy, T. S. Svalova, A. V. Ivanova, A. N. Kozitsina, P. A. Slepukhin, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *ARKIVOC*, 2016, 279.
21. O. N. Chupakhin, V. N. Charushin, *Tetrahedron Lett.*, 2016, **57**, 2665.
22. V. N. Charushin, O. N. Chupakhin, *Metal Free C—H Functionalization of Aromatics. Nucleophilic Displacement of Hydrogen*, in *Topics in Heterocyclic Chemistry*, Springer, 2014, **37**, 283 p.
23. Website of the portable detector of nitro-explosives Nitroscan: http://nitroscan.pro.
24. G. M. Sheldrick, *Acta Crystallogr*, 2008, **A64**, 112.

Received October 26, 2017;
in revised form November 29, 2017;
accepted March 12, 2018