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New and efficient high Stokes shift fluorescent compounds: unsymmetrically substituted 1,2-bis-(5-phenyloxazol-2-yl)benzenes via microwave-assisted nucleophilic substitution of fluorine

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ABSTRACT

Two new unsymmetric derivatives of 1,2-bis-(5-phenyloxazol-2-yl)benzene (*ortho*-POPOP) were synthesized via microwave-assisted nucleophilic substitution of fluorine which appears to be significantly more efficient compared with conventional thermal activation. The compounds synthesized are characterized by high fluorescence Stokes shifts (6000–11,000 cm^{-1}) in solvents of various polarity, intermediate-to-high fluorescence quantum yields and lifetimes in the range of several nanoseconds.

Fluorescent organic compounds possessing high Stokes shift values[1] are prospective candidates for their practical application in various fields of science and technology, where high concentrations or long optical paths are required,[2] for example, in scintillation techniques,[3] sunlight collection, and conversion of its energy into electricity,[4] electroluminescent light sources (OLEDs),[5] fluorescent chemosensors,[6] various biological applications, etc. Several physico-chemical mechanisms can be applied to increase the fluorescence Stokes shift of organic compounds,[7] however not all of them lead to emissions with high quantum yields.[8] The most popular and most studied is the excited state proton transfer reaction,[9] however it is usually connected with high radiationless excitation energy losses.[10] To our understanding, excited state conformational transformations resulting in the formation of more planar molecular structures[11] have several advantages in producing high Stokes shifted fluorescence emission[12] over the alternative twisting mechanisms,[13] which also induce radiationless excited state deactivation in most of the known cases.[14]

Derivatives of 1,2-bis-(5-phenyloxazol-2-yl)benzene[15] are *ortho*-analogs of the well-known scintillation luminophore POPOP [1,4-bis-(5-phenyloxazol-2-yl)benzene]. They belong to the class of efficient fluorescent organic compounds with abnormally high Stokes shifts.[16] In contrast to their planar *para*-isomers,[17] molecules of the title series are characterized by essential non-planarity caused by the steric repulsion of two bulky heterocyclic moieties introduced into the *ortho*-positions of the central benzene ring.[18] To minimize the steric hindrance the heterocycles move out of the plane of the central phenylene forming, with the latter, dihedral angles in the range 30–80°. The resulting disruption of intramolecular conjugation shifts the electronic absorption spectra of *ortho*-POPOPs towards the shorter-wavelength region with respect to the absorption of their planar *para*-isomers. In contrast, the fluorescence emission of *ortho*-POPOPs is observed at even longer wavelengths compared to the *para*-analogs, reflecting restoration of the conjugation in the lowest singlet excited state in the flattened molecule.[19] In most cases the excited state planarization of the *ortho*-POPOP molecules is not accompanied by essential radiationless deactivation and the observed fluorescence quantum yields remain reasonably high.[20]

Further increase of the Stokes shift values is possible by combination of several photophysical mechanisms in one molecule: for example, excited state planarization and solvatochromic effects. Asymmetrization of the electronic density distribution by introduction of highly electron-donating and/or electron-withdrawing substituents into the *ortho*-POPOP molecule leads to a significant rise in its excited state dipole moment, increased sensitivity to solvent polarity, and thus enlarges the fluorescence Stokes shift in polar media.[19a]

The key steps in the synthesis of the unsymmetrically substituted *ortho*-analogs of POPOP (Scheme 1) are the acylation of ω-

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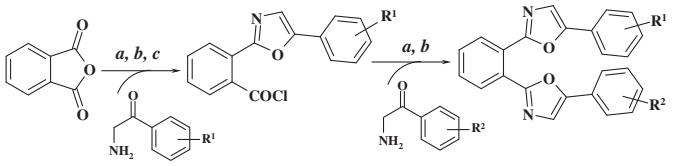


Scheme 1. Typical method for the synthesis of unsymmetrically substituted *ortho*-analogs of POPOP. Reagents and conditions: (a) (chloro)anhydrides in acetone/benzene, aqueous ω-amino acetophenone hydrochlorides, Na_2CO_3, room temperature, 0.5 h; (b) concentrated H_2SO_4, 60 °C, 3 h; (c) $SOCl_2$, 0.5 h reflux.

amino acetophenones using carboxylic acid anhydrides or acyl chlorides, steps (a), and two oxazole ring-closures in acidic media, steps (b). In many cases, substituents of different electronic nature, R^1 and R^2, introduced into the intermediates can affect the cyclization decreasing significantly the yields of the final products. The interests of our group include the development of new and efficient methods for the synthesis of novel derivatives of *ortho*-POPOP with improved fluorescence properties.

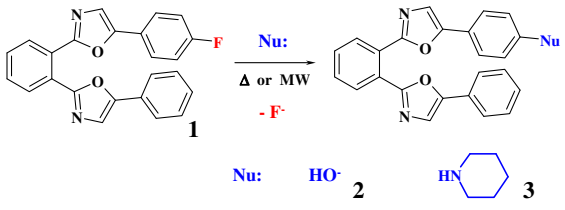
The aim of this Letter is to report a novel approach for the synthesis of unsymmetrically substituted *ortho*-analogs of POPOP, which increases the variety within this series of high Stokes shift fluorescent dyes. This work is based on the nucleophilic substitution of a halogen atom[21] which is easily introduced into the *ortho*-POPOP molecule by a traditional method as shown in Scheme 1. Successful examples of such reactions for the synthesis of dialkylamino-substituted fluorescent compounds can be found in the literature.[22] Recently, we reported the synthesis and X-ray crystal structure investigation of fluoro-substituted *ortho*-POPOP **1**.[23] Fluorine could be replaced by an appropriate nucleophilic group by extended heating in a sealed vessel (Scheme 2).

In the case of relatively weak nucleophilic agents such as secondary amines, the reaction performed under conventional heating proceeds extremely slowly and was accompanied by the formation of significant amounts of colored impurities. This led us to test microwave irradiation as an alternative method,[24] which proved to be more convenient and rapid (Table 1).

Compounds **2** and **3** obtained by these different experimental methods were chemically identical, however, the purity of those synthesized via thermal activation was significantly worse. The appearance of noticeable amounts of by-products using microwave activation was practically not observed. Compounds prepared in this manner needed only chromatographic separation from the traces of the starting compound **1** remaining.

The effect of microwave irradiation on the reaction time in the case of the strong nucleophilic agent, OH^-, application of which resulted in the formation of compound **2**, was less significant, than in the case of compound **3** (a weak nucleophile). However, in this case a 1.4 fold increase in the yield was detected.

The optical properties of the starting and newly synthesized derivatives of *ortho*-POPOP were determined in aprotic solvents of different polarity and ethanol (Table 2).[29] Owing to the excited state conformational rebuilding typical of any *ortho*-analog of



Scheme 2. Nucleophilic substitution of the F atom in compound **1** resulting in the formation of compounds **2** and **3**.

Table 1
Synthesis of electron-donor substituted derivatives of *ortho*-POPOP by nucleophilic substitution of fluorine under conventional and microwave conditions

Compound	Activation	Reaction duration (h)	Yield (%)
2	Thermal[25]	8	58
	Microwave[26]	2	82
3	Thermal[27]	100	64
	Microwave[28]	3	73

Table 2
Spectral properties of the investigated unsymmetrically substituted *ortho*-analogs of POPOP

Solvent	ν_a	λ_a	ν_f	λ_f	$\Delta\nu_{ST}$	φ_f	τ_f
F-substituted ortho-POPOP, ***1***							
Hexane	30,960	323	23,640	423	7320	0.72	4.02
Toluene	30,480	328	23,200	431	7280	0.71	3.95
1,4-Dioxane	30,660	326	23,160	432	7500	0.86	4.45
1,2-DCE	30,620	327	23,100	433	7520	0.84	4.31
EtOAc	30,940	323	23,180	432	7760	0.68	4.27
DMF	30,840	324	22,880	437	7960	0.63	4.47
MeCN	30,860	324	22,940	436	7920	0.54	4.41
EtOH	30,760	325	22,840	438	7920	0.52	5.02
OH-substituted ortho-POPOP, ***2***							
Hexane	30,440	329	23,080	433	7360	0.62	3.70
Toluene	30,640	326	22,520	444	8120	0.59	3.41
1,4-Dioxane	30,460	328	21,980	455	8480	0.57	3.93
1,2-DCE	30,520	328	21,880	457	8640	0.64	4.08
EtOAc	30,700	326	21,840	458	8860	0.55	4.17
DMF	30,900	323	20,620	485	10,280	0.59	4.47
MeCN	31,020	322	20,960	477	10,060	0.65	4.86
EtOH	30,600	327	20,580	486	10,020	0.23	2.42
Piperidyl-substituted ortho-POPOP, ***3***							
Hexane	29,940	334	23,640	423	6300	0.56	1.49
Toluene	29,060	344	21,840	458	7220	0.40	1.80
1,4-Dioxane	28,980	345	21,100	474	7880	0.64	2.64
1,2-DCE	29,080	344	20,280	493	8800	0.56	3.03
EtOAc	29,320	341	20,120	497	9200	0.42	2.88
DMF	28,820	347	19,500	513	9320	0.65	3.28
MeCN	28,900	346	19,460	514	9440	0.31	2.53
EtOH	29,160	343	18,060	554	11,100	0.39	1.78

ν_a, λ_a,–Positions of the long-wavelength absorption band (cm^{-1}/nm), ν_f, λ_f,–positions of the fluorescence band (cm^{-1}/nm), $\Delta\nu_{ST}$–fluorescence Stokes shift (cm^{-1}), φ_f–fluorescence quantum yield with respect to quinine sulfate in 0.1 M aqueous H_2SO_4,[30] τ_f–mean fluorescence lifetime (ns).

POPOP, its fluorescence emission decay laws were rather complicated and fitted satisfactorily only by bi-exponential functions with positive pre-exponentials. Thus, the fluorescence lifetimes presented in Table 2 are the mean values calculated using the common equation[1]: $\tau = \sum \alpha_i \tau_i^2 / \sum \alpha_i \tau_i$, where τ_i is the fitted decay time and α_i the corresponding pre-exponential factor. Photophysical data for compound **1** were not published previously and hence they are included in Table 2 and discussed here briefly.

High fluorescence Stokes shifts within the range of 6300–11,100 cm^{-1} (Fig. 1, Table 2) are typical of all the studied compounds. Surprisingly, the fluorescence quantum yields of fluorine-substituted molecule **1** were the highest of all the known derivatives of *ortho*-POPOP with relatively high mean lifetimes in the range of 4–5 ns. This is a reflection of the decreased radiationless decay efficiency caused by the presence of fluorine. The solvatochromism of compound **1** was not very high, indicating the intermediate positive mesomeric effect of the fluorine atom as a substituent in heteroaromatic conjugated molecules. Thus, F has relatively low influence on the excited state electron density redistribution and the total increase of the excited state dipole moment.

The hydroxy derivative **2** demonstrates a pronounced Stokes shift increase with solvent polarity from 7300 to 10,000 cm^{-1}. Its fluorescence lifetime shows a clear tendency to increase in aprotic solvents as well and in contrast, nearly a 2-fold decrease together

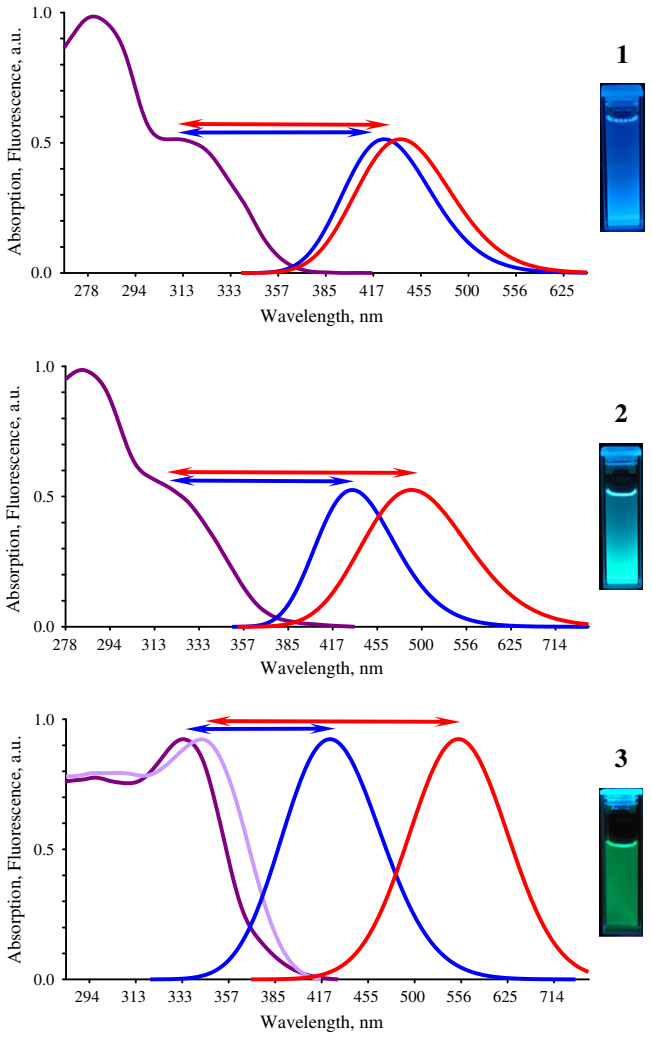


Figure 1. Electronic absorption spectra of compounds **1**–**3** in hexane (violet, light violet for **3** in EtOH). Fluorescence spectra excited at 330 nm in hexane (blue) and EtOH (red), Stokes shifts are shown by arrows of the corresponding color. Insets: fluorescence in EtOH.

with the fluorescence quantum yield in ethanol. Probably, this is the effect of specific interactions with protic solvent molecules, however, excited state OH group photodissociation was not observed as was the case when the alcohol solution was made basic.

Introduction of the most pronounced electron-donor group within the examined series (compound **3**) results in a definite systematic decrease in both the fluorescence quantum yield and mean lifetime, however they still remain reasonably high. The ethanol solution of **3** demonstrated further acceleration of radiationless decay, but it was not as high as could be expected in the cases when formation of twisted intramolecular charge transfer (TICT) states took place.[13,14] We note, that a significant Stokes shift increase was observed for **3** on going from acetonitrile to ethanol. This is a reflection of the role of hydrogen bonding in the photophysics of this compound, connected with the increase in the electron-withdrawing parameters of its H-bonded oxazole rings and intensification of the intramolecular excited state donor–acceptor interactions.

In conclusion, a new approach for the synthesis of unsymmetrically substituted *ortho*-analogs of POPOP including aromatic nucleophilic substitution of a fluorine atom has been elaborated. Microwave irradiation makes the above reaction significantly more efficient, clean and rapid, especially in the case of the relatively weak nucleophilic reagent—the secondary cyclic amine piperidine. Even in the case of the strong nucleophile OH^-, we obtained an increase in the yield and less by-products.

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24. A monomode microwave system Emrys™ Creator EXP from Biotage (Uppsala, Sweden) equipped with an IR temperature sensor and pressure control system was used for MW-assisted synthesis. The absorption mode was set to 'normal' with the initial power at 300 W. Process vials with 5 ml of the reaction mixture volume were used.
25. 1-[5-(4-Hydroxyphenyl)oxazol-2-yl]-2-(5-phenyloxazol-2-yl)benzene (**2**). *Thermal activation*: A solution of 0.3 g (7.8×10^{-4} mol) of compound **1** with 0.1 g of KOH in DMSO (15 ml) was heated over 8 h using a glycerol bath at 120 °C with periodic monitoring by fluorescence at an excitation wavelength of 330 nm (by cooling and removing microliter portions of the reaction mixture for analysis). The reaction mixture was poured into 100 ml of cold H_2O and acidified with AcOH. The resulting precipitate was filtered, washed with H_2O and dried. Purification was done by column chromatography on silica/benzene. Yield 0.174 g, (4.6×10^{-4} mol, 58%).
26. 1-[5-(4-Hydroxyphenyl)oxazol-2-yl]-2-(5-phenyloxazol-2-yl)benzene (**2**). *Microwave activation*: A solution of 0.3 g (7.8×10^{-4} mol) of compound **1** with 0.1 g of KOH in DMSO (5 ml) was heated to 120 °C for 2 h in a closed glass vial under microwave irradiation (visual monitoring by fluorescence color). Separation and purification was as described above. Yield 0.246 g (6.5×10^{-4} mol, 82%). *Compound* **2**: $C_{24}H_{16}N_2O_3$, white fine-crystalline solid, mp 102–103 °C, ^{1}H NMR (Varian Mercury VX-200, 200 MHz, DMSO-d_6): 6.7 (d, J = 7.6 Hz, 2H), 7.28–7.31 (m, 5H), 7.49–7.52 (m, 3H), 7.67 (d, J = 7.6 Hz, 2H), 7.85 (s, 1H), 8.08 (m, 2H), 9.2 (br s 1H). MS (Varian 1200 L, EI, 70 eV): 381, 380 (M^+), 351, 324, 303. No molecular ions for initial compound **1** and its most probable first fragment ions were detected in the MS of sample **2** (382, 363/362, 356).

27. 1-{5-[4-(*N*-Piperidyl)phenyl]oxazol-2-yl}-2-(5-phenyloxazol-2-yl)benzene (**3**). *Thermal activation*: A solution of 0.3 g (7.8×10^{-4} mol) of compound **1** in a mixture of piperidine (2 ml) and DMF (0.5 ml) was heated to 200 °C in a steel autoclave over 100 h (more than 2 weeks, up to 8 h/working day) with monitoring of the reaction progress by periodic removal microliter samples of the reaction medium for fluorescence analysis (excitation at 350 nm). After the reaction was complete, the mixture was poured into 100 ml of cold H_2O, and the resulting precipitate filtered, washed with H_2O and dried. Purification was accomplished by column chromatography on silica/benzene. Yield 0.22 g (5×10^{-4} mol, 64%).
28. 1-{5-[4-(*N*-Piperidyl)phenyl]oxazol-2-yl}-2-(5-phenyloxazol-2-yl)benzene (**3**). *Microwave activation*: A solution of 0.3 g (7.8×10^{-4} mol) of compound **1** in piperidine (2 ml) and DMF (0.5 ml) was heated to 200 °C in a closed glass vial under microwave irradiation (visual monitoring by fluorescence color). Separation and purification was as described above. Yield 0.26 g (5.7×10^{-4} mol, 73%). *Compound* ***3***: $C_{29}H_{25}N_3O_2$, yellow amorphous solid, ^{1}H NMR (200 MHz, DMSO-d_6): 1.6 (m, 6H), 3.73 (m, 4H), 7.42 (d, J = 7.2 Hz, 2H), 7.55 (m, 3H), 7.72 (d, J = 7.2 Hz, 4H), 7.80 (s, 2H), 8.00 (m, 2H), 8.28 (d, J = 7.5 Hz, 2H). MS (high fragmentation, only the most intense fragment ion masses are listed): 448, 447 (M^+), 428, 412, 399, 398. No molecular ions for initial compound **1** and its most probable first fragment ions were detected in the MS of sample **3**.
29. Electronic absorption spectra were measured on a HITACHI U3210 spectrophotometer and fluorescence spectra on a HITACHI F4010 fluorescence spectrometer. Synchronous scan fluorescence spectra were applied as a simple test indicating the purity of newly synthesized compounds. Fluorescence lifetimes were detected on a sub-nanosecond kinetic spectrometer, consisting of an MDR-12 monochromator (LOMO, Russia), a TimeHarp 200 TCSPC device, a PLS 340-10 picosecond LED driven by a PDL 800-B device (PicoQuant GmbH, Germany) and a Hamamatsu H5783P PMT (Hamamatsu, Japan).
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