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Synthesis and evaluation of photophysical properties of Series of π-conjugated oxazole dyes

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ABSTRACT

Incorporation of π-conjugated spacers at the 2 or 5 position of a 2,5-disubstitutedaryloxazole led to new series of fluorescent dyes. They show emissions from visible to 700 nm along with significant Stokes shift up to 208 nm and a strong solvatochromic fluorescence. These compounds are easily accessible in one step through direct C–H bond functionalization.

Discovering effective fluorescent molecules has been a long-standing goal in the field of chemistry. Indeed, such photoactive molecules find valuable applications as biomolecular probes, sensor elements, and as building blocks in optical materials. Although well-known fluorophores such as fluorescein, rhodamine, BODIPY, and cyanines are currently used in many research fields, they do not always satisfy the criteria of an ideal fluorophore: high absorption coefficient and quantum yield, a large Stokes shift, long lifetime, high chemical and photostability and, biocompatibility. Therefore, there is a continuing interest in developing new fluorescent dyes.[1,2] The 2,5-diaryloxazole unit is also an attractive building block for the construction of dyes with favorable photophysical properties, due to its inherently strong absorption and luminescence in the UV–vis spectrum, a large wavelength shift, and a high quantum yield. Consequently, its derivatives have been the focus of intensive work for the synthesis of π-conjugated materials.[3–8] 2,5-diaryloxazoles have already found use as tools for the detection of radiolabelled bioanalytes and the determination of biological processes such as protein activity and measurement of important ions, such as Ca^{2+} and H^{+}.[9–14] Their two-photon properties have also been recently reported for applications in multi-photon fluorescence microscopy.[15,16] Therefore, the synthesis of even more-evolved 2,5-disubstitutedoxazole fluorophores is of considerable interest. In this context, we thought to incorporate classical π-conjugated spacers such as C=C double bonds or C≡C triple bonds on the C-2 or C-5 position of the oxazole core, in order to improve and fine-tune the fluorescence properties. Considering the wide range of possible applications, their synthesis needs to be straightforward. To meet this challenge, we have recently developed methods based on the direct functionalization of C–H bond of azoles, and in particular oxazoles, that allowed an efficient and rapid access to such fluorescent dyes.[17–22]

Herein, we report the synthesis and the photophysical properties of new chromophores based on the oxazole scaffold substituted with styryl or alkynyl groups. The influence of these structural changes on their fluorescence properties is discussed.

The synthetic route to the target molecules **7**–**20** relies on the direct functionalization of C–H bonds of various 5-aryloxazoles **1**–**6** with aryl, vinyl or alkynyl bromides using previously reported procedures (Schemes 1 and 2).

The 5-aryl oxazoles **1**–**6** were easily prepared in a single step by the van Leusen reaction of the appropriate commercially available aromatic aldehydes with *p*-toluenesulfonylmethylisocyanide (TosMIC) and K_2CO_3 in refluxing MeOH. The 2,5-diaryloxazole derivatives **7a**, **7f**, **8i**, **8j,** and **9k** were prepared in moderate to good yields by a direct arylation reaction through two different protocols. In the case of **7a** and **7f**, a microwave-assisted palladium/copper co-mediated direct arylation in DMF at 150 °C was used. While for compounds **8i**, **8j,** and **9k**, reaction conditions involving tetrakis palladium complex in the presence of a strong base, *t*BuOLi, in dioxane at 120 °C and the corresponding aryl bromide were implemented. The *E*-5-aryl-2-styryloxazoles **10b**–**d**, **11b**, **12a**,**c** and **13k** were synthesized, as a single stereoisomer, by a copper-catalyzed

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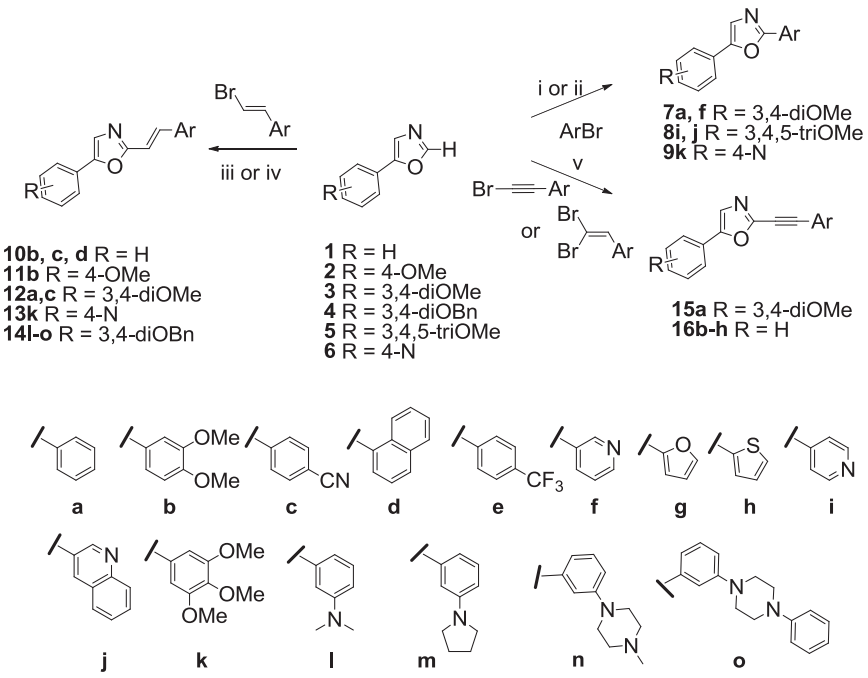
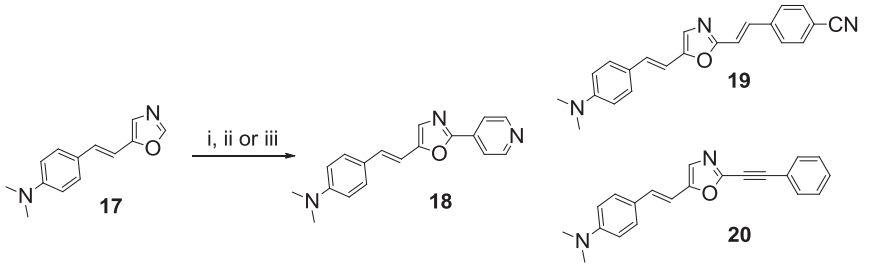


Reaction conditions i) $Pd(OAc)_2$/CuI, K_2CO_3, DMF, MW, 150 °C for **7a** (60%) and **7f** (63%); ii) $Pd(PPh_3)_4$ 5 mol%, *t*BuOLi , dioxane 120 °C for **8i** (72%), **8j** (93%) and **9k** (53%); iii) CuI 10 mol%, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine 20 mol%, *t*BuOLi, dioxane 100 °C for **10b** (82%), **10c** (70%), **10d** (71%), **11b** (75%), **12a** (73%), **12c** (64%), **13k** (88%); iv) protocol iii) with *E*-metabromobromostyrene followed by reaction with the appropriate amine, X-Phos, Pd_2dba_3, *t*BuONa, toluene, 100 °C for **14l** (83%), **14m** (68%), **14n** (71%) and, **14o** (79%) ; v) CuBr.SMe_2 cat, DPE-Phos cat, *t*BuOLi, dioxane 120 °C, 1h, **15a** (85%), **16b** (82%), **16c** (66%), **16d** (84%), **16e** (76%), **16f** (73%), **16g** (61%) and **16h** (73%).

Scheme 1. Reaction conditions: (i) $Pd(OAc)_2$/CuI, K_2CO_3, DMF, MW, 150 °C for **7a** (60%) and **7f** (63%); (ii) $Pd(PPh_3)_4$ 5 mol %, *t*BuOLi, dioxane 120 °C for **8i** (72%), **8j** (93%) and **9k** (53%); (iii) CuI 10 mol %, *trans*-*N*-*N*′-dimethylcyhexane-1,2-diamine 20 mol %, *t*BuOLi, dioxane 100 °C for **10b** (82%), **10c** (70%), **10d** (71%), **11b** (75%), **12a** (73%), **12c** (64%), **13k** (88%); (iv) protocol (III) with *E*-metabromobromostyrene followed by reaction with the appropriate amine, X-Phos, Pd_2dba_3, *t*BuONa, toluene, 100 °C for **14l** (83%), **14m** (68%), **14n** (71%), **14o** (79%); (v) CuBr·SMe_2 cat, DPE-Phos cat, *t*BuOLi, dioxane 120 °C, 1 h, **15a** (85%), **16b** (82%), **16c** (66%), **16d** (84%), **16e** (76%), **16f** (73%), **16g** (61%) and **16h** (73%). Synthesis of 2-aryl, vinyl, or alkynyl oxazoles by direct C–H bond functionalization.



Reaction conditions: i) 4-bromopyridine, $Pd(PPh_3)_4$ 5 mol%, *t*BuOLi , dioxane 120 °C, 89% for **18**; ii) *E*-4-cyanobromostyrene,CuI 10 mol%, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine 20 mol%, *t*BuOLi, dioxane 100 °C, 86% for **19**; iii) Bromophenylacetylene, CuBr.SMe_2 5 mol%, DPE-Phos 10 mol%, *t*BuOLi, dioxane 120 °C, 53% for **20**.

Scheme 2. Reaction conditions: (i) 4-bromopyridine, $Pd(PPh_3)$ 5 mol %, *t*BuOLi, dioxane 120 °C , 89% for **18**; (ii) *E*-4-cyanobromostyrene, CuI 10 mol %, *trans N*-*N*′-dimethylcyclohexane-1,2-diamine 20 mol %, *t*BuOLi, dioxane 10 °C, 86% for **19**; (iii) bromophenlacetylene, CuBr·SMe_2, 5 mol %, DPE-Phos 10 mol %, *t*BuOLi, dioxane 120 °C, 53% for **20**. Synthesis of compounds **18**, **19,** and **20**.

direct alkenylation protocol using the appropriate styryl bromides. In the cases of **14l**–**o**, this latter direct alkenylation was conducted with *E*-metabromostyrene and followed by a subsequent coupling reaction with various amines in the presence of Pd_2dba_3, X-Phos as ligand, *t*BuONa as base in toluene at 100 °C. Lastly, the triple bond spacer in **15a** and **16b**–**h** was introduced via a direct alkynylation reaction with either alkynyl bromides or 1,1-dibromo-1-alkenes as coupling partner under copper catalysis in the presence of *t*BuOLi in dioxane at 120 °C.

We also chose to incorporate an ethenyl spacer on the C-5 position of the oxazole in order to increase the electronic delocalization/charge transfer (Scheme 2). Therefore, chromophores **18**, **19,** and **20** were prepared according to the procedures described above starting with (*E*)-*N*,*N*-dimethyl-4-(2-(oxazol-5-yl)vinyl)aniline **17**.

The absorption and emission properties of all synthesized oxazoles were studied by recording the UV–vis and fluorescence spectra in dichloromethane at room temperature at low concentrations (Table 1). All compounds bearing a double bond are photostable and no *cis*–*trans* isomerization was observed in the analysis conditions.

These compounds show maximum absorption wavelengths in the UV or visible region (320–432 nm). Most of them are fluorescent in dichloromethane with quantum yields ranging from 0.01 to 0.98 and they emit from 380 to 640 nm (Fig. 1). The photophysical properties of these disubstituted oxazoles are modulated by changing the donor/acceptor groups or the length of the conjugation. When both substituents of the oxazole ring are donor groups, poor or no fluorescence is expected since no charge transfer can

Table 1
Spectral properties data

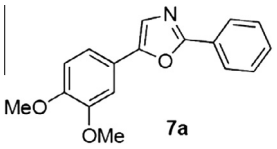
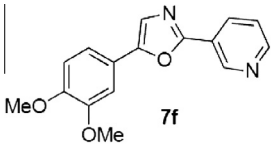
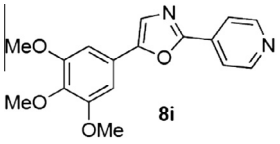
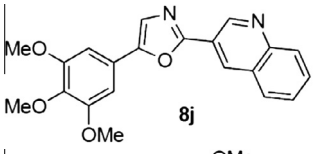
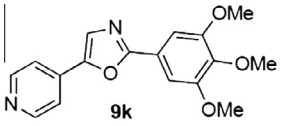
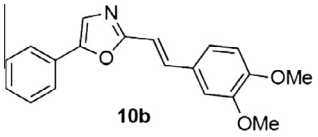
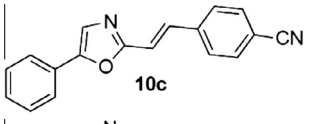
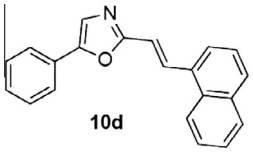
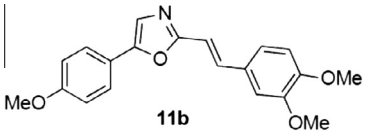
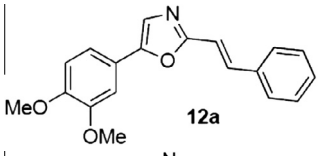
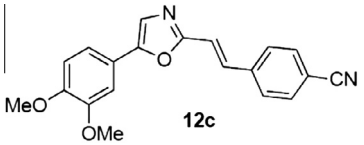
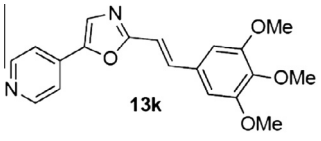
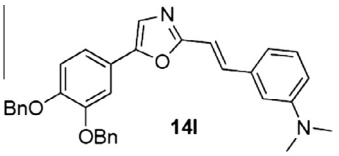
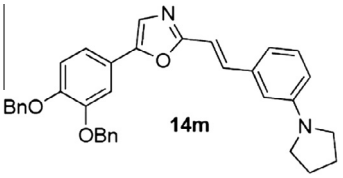
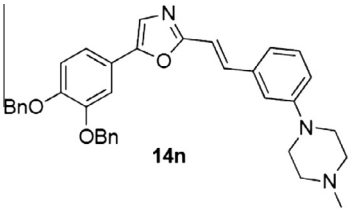
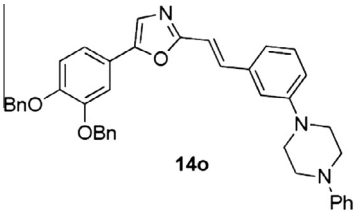
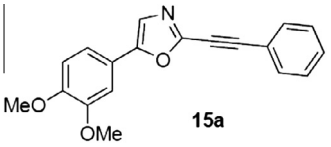
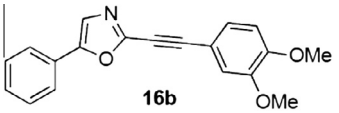
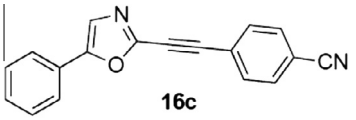
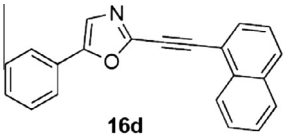
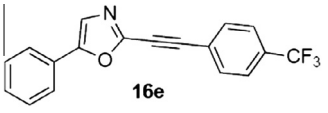
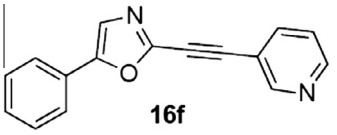
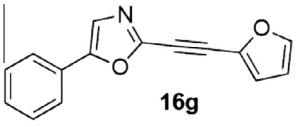
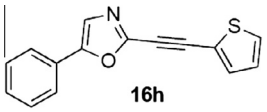
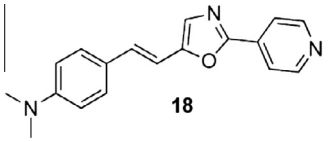
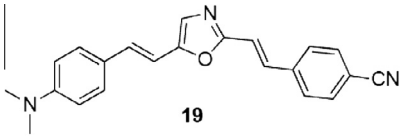
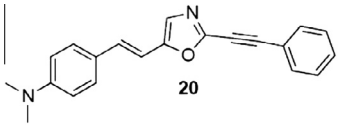
Entry	Analogs	λ_{abs} (ε M^{-1} cm^{-1})	λ_{em} (nm)	δ_{stokes} (nm)	Φ_F
1	 **7a**	322 (20,000)	400	78	0.19
2	 **7f**	330 (8700)	420	90	0.98
3	 **8i**	332 (32,500)	465	131	0.76
4	 **8j**	353 (33,700)	458	103	0.76
5	 **9k**	326 (39600)	417	91	0.54
6	 **10b**	355 (35,800)	420	65	0.01
7	 **10c**	360 (38,500)	450	90	0.65
8	 **10d**	357 (31,800)	440	83	0.32
9	 **11b**	360 (41,300)	435	75	0.08
10	 **12a**	350 (33,100)	450	100	0.52
11	 **12c**	370 (22,500)	500	130	0.38
12	 **13k**	352 (38,000)	463	111	0.02

Table 1 (*continued*)

Entry	Analogs	λ_{abs} (ε M^{-1} cm^{-1})	λ_{em} (nm)	δ_{stokes} (nm)	Φ_F
13	 **14l**	350 (18,000)	490	140	0.37
14	 **14m**	353 (28,900)	485	132	0.35
15	 **14n**	354 (28,700)	465	111	0.23
16	 **14o**	355 (32900)	500	145	0.11
17	 **15a**	330 (34,500)	410	80	0.49
18	 **16b**	330 (43300)	390	60	0.04
19	 **16c**	345 (21,500)	410	65	0.28
20	 **16d**	350 (31,700)	400	50	0.28
21	 **16e**	320 (28,600)	390	70	0.24
22	 **16f**	330 (27,700)	380	50	0.13
23	 **16g**	325 (36,800)	—	—	<0.01

(*continued on next page*)

Table 1 (*continued*)

Entry	Analogs	λ_{abs} (ε M^{-1} cm^{-1})	λ_{em} (nm)	δ_{stokes} (nm)	Φ_F
24	 **16h**	325 (20,100)	—	—	<0.01
25	 **18**	396 (21,000)	550	154	0.65
26	 **19**	432 (28,700)	640	208	0.50
27	 **20**	390 (35,700)	515	125	0.24

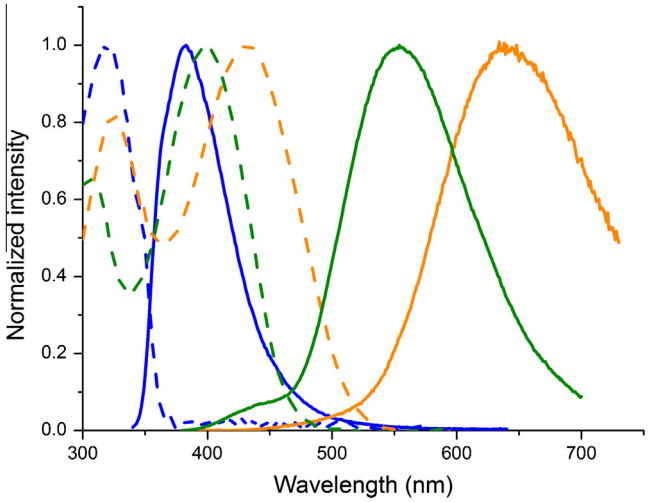


Figure 1. Normalized UV–vis (broken lines) and emission spectra (solid lines) of compounds **16f** (blue), **18** (green), and **19** (orange). All spectra were recorded at room temperature with *c* from 10^{-6} to 10^{-5} M.

occur like in push–pull system. This is indeed the case of compounds **16g** and **16h** bearing respectively a furan or a thiophene (Table 1, entries 23–24) whereas compounds **11b** and **14l–o** show moderate fluorescence. Interestingly, it seems to be more efficient in term of quantum yield to place the donor group at the C-5 position on the oxazole ring than at the C-2 position (Table 1, entries 3 vs 5 and entries 6 vs 10). This intriguing feature has not yet been reported and could be helpful to design even better fluorophores.

The diaryloxazoles **7a**, **7f**, **8i–j,** and **9k** emit between 400 and 465 nm (Table 1, entries 1–5). By extending the conjugation with a double bound at the C-2 position of the oxazole ring, we obtained compounds with higher values of λ_{em}, ranging from 420 to 500 nm (Table 1, entries 6–16). The replacement of the double bond by a triple bond results in a hypsochromic shift, the maximum emission wavelengths ranging from 380 to 410 nm. The 2,5-diaryloxazole **7a** emits at 400 nm while the analogous 2-styryloxazole **12a** emits at 450 nm and the 2-alkynyloxazole **15a** at 410 nm.

The Stokes shifts are much more important in the case of the 5-aryl-2-styryloxazoles than in the case of 2,5-diaryloxazoles or 2-alkynyl-5-aryloxazoles. For example, the Stokes shifts of **10c** and **10d** are respectively, 90 and 83 nm, while the ones of **16c** and **16d** are 65 and 50 nm. Interestingly, the replacement of the aryl group at the C-5 position of the oxazole ring by a styryl group induces dramatic changes on both absorption and emission maximum wavelengths (Table 1, entries 25–27). Indeed, a bathochromic shift is observed for both λ_{absmax} and λ_{em} (compare compounds **8i**/**18**, **12c**/**19,** and **15a**/**20**). Compound **19** gives the most red-shifted emission (640 nm) which is consistent with the extension of the conjugation in both substituents of the oxazole ring. Moreover, the Stokes shifts are larger with these three 5-styryloxazoles, with impressive values ranging from 125 to 208 nm. This reduces the overlap between the absorption and the emission bands and therefore reduces the reabsorption effect; an important criterion for an effective fluorophore.[23–25] As already observed for other series, the 2-styryloxazole **19** presents a higher Stokes shift than the corresponding 2-aryloxazole **18** or 2-alkynyloxazole **20**. Finally, analogous to 2,5-diaryloxazoles, the π-conjugated diaryloxazole **19** might behave as a two-photon absorber and therefore could be excited at NIR wavelength.[15]

A fluorosolvatochromic study has been carried out on compounds **18** and **20** (Fig. 2). A bathochromic shift of the emission band can be observed with increasing solvent polarity. This phenomenon has been fully documented with push–pull fluorophores and is evidence of a strong interaction charge transfer in the lowest excited state.[26–28] As an example, compound **18** exhibits a large spectrum from blue to orange.

The 5-aryl-2-pyridyloxazole series has been described as pH probes.[10] Recently, Cho and co-workers described the use of 2,5-diaryloxazole as a two-photon pH probe in human tissues.[15] As several of our compounds contain nitrogen atoms which can be protonated, we decided to study the effect of protonation on the optical properties of disubstituted oxazoles **14l** and **20**. Significant color changes were observed in dichloromethane solutions upon addition of TFA: a bathochromic shift for **14l**, and a hypsochromic shift for **20** (Fig. 3). We also observed a partial quench of the emission. In both cases, the donor character of the dimethylamino group is reduced upon protonation of the amino substituent. This decreases the push–pull character of compound **20** explaining the blue-shift. In the case of compound **14l**, the opposite effect is observed since the push–pull character is increased.

We report herein a new series of fluorophores based on the 2,5-disubstituted oxazole scaffold. These fluorophores are easily and

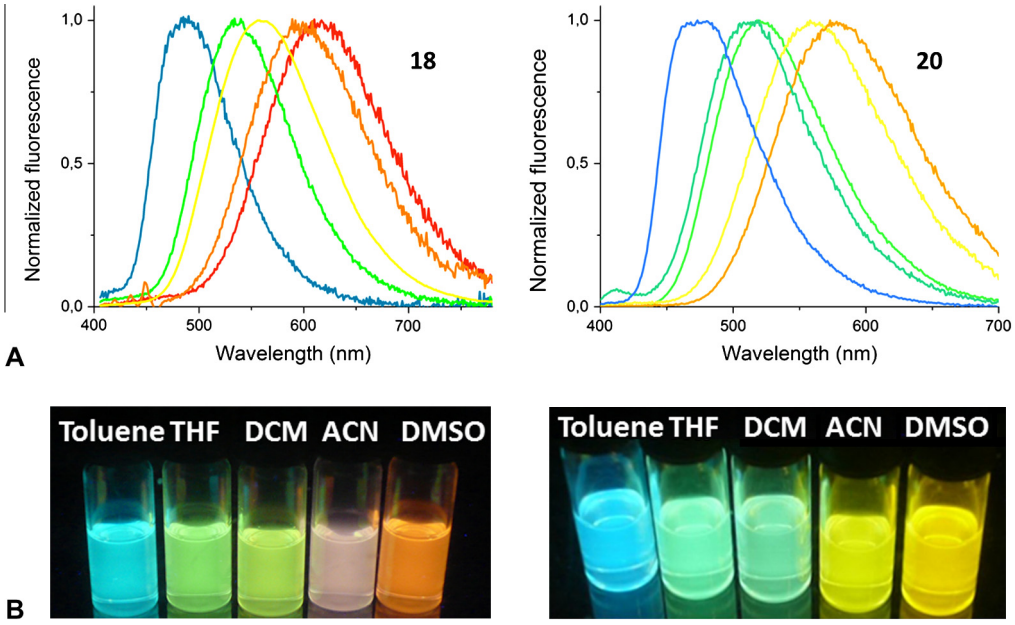


Figure 2. (A) Normalized emission spectra of **18** and **20** with respectively toluene, THF, DCM, acetonitrile, and DMSO. All spectra were recorded at room temperature with *c* 10^{-5} M. (B) Compounds **18** and **20** under UV irradiation.

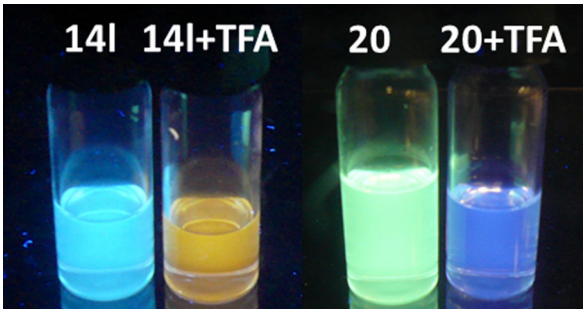


Figure 3. Color changes of dichloromethane solutions of (A) oxazole **14l** and (B) oxazole **20** under UV irradiation. All spectra were recorded at room temperature with *c* 10^{-5} M. [TFA] = 10^{-3} M.

efficiently accessible by direct arylation, alkenylation, or alkynylation of 5-aryl or 5-styryloxazoles. Generally, the presence of a styryl group either at position 2 and/or position 5 of the disubstituted oxazoles enhances the Stokes shift with an exceptionally large value for the 2,5-distyryloxazole **19** (208 nm). These styryl oxazoles can be a good starting point for the design of even-better fluorophores.

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Supplementary data

Supplementary data (experimental details, spectroscopic data, copies of ^{13}H and ^{13}C NMR, HPLC data for all new compounds are provided as well as absorption and emission spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.037.

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