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COMMUNICATION

DPO and POPOP carboxylate-analog sensors by sequential palladium-catalysed direct arylation of oxazole-4-carboxylates†

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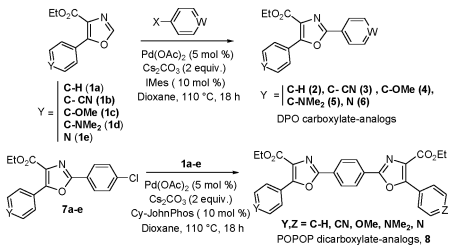
Sequential palladium-catalysed direct (het)arylation of oxazole-4-carboxylates is achieved to give rapid access to DPO and POPOP (di)carboxylate-analogs. Three novel DPO- and POPOP-type sensors with unusual Stokes shifts and high quantum yields are discovered.

Fluorescent compounds are one of the most attractive tools for quantifying molecular interaction events and they are currently extensively used for detection of bioanalytes, receptor/ligand binding and environmental contaminants.[1] Among the wide variety of synthetic or natural organic luminophores only a few of them meet specific criteria[1d,2] such as bisarylated oxazole and thiazole scaffolds which exhibit the necessary fluorescence properties characterized by minimal overlap absorption and emission spectra, as well as an increased value of the Stokes fluorescence shift over the whole visible spectrum.[3] 2,5-Diphenyloxazole (DPO) and 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP) are thus major components of many commercially available plastic and liquid scintillation cocktails serving as dye laser agents, tracers and probes in medico-biological research and radioanalytical chemistry.[4] In recent years, the SPA (scintillation proximity assay) procedure consisting of labeling the receptor molecule with SPA beads has emerged as an alternative to the use of costly and unfriendly scintillation cocktails. This elegant approach which allows real-time quantitative dynamic detection directly useful in 'live' cells attracts much more interest in the preparation of functionalized DPO and POPOP analogs. Most of the efforts have been directed towards the preparation of 4-functionalized DPO analogs in order to covalently or non-covalently attach the sensor reporter to a protein, a polymer matrix or an imprinted polymer to quantify receptor/ligand interaction, or to an azacrown for potassium signaling for instance.[4b,5] Other DPO analogs have also been prepared such as water-soluble Dapoxyl for bioanalyte detection, LysoSensor and 2- and 4-PYMPO for pH probes.[6] Therefore the preparation of more synthetically challenging POPOP analogs remains sparse in spite of their attractive potential as highly effective sensors as well as new materials.[4e,7] So far, the recent advances in transition metal-catalysed direct C–H arylation of heterocycles[8] that offer an alternative reliable method to classical cross-coupling methodology have been little exploited to design neat syntheses of heterocyclic fluorophores.[3e,9] Herein, highly valuable 4-carboxylated DPO and POPOP (di)carboxylate-analogs including Dapoxyl™ analogs are prepared by sequential palladium-catalyzed direct (het)arylation of 5-arylated oxazole-4-carboxylates (Scheme 1) and their physical properties are examined.



Scheme 1 Preparation of DPO POPOP mono(di)carboxylate-analogs through sequential Pd(0)-catalyzed direct (het)arylation of **1a–e** with halo(het)arenes.

A panel of 5-arylated oxazole-4-carboxylates **1a–e** was first prepared in high yield and multigram quantities by treating commercially available ethyl isocyanoacetate with adequate 4-substituted benzoyl chlorides under basic conditions.[10] Initially, the direct palladium-catalyzed phenylation of **1a** with phenyl iodide and chloride was investigated (Scheme 1) under $Pd(OAc)_2$ pre-catalyst and Cs_2CO_3 base employing the three optimal ligand/solvent pairs, P(*o*-tol)$_3$ in toluene and Buchwald's JohnPhos or IMes ligands in dioxane, previously designed for regioselective C2 direct phenylations of the ethyl oxazole-4-carboxylate with phenyl iodide.[11] The results depicted in Table 1 (entries 1–6) showed clearly that the IMes ligand is the most effective ligand in direct phenylation of **1a** with phenyl iodide providing the DPO carboxylate-analog **2** in quantitative yield. The direct coupling of all selected 5-arylated oxazole-4-carboxylates **1a–f** with iodo(het)arenes was then achieved using the IMes/dioxane combination and successfully providing DPO carboxylate-analogs **3–6** including three Dapoxyl-analogs **4b**, **5b** and **6b** in fair to high yields (Table 1, entries 7–12).

The IMes ligand proved to be poorly effective in the direct coupling of **1a** with phenyl chloride (Table 1, entry 6). It was then also selected to secure the selective direct coupling of 5-arylated

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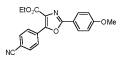
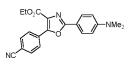
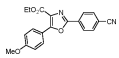
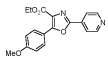
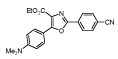
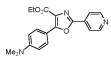
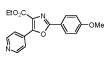
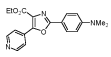
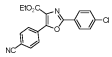
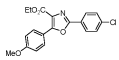
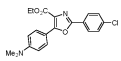
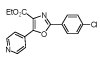
Table 1 Preliminary study of direct palladium-catalyzed direct phenylation of **1a** with phenyl idodide and chloride, preparation of DPO carboxylate-analogs **2–7**[a]

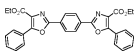
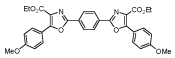
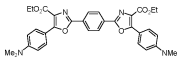
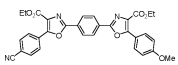
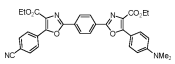
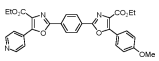
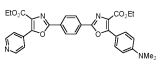
Entry	SM	X	W	L–Solv.	Product		Yield[b] (%)
1	**1a**	I	CH	P–T			65
2	**1a**	I	CH	JP–D			38
3	**1a**	I	CH	I–D		**2**	**100**
4	**1a**	Cl	CH	P–T			30
5	**1a**	Cl	CH	JP–D			85
6	**1a**	Cl	CH	I–D			28
7	**1b**	I	C-OMe	I–D		**3a**	83
8	**1b**	Br	C(NMe_2)	I–D		**3b**	24 (92)[c]
9	**1c**	I	C(CN)	I–D		**4a**	94
10	**1c**	I	C(CN)	I-D		**4b**	79
11	**1d**	I	N	I–D		**5a**	61
10	**1d**	I	C(CN)	I–D		**5b**	57
11	**1e**	I	C(OMe)	I–D		**6a**	82
12	**1e**	Br	C(NMe_2)	I–D		**6b**	45
13	**1a**	I	C–Cl	I–D		**7a**	87
14	**1b**	I	C–Cl	I–D		**7b**	66
15	**1c**	I	C–Cl	I–D		**7c**	91[d]
16	**1d**	I	C–Cl	I–D		**7d**	90[d]
17	**1e**	I	C–Cl	I–D		**7e**	78

[a] Conditions: P = P(*o*-Tol)$_3$, JP = Cy-JohnPhos, I = IMes, T = Toluene, D = dioxane, substrate (1 equiv.), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (2 equiv.), 110 °C, 18 h. [b] Yield of isolated product. [c] Cy-JohnPhos used. [d] 10% of $Pd(OAc)_2$ and 20% of ligand.

oxazole-4-carboxylates with 1,4-iodo(bromo)chloroarenes to prepare the chlorinated DPO carboxylate-analogs **7** (Scheme 1). Interestingly, various chlorinated DPO carboxylate-analogs **7a–e** were produced in good yields (Table 1, entries 13–17). However, the use of two equivalents of electrophile were sometimes required along with increasing amounts of catalyst (10 mol%) to optimize the yield of chlorinated oxazole-4-carboxylates **7a–e** (Table 1, entries 15,16). Notably, the direct coupling remained highly selective on the iodide and bromide atoms and moreover the 4-carboxylate DPO chloro-anaolgs **7a–e** were accompanied with small amounts of their corresponding dimers (<10%) in spite of using an excess of 1,4-iodo(bromo)chloroarenes. These latter chlorinated DPO-analogs **7a–e** were exploited to prepare the POPOP dicarboxylate-analogs **8** by adding a second direct arylation step in dioxane with the 5-arylated-4-carboxylates (Scheme 1). The Cy-JohnPhos ligand was selected for this second operation on account of the good performance of the JohnPhos/dioxane pairing in the direct coupling of **1a** with phenyl chloride (Table 1, entry 5).

Surprisingly the first assay of the subsequent direct arylation of 7a with 5-phenyloxazole-4-carboxylates **1a** using the JohnPhos/dioxane pair produced the expected POPOP-carboxylate-analog **8a** in 19% very poor yield. However, pleasingly, both symmetrical dimethoxylated and diaminated POPOP carboxylate-analogs **8b** and **8c** were prepared quantitatively following the same procedure (Table 2, entries 2,3). In the same way, the unsymmetrical POPOP dicarboxylate-analogs **8d–g** were also

Table 2 Preparation of POPOP dicarboxylate-analogs **8a–g**[a]

Entry	Cl-DPO **7**	5-Ar-Oxa. **1a–e**	POPOP analogs		Yield[b] (%)
1	**7a**	**1a**		**8a**	22
2	**7c**	**1c**		**8b**	98
3	**7d**	**1d**		**8c**	99
4	**7b**	**1c**		**8d**	39
5	**7c**	**1b**			86
6	**7b**	**1d**		**8e**	36
7	**7d**	**1b**			95
8	**7e**	**1c**		**8f**	77
9	**7c**	**1e**			92
10	**7e**	**1d**		**8g**	87
11	**7d**	**1e**			98

[a] Conditions: substrate (1 equiv.), $Pd(OAc)_2$ (5 mol%), Cy-JohnPhos ligand (10% mol), Cs_2CO_3 (2 equiv.), 110 °C, 18 h. [b] Yield of isolated product.

Table 3 Luminescent properties of DPO dicarboxylate-analogs **2–6** and POPOP dicarboxylate-analogs **8** in CH_2Cl_2

Entry	Analogs	ε (M^{-1} cm^{-1})	λ^{max}_{abs} (nm)	λ_{em} (nm)[a]	Stokes shift (nm)	ϕ[c]
1	DPO	31 632	307	365[b]	58	0.78
2	2	28 127	300	368[b]	68	0.48
3	3a	5853/6236	268/337	421	84	0.42
4	**3b**	19 082/14 311	300/379	**541**	**162**	**0.48**
5	4a	25 189	334	429	95	0.27
6	4b	13 848	325	410	85	0.37
7	5a	17 419	383	518	135	0.62
8	**5b**	11 438/18 220	246/380	490	**110**	**0.87**
9	6a	18 809/18 420	275/323	407[b]	132	0.34
10	**6b**	17 950/14 711	310/366	516	**150**	**0.71**
11	POPOP	48 575	361	419	58	0.77
12	8a	14 848	330	385/409	55	0.69
13	**8d**	45 933	355	**467**	**112**	**0.80**
14	8e	28 426	325	434	109	0.32
15	8f	62 528	350	454	104	0.60
16	8g	50 618/43 213	320/365	430[b]/530[b]	110	0.37

[a] Excitation at 360 nm. The quantum yields of fluorescence were determined at 25 °C with harmane in H_2SO_4 0.1 M ($\phi = 0.90$) as the reference standard. [b] Excitation at 300 nm. [c] ±10%.

successfully prepared (Table 2, entries 4–11) including notably two pyridinated POPOP dicarboxylate-analogs **8f–g** isolated in almost quantitative yield through two distinct routes, the direct coupling of the electron-withdrawing **7b,7e** as well as the electron-donating **7c**, **7d** chlorinated DPO carboxylate-analogs with the corresponding electrophiles (Table 2, entries 8–11).

The optical properties of the novel DPO carboxylate-analogs **2–6** were first evaluated (Table 3-entries 1–10). Two highly luminescent novel DPO carboxylate-Dapoxyl-analogs **5b**, **6b** with larger Stokes shifts than DPO (110, 150 nm respectively *vs.* 58 nm for the DPO reference), maintaining notably high quantum yields (0.87 and 0.71 respectively *vs.* 0.78 for DPO reference), were identified. Consequently, the emission maxima of **5b** and **6b** were then located at 490 and 516 nm as shown in Fig. 1. Remarkably, the unsymmetrical DPO carboxylate-analog **3b** flanked with cyano and dimethylamino functions as electron-acceptor and electron-donor groups exhibits a rare Stock shift in this series (542 nm) but the quantum yield is lower than the DPO reference (0.48 *vs.* 0.78).

In contrast with the DPO carboxylate-analog series, the evaluation of the optical properties of the POPOP-dicarboxylate-analogs **8** (Table 3, entries 11–16) revealed that the unsymmetrical cyanated and dimethoxylated POPOP dicarboxylate-analog **8d** exhibits a much larger Stokes shift than the cyanated and aminated POPOP dicarboxylate-analog **8e** as well as both pyridinylated POPOP dicarboxylate-analogs **8f** and **8g**. This trend suggests that the luminescence of the POPOP dicarboxylate-analogs is not based upon an intrinsic electron long displacement from the electron-donating to the electron-withdrawing group. In summary, we

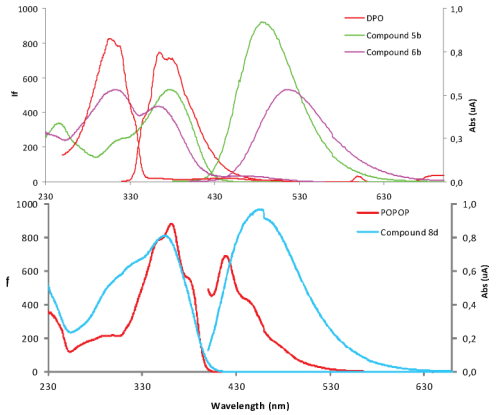


Fig. 1 Absorption and emission spectra in CH_2Cl_2 at 25 °C of DPO and POPOP references and their optimal dicarboxylate-analogs **5b, 6b** and **8d**.

report here a highly efficient access to highly valuable DPO and POPOP-(di)carboxylate-analogs by palladium-catalysed direct (het)arylation of 5-arylated oxazole-carboxylates prepared in advance through a single-step condensation of benzoyl chlorides and commercially available ethyl isocyanoacetate.[9] This study has led to the discovery of three DPO- and POPOP-type sensors with a two-and three-fold Stokes shift as compared with their DPO and POPOP references, and with high quantum yields.

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