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Conversion of 3-Bromo-2*H*-coumarins to 3-(Benzofuran-2-yl)-2*H*-coumarins under Palladium Catalysis: Synthesis and Photophysical Properties Study

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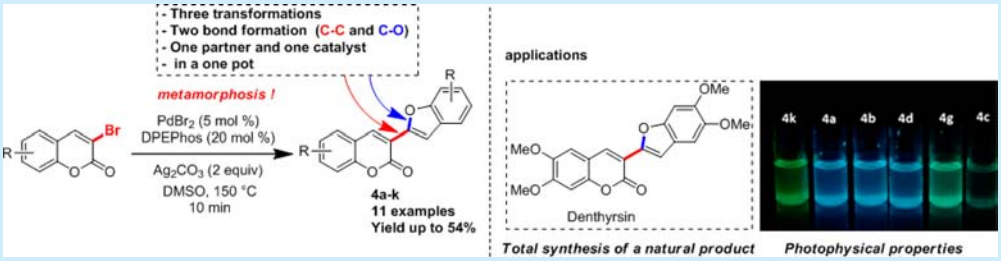
Supporting Information



ABSTRACT: An intriguing conversion of 3-bromo-2*H*-coumarins to 3-(benzofuran-2-yl)-2*H*-coumarins under palladium catalysis is reported. The process involves, from only one single starting material, three transformations and two bond formations in one pot: C−C bond formation via C−H activation and C−O bond formation through 2*H*-coumarin-to-benzofuran ring contraction under palladium catalysis. Moreover, the photophysical properties of all synthesized compounds were studied.

The 2*H*-coumarin nucleus is a common motif in many classes of biologically active compounds (Figure 1).[1] It constitutes a major class of pharmaceuticals including antitumor, antioxidant, anti-inflammatory, anti-HIV, anticoagulant, as well as antibacterial agents.[1a,f,j] In addition, 3-heteroaryl-2*H*-coumarins have been widely used as powerful fluorescent dyes for biological applications such as live cell imaging.[2] The unique structure of 2*H*-coumarin has many advantages including a large Stokes shift, a high fluorescence quantum yield, as well as excellent light photostability.

As part of our continuing efforts at the functionalization of heterocycles via transition-metal-catalyzed reactions,[3] we recently reported an efficient protocol for the synthesis of biheterocycles based on quinolinone and 2*H*-coumarin scaffolds through the palladium-catalyzed decarboxylative couplings of quinolinone-3-carboxylic acids with 3-bromo-2*H*-coumarins (Scheme 1).[4] Based on these results, we examined

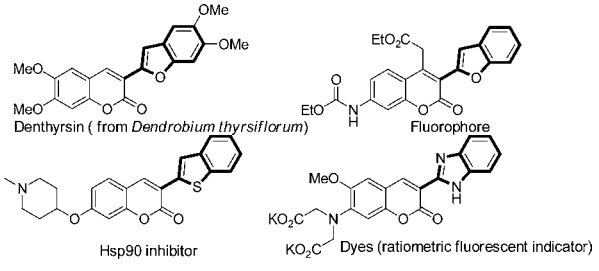
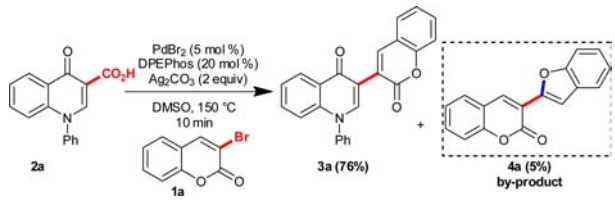


Figure 1. Examples of biologically active 2*H*-coumarins.

Scheme 1. Early Observation of the Formation of 4a



the ability of this transformation to achieve the synthesis of **3a** (Scheme 1) on a gram scale for further critically important biological investigation. Pleasingly, increasing the scale of the reaction (from 0.5 to 5 mmol) did not have a significant impact on the efficiency of the reaction, and we were able to obtain **3a** in a 70% yield together with the byproduct **4a**. This byproduct, although obtained in only 5% yield, pointed to the principal feasibility of this alluring conversion of 3-bromo-2*H*-coumarin

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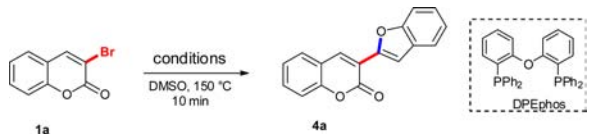
into a complex structure in one step. If further developed, such a transformation could give fast access to substituted 3-(benzofuran-2-yl)-2*H*-coumarins, thus eliminating the need to use benzofuran derivatives as the starting material for functionalization with 2*H*-coumarins. Herein, we report our success in the development of this protocol.

We began our investigations by fine-tuning the conditions of this novel transformation using 3-bromo-2*H*-coumarin **1a** as a model study (Table 1). When the reaction of **1a** was performed

Table 1. Optimization of the Transformation of 1a to 4a[a]



entry	[Pd]	ligand	base	yield[b] (%)
1	$PdBr_2$	DPEPhos	Ag_2CO_3	52
2		DPEPhos	Ag_2CO_3	0
3	$PdBr_2$		Ag_2CO_3	traces
4	$PdBr_2$	DPEPhos		0

[a]Conditions: **1a** (0.5 mmol), $PdBr_2$ (5 mol %), DPEphos (20 mol %), and DMSO (2 mL) were heated in a sealed tube at 150 °C for 10 min under argon atmosphere. [b]Yield of isolated **4a**.

using our previously reported procedure [$PdBr_2$ (5 mol %), DPEphos (20 mol %), Ag_2CO_3 (2 equiv) in DMSO at 150 °C for 10 min], by simply omitting the addition of the quinolone **2a** (Scheme 1), we were delighted to find that 3-(benzofuran-2-yl)-2*H*-coumarin **4a** was isolated in 52% yield (Table 1, entry 1).

Next, we decided to investigate the influence of each reactant (palladium, phosphine, and base) in the outcome of the reaction. It turned out that no product was formed in the absence of the catalyst $PdBr_2$ (entry 2). Moreover, as shown in entries 3 and 4, DPEPhos ligand as well as the base Ag_2CO_3 are necessary for the success of the reaction since no product was observed in the absence of each of the reactants. In the next set of experiments, we attempted to improve the yield of **4a**. After a series of assays (not shown in Table 1), the use of high catalyst loading (up to 20 mol %) and elevated temperatures (up to 170 °C) combined with a prolonged reaction time did not lead to any improvement. Thus, the best conditions were found to require **1a** (1 equiv), $PdBr_2$ (5 mol %), DPEPhos (20 mol %), Ag_2CO_3 (2 equiv), and DMSO in a sealed tube at 150 °C for 10 min. Accordingly, **4a** was obtained in a 52% yield (entry 1). Even if the yield is moderate, one can note that the process involves, from only one single starting material, three transformations and two bonds formation in a one-pot process: C−O bond formation through ring-contraction and C−C bond formation.

To confirm the structure of **4a**, X-ray diffraction studies were performed (Figure 2). The corresponding crystal of **4a** was obtained, and X-ray analysis showed that it is organized in a solid state as a trimer in a parallel geometry (Figure 2). Analysis of the aromatic nucleus of the 2*H*-coumarin ring indicates that the trimer may be stabilized by a $\pi-\pi$ staking interaction in a head-to-tail configuration (Figure 2; see the Supporting Information for details).

Although the exact mechanism of the reaction is still not clear, based on literature precedents and LC−MS analysis, we suggest a possible pathway as depicted in Scheme 2. The 3-

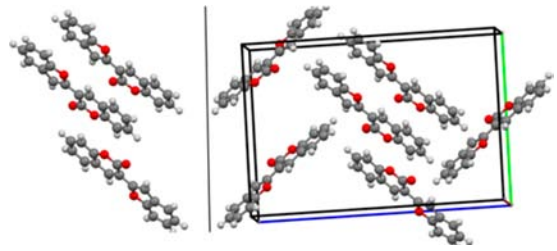
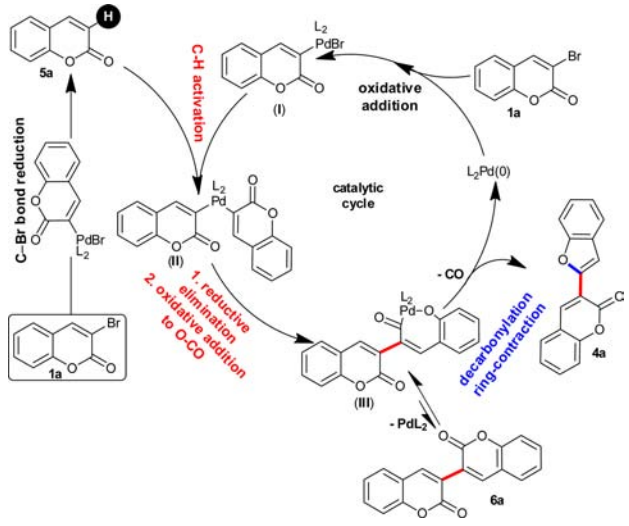


Figure 2. Single-crystal X-ray structure of **4a**.

Scheme 2. Plausible Catalytic Cycle for the Formation of 4a



bromocoumarin nucleus **1a** may be converted at first into the intermediate **II** through C−Br bond reduction of **1a** to provide **5a** followed by a C−H activation process with another 3-bromo-2*H*-coumarin molecule.[5] After a reductive elimination step, **II** would evolve into **III** through an oxidative addition of the Pd(0) to the O−CO bond of the 2*H*-coumarin ring.[6] This intermediate **III** is in equilibrium with a bis-coumarin **6a**. Finally, a CO migration[5a,6e,7] in **III** and reductive elimination furnished 3-(benzofuran-2-yl)-2*H*-coumarin product **4a** (Scheme 2). These mechanistic assumptions were supported by a kinetic study of the reaction model. After the reaction proceeded for 2 min, compounds **5a** and **6a** were detected by LC−MS (an intensive peak for **5a** and a small peak for **6a**, see the SI). During the reaction time, the peak intensity of **5a** decreases in favor of **6a**, and at the same time, the peak of the final compound **4a** increases in intensity (see the SI). These results combined with other mechanistic investigations reported in the SI are in agreement with the mechanism suggested bellow.

Prompted by these exciting results, we subsequently investigated the substrate scope for the Pd-catalyzed transformation of various substituted 3-bromo-2*H*-coumarins **1a**−**k**[7] (Scheme 3). Overall, the method works well and tolerates a large variety of electron-rich and electron-deficient groups on the aromatic ring of 2*H*-coumarins. Substrates having electron-donating groups (e.g., −Me, −OMe) on the C5, C6, C7, and C8 positions of the 2*H*-coumarins **1b**−**g** led to the formation of the corresponding 3-(benzofuran-2-yl)-2*H*-coumarins **4b**−**g** in acceptable yields ranging from 30% to 54%. Surprisingly, this protocol tolerated also the presence of halogen atoms (e.g., −Br, −Cl) on the C6 position of the 2*H*-coumarin nucleus,

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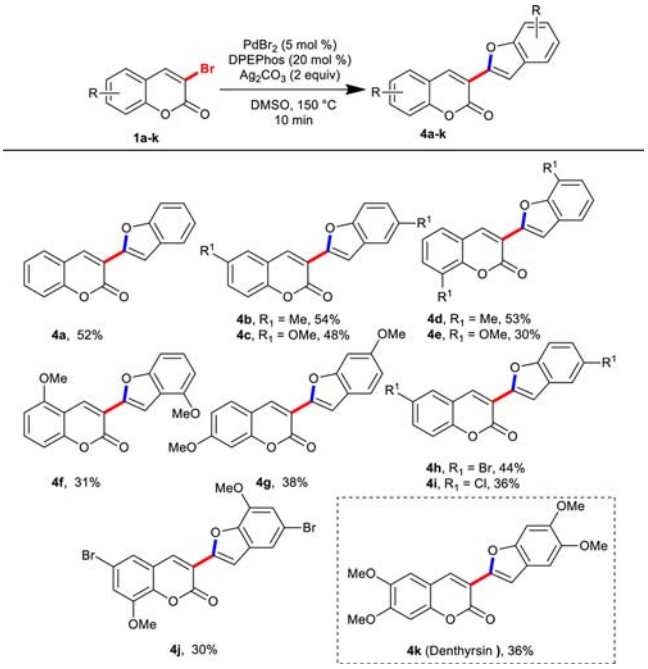
Scheme 3. Scope of 2*H*-Coumarins 1a–k[a]



[a]Conditions: 3-bromo-2*H*-coumarins **1a–k** (0.5 mmol), $PdBr_2$ (5 mol %), DPEphos (20 mol %), DMSO (2 mL) under argon at 150 °C for 10 min.

yielding dihalogenated 3-(benzofuran-2-yl)-2*H*-coumarin derivatives **4h–j**, which may be useful for regioselective cross-coupling reactions. Finally, the synthetic potential of this protocol was well-illustrated by a concise synthesis of denthyrsin **4k**, a very cytotoxic natural compound (IC_{50} = 450 nM against K562 cancer cells) isolated from *Dendrobium thyrsiflorum*.[8]

With these encouraging results in hand, we next turned our attention to examination of the absorption and emission properties of these 3-(benzofuran-2-yl)-2*H*-coumarins **4** by recording the UV–vis and the emission spectra in DMSO at 25 °C and at low concentrations (Table 2). Compounds **4a–k** exhibit maximum absorption wavelengths between 373 and 411 nm with strong molar extinction coefficients (18300 to 33200 $M^{-1}cm^{-1}$). They emit between 400 and 500 nm in DMSO and have moderate to high fluorescence quantum yields (ranging from 0.07 to 0.99) except for compound **4k**, which is poorly emissive. The position and the nature of the substituent on the 2*H*-coumarin ring are essential for the photophysical properties. The compounds bearing a methoxy group exhibit a bathochromic shift in either the absorption (except for **4e** and **4j**) or the emission wavelengths. The presence of a methoxy group on the C6 position of the 2*H*-coumarin ring is detrimental for the fluorescence quantum yield (see **4c** vs **4a** and **4k** vs **4g**), although the presence of the same group on the C5 or C7 position does not have a strong effect (see **4f** and **4g**). The quenching of fluorescence observed for compounds **4h–j** is due to the internal heavy atom effect.[9] The fluorescence quantum yields as well as the absorption and emission wavelengths are not affected by the presence of a methyl group either on the C6 or C8 position (compounds **4b** and **4d**). Therefore, the brightest compounds are **4a**, **4b**, and **4d** as illustrated by Figure 3.

Table 2. Photophysical Properties of 4a–k in DMSO

compd	λ_{abs} (nm) (ε_{abs} M^{-1} cm^{-1})	λ_{em} (nm)	Φ_F	brightness = $\varepsilon_{abs}x\Phi_F$ (M^{-1} cm^{-1})
4a	371 (32500)	450	0.99	32200
4b	377 (30400)	448	0.83	25200
4c	389 (21500)	484	0.16	3400
4d	373 (29800)	456	0.88	26200
4e	359 (28700)	488	0.11	3100
4f	389 (20200)	484	0.68	13700
4g	394 (28900)	484	0.75	21700
4h	374 (30700)	444	0.20	6100
4i	373 (33200)	488	0.20	6600
4j	359 (29500)	387	<0.005	<150
4k	411 (18300)	500	0.07	1280

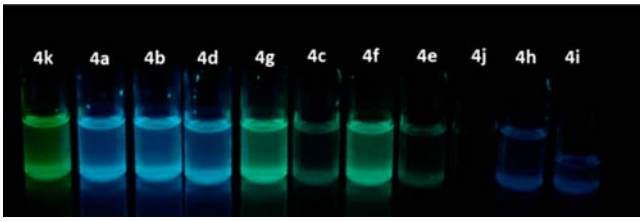


Figure 3. Compounds **4a–k** (0.5 mM) in DMSO under UV irradiation (312 nm).

A fluorosolvatochromic study was carried out on the brightest compound **4a** (Table 3). A bathochromic shift of the emission band can be observed with increasing solvent polarity. This fluorosovatochromism is evidence of a strong interaction charge transfer in the lowest excited state.[10] We can also observe increasing Stokes shift from 3600 cm^{-1} in toluene to 6340 cm^{-1} in water. The same trend is observed for **4b–g** (see Table 4, SI). Compound **4a** exhibits high fluorescence quantum yields from 0.15 in water to 0.99 in DMSO. The fluorescence quantum yield in water is impressively high for this solvent and is very interesting for its potential use as a fluorophore in biological media. It must be noted that the other dyes were less emissive in water. The high quantum yields obtained for **4a** lead to high brightnesses (Figure 3).

Table 3. Photophysical Properties of 4a in Various Solvents

solvent (E_T^N)	λ_{abs} (nm)/ λ_{em} (nm)	ε_{abs} (M^{-1} cm^{-1})	Stokes shift (cm^{-1})	Φ_F	brightness = $\varepsilon_{abs}x$ Φ_F (M^{-1} cm^{-1})
MePh (0.10)	373/431	34100	3600	0.88	30000
AcOEt (0.23)	368/433	34100	4080	0.79	27000
MeCN (0.46)	366/442	32100	4700	0.75	24000
DMSO (0.44)	371/450	32500	4730	0.99	32000
H_2O (1.00)	365/475	7500	6340	0.15	1100

In conclusion, we successfully developed an original and practical avenue for the synthesis of 3-(benzofuran-2-yl)-2*H*-coumarins. The protocol exhibited a broad substrate scope with respect to 2*H*-coumarin substrates, thus providing an attractive alternative to the existing methods for the synthesis of 3-(benzofuran-2-yl)-2*H*-coumarins **4** as fluorescent dyes for biological applications.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00069.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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