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An appraisal of the Suzuki cross-coupling reaction for the synthesis of novel fluorescent coumarin derivatives

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ABSTRACT

We report the chemical design and development of 3-aryl-substituted 7-alkoxy-4-methylcoumarins with enhanced fluorogenic properties. The 3-aryl substituents are installed via an optimized Suzuki–Miyaura cross-coupling (SMC) reaction between a 7-alkoxy-3-bromo-4-methylcoumarin and aryl boronic MIDA esters using $Pd(OAc)_2$/XPhos in a catalytic system with K_2CO_3 in aqueous THF. Under these conditions, an exocyclic ester functionality is found to be unaffected. Subsequent saponification revealed a carboxylic acid functionality that is suitable for conjugation reactions. Evaluation of their fluorescence properties indicated that the installed 3-heteroaryl substituent, particularly benzofuran-2-yl, resulted in a significant red shift of both the excitation and emission wavelengths.

Fluorescence bio-imaging has widespread uses in biochemical and cellular research. In this context, fluorescent probes, such as tagged or labeled biomolecules are indispensable tools for monitoring molecular changes continuously in the intracellular environment at low concentrations.[1] In the selection of a suitable fluorogenic tag, the fluorophore should have a number of desired characteristics, including chemical and photo-stability, a high quantum yield, a large Stokes' shift, good solubility under physiological conditions, and low cell toxicity. For example, high fluorescent quantum yields are important to reduce (i) the concentration of the probe, which in turn minimizes potential toxicity, and (ii) interference from endogenous components of the cells.[2]

In this regard, coumarin derivatives have many of the important desirable features, including small size, easy to manipulate synthetically, low toxicity, large Stokes' shifts to avoid a significant overlap of the excitation and emission spectra, and good photo-stability.[3–5]

Coumarin derivatives are already used as fluorescent sensors for Mg^{2+},[6] Hg^{2+},[7] and cytochrome P450 function.[8] A typical feature of the fluorogenic coumarin moiety is the presence of an electron-donating group at the 7-position. However, a limitation of fluorogenic coumarin derivatives when used for bio-imaging is the interference of background fluorescence from components of the cells, primarily due to the short excitation wavelength of coumarin in the UV region.[9] In order to address this limitation, both the absorption and emission maxima of coumarin could be shifted to longer wavelengths by installing a heteroaromatic substituent at the 3-position, which effectively extends the π system of the coumarin moiety.[9] We[10] and others[4,11] have adopted this approach; for example, the Bauerle and Wang groups confirmed that the fluorescence intensity was enhanced by modification of the parent coumarin at the 3-position.[4f,11]

Thus, in order to exploit many of the unique features of fluorogenic coumarin, we have designed and synthesized a panel of multifunctional coumarin tags, 6-[(3-aryl-4-methylcoumarin-7-yl)oxy]hexanoic acids, which are capable of conjugation reactions with substrates via, for example, amide bond formation. The fluorogenic properties of our coumarin tags are enhanced by the unique heteroaryl substituent at the C3-position. We report, for the first time, an extensive appraisal of the Pd(0)-catalyzed Suzuki–Miyaura cross-coupling (SMC) reaction conditions for the installation of the desired heteroaryl substituent.

Thus, the desired intermediate ethyl 6-[(3-bromo-4-methylcoumarin-7-yl)oxy]hexanoate (**3**) was obtained from 7-hydroxy-4-methylcoumarin (**1**) in two steps (Scheme 1). In the first step, the alkylation of the phenolic group with ethyl 6-bromohexanoate was carried out in DMF at 75 °C for 4 h, which gave the product **2** in 85% yield. Since aryl bromides and iodides are often used in SMC reactions due to their high reactivity, by facilitating the oxidative addition step in the SMC catalytic cycle,[12] we next considered regioselective bromination of our intermediate **2**. Direct bromination of aromatic compounds using bromine generates toxic and corrosive HBr, which is hazardous to the environment;[13] the reaction

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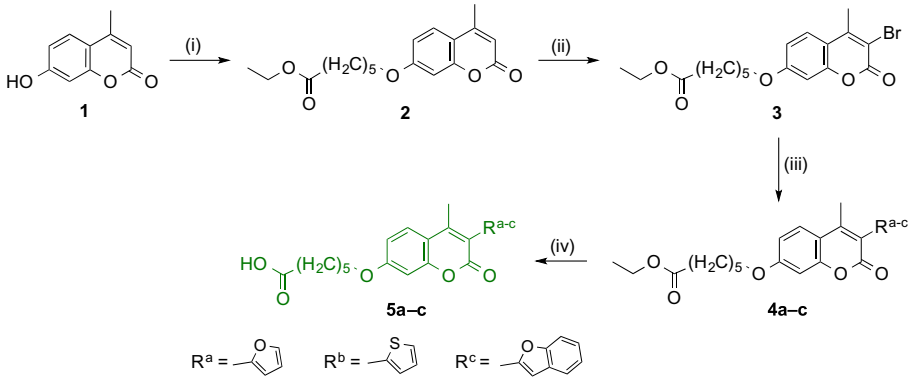

Scheme 1. Synthesis of fluorescent 7-alkoxy-3-aryl-4-methylcoumarin derivatives. Reagents and conditions: (i) ethyl 6-bromohexanoate, K_2CO_3, DMF, 75 °C; (ii) NBS, NH_4OAc; (iii) catalyst/ligand, base, 60–70 °C; (iv) LiOH, 5 equiv, THF–H_2O (3:2).

is also generally non-selective, forming mixtures of mono- and polybrominated products.[14] *N*-Bromosuccinimide (NBS) is considered a superior brominating agent due to the ease of its handling and low cost.[13] Thus, treatment of intermediate **2** with NBS, in the presence of NH_4OAc, for 30 min at ambient temperature afforded **3** in excellent yield (85%).

Next, Pd(0)-catalyzed cross-coupling of intermediate **3** with various heteroaryl boronic esters was evaluated. In order to gauge the potential of established SMC methodologies, 2-furan boronic acid was used as a model coupling substrate. Among the various reported SMC reaction conditions, $Pd(dppf)_2$ as catalyst and K_2CO_3 as the base suspended in 1,4-dioxane are considered highly efficient in cross-coupling conjugation of aryl halides with various boronic compounds.[12c] Therefore, this protocol was applied to our coumarin scaffold **3**.

Initially, when coumarin **3** was allowed to react with 1.5 equiv of furan boronic acid at 70 °C for 24 h, the 3-furyl product **4a** was obtained in trace amounts (Table 1, entry 1), with near complete recovery of the starting material **3**. Although an increase in the boronic acid quantity (2 equiv) improved the reaction, the conversion was still poor (Table 1, entry 2). This inefficiency was attributed to the instability of the substrate 2-furan boronic acid, since it is known to decompose via protodeboronation.[15] Moreover, the protodeboronation is thought to be accelerated by heat in the presence of a base.[15] However, decreasing the quantities of the base to one equivalent did not improve the conversion (Table 1, entry 3). To overcome this problem, 2-furan boronic MIDA ester was used since it is considered to be more stable than the corresponding boronic acid.[15] Although the reaction was slow and did not reach completion (Table 1, entry 4), it gave an improved and consistent result. Consequently, furan MIDA ester was used in subsequent evaluation of the SMC reaction.

The role of the base in SMC reactions is thought to accelerate the transmetallation rate through the coordination of a negatively charged base to the boron atom and to increase its nucleophilicity for transmetallation.[12c,16] The bases most commonly employed for SMC are K_3PO_4, Na_2CO_3, and K_2CO_3. Others, including LiOH, KOH, and KF have also been used.[17] The base can be used in aqueous solution or as a suspension in 1,4-dioxane or DMF.[16b] At present, the choice of base is still empirical and no general rule for their selection has been established. In our system, changing the base to an organic base, for example, triethylamine and *N*-methylmorpholine (NMM) afforded the coupled product **4a** in trace amounts (Table 1, entries 5 and 6).

Cesium base compounds are known to be superior to their potassium analogues with respect to reaction time and yield.[18] Littke and et al. used Cs_2CO_3 and found that the coupling reaction was more rapid in the presence of cesium compounds.[12b] Hence, by changing the base to Cs_2CO_3, the progress of our SMC reaction improved to 35%, but the conversion was still incomplete (Table 1,

Table 1
Optimized Pd-catalyzed Suzuki cross-coupling reactions of ethyl 6-[(3-bromo-4-methylcoumarin-7-yl)oxy]hexanoate (**3**) with boronic acid or MIDA esters

Entry	Aryl boronic acid or ester (2 equiv)	Catalytic system	Base (3 equiv)	Solvent	Time (h)	Conversion rate[a] (%)
1	2-Furan boronic acid [b]	$PdCl_2(dppf)$	K_2CO_3	1,4-Dioxane	24	<0.2
2	2-Furan boronic acid	$PdCl_2(dppf)$	K_2CO_3	1,4-Dioxane	30	19
3	2-Furan boronic acid	$PdCl_2(dppf)$	K_2CO_3[c]	1,4-Dioxane	26	2
4	2-Furan boronic MIDA	$PdCl_2(dppf)$	K_2CO_3	1,4-Dioxane	30	22
5	2-Furan boronic MIDA	$PdCl_2(dppf)$	Et_3N	1,4-Dioxane	24	2
6	2-Furan boronic MIDA	$PdCl_2(dppf)$	NMM	1,4-Dioxane	26	<0.2
7	2-Furan boronic MIDA	$PdCl_2(dppf)$	Cs_2CO_3	1,4-Dioxane	24	35
8	2-Furan boronic MIDA	$PdCl_2(dppf)$	K_2CO_3	1,4-Dioxane/H_2O	20	71
9	2-Furan boronic MIDA	$PdCl_2(dppf)$	Et_3N	1,4-Dioxane/H_2O	23	9
10	2-Furan boronic MIDA	$PdCl_2(dppf)$	NMM	1,4-Dioxane/H_2O	24	<0.2
11	2-Furan boronic MIDA	$PdCl_2(dppf)$	K_2CO_3/TBAB	1,4-Dioxane/H_2O	22	46
12	2-Furan boronic MIDA	$PdCl_2(dppf)$	K_2CO_3	DMF/H_2O	24	<0.2
13	2-Furan boronic MIDA	$PdCl_2(dppf)$	K_2CO_3	THF/H_2O	5	71
14	2-Furan boronic MIDA	$Pd(PPh_3)_4$	K_2CO_3	THF/H_2O	23	58
15	2-Furan boronic MIDA	$Pd(OAc)_2/P(Ph)_3$	K_2CO_3	THF/H_2O	22	48
16	2-Furan boronic MIDA	$Pd(OAc)_2$/XPhos	K_2CO_3	THF/H_2O	2.5	71
17	2-Thiophene boronic MIDA	$Pd(OAc)_2$/XPhos	K_2CO_3	THF/H_2O	4	76
18	2-Benzo[*b*]furan boronic MIDA	$Pd(OAc)_2$/XPhos	K_2CO_3	THF/H_2O	4	90

[a] Conversion rate is based on a combination of isolated yields (following a simple work-up) and purity determined by ^1H NMR and RP-HPLC.
[b] 1.5 equiv.
[c] 1.0 equiv.