



Palladium-catalyzed coupling reactions of 4-coumarinyl triflates with indoles leading to 4-indolyl coumarins



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ABSTRACT

A convenient and efficient approach for the synthesis of 4-indolyl coumarins and 4-indolyl quinolinones was developed via palladium-catalyzed coupling reactions between 4-coumarinyl triflates/4-trifluoromethanesulfonyloxyquinolinones and indoles. Biological evaluation revealed that some of the obtained products exhibited *in vitro* antiproliferative activities on human-derived prostate, stomach, lung, breast cancer cell lines.

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Introduction

Coumarin is a key core structure found in a wide range of natural products and biological molecules with remarkable pharmacological properties.¹ Importantly, 4-substituted coumarins as a privileged scaffold, have attracted much attention because of their wide activities as antiprotozoal,² anticancer,³ anti-HIV,⁴ antimalarial,⁵ antibacterial,⁶ and cytotoxic properties.⁷ In particular, 4-indolyl coumarins exhibited a potent antiproliferative activity on HBL100 human epithelial mammary cell line.⁸ Thus, the development of efficient methods for construction of this kind of compound is of great value and numerous attempts have been made by organic chemists in the past decades.

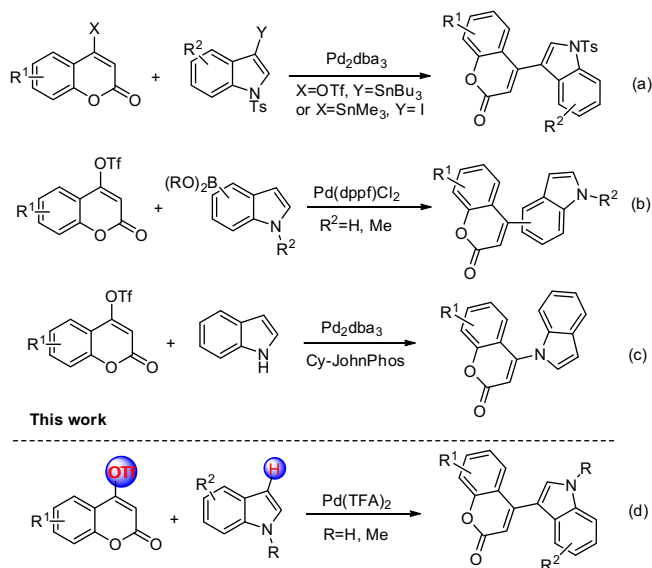
Early in 1994, Ortar reported the synthesis of 4-indolyl coumarins by palladium-catalyzed coupling reaction of organostannanes with triflates and halides (Scheme 1a).⁹ Recently, Combes et al. reported biologically active 4-indolyl coumarins were obtained by treatment of 4-coumarinyl triflates with either indolylboronic acids or their pinacolate esters under Suzuki–Miyaura cross-coupling conditions (Scheme 1b).⁸ Beletskaya realized an easy access to 4-indolyl coumarins through palladium-mediated reactions of N–H indoles with 4-coumarinyl triflates (Scheme 1c).¹⁰ However, these processes still suffer from some drawbacks, for instance,

the limited substrate scope, the insufficient merit of using organostannanes, 3-iodoindol, indolylboronic acids, or pinacolate esters as starting materials in the practical sense. Therefore, a simple new approach that provides direct and efficient access to 4-indolyl coumarins would be highly desirable and enrich the structural diversity of 4-indolyl coumarins. Herein, we present a novel and practical procedure to synthesis various 4-indolyl coumarins via palladium-catalyzed cross-coupling reactions of 4-coumarinyl triflates with indoles (Scheme 1d).

Since substituted 4-hydroxycoumarins are commercially available, triflates **1** could be readily prepared according to the known procedures.¹¹ Optimization of the reaction conditions was carried out using 4-coumarinyl triflate **1a** with 1-methylindole **2a** as the model substrates. Some screening results are shown in Table 1. As summarized, it was found that using Pd(TFA)₂ as catalyst gave the best result, whereas other palladium sources, such as Pd(OAc)₂, PdCl₂, PdBr₂, Pd(PPh₃)₂(OAc)₂, and PdSO₄ were less effective or ineffective (entries 1–6). With an attempt to improve the yield of the reaction, further efforts related to the influence of solvents were examined. While with DMSO, CH₃CN as the solvents, only trace of the product **3a** was detected (entries 7 and 10). DMF and dioxane provided **3a** in 25% and 38% yields respectively (entries 8–9). Xylene was the most suitable solvent and resulted in the desired product **3a** being obtained in 45% yield (entry 6). A better result was achieved upon employing 4 equiv of 1-methylindole **2a** with 62% yield (entry 11). Prompted by this result, we then screened the ligand and base in this transformation. The presence

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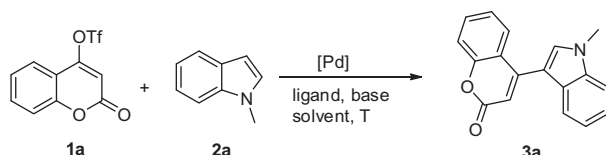
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Scheme 1. Construction of 4-indolyl coumarins with different strategies.

of tricyclohexylphosphine and K_2CO_3 gave the corresponding product **3a** in 75% yield (entry 13). The reaction failed to afford the desired product when phen/ Cs_2CO_3 was employed (entry 12). Other ligand and bases such as PPh_3 , Na_2CO_3 , K_3PO_4 were also conducted, but provided no improvements (entries 14–16). In addition, obviously decreased yields were obtained while further attempt to adjusting the reaction temperature (entries 18–19). Furthermore, the yield of **3a** was slightly decreased to 72% in the absence of base (entry 17). Therefore, we decided to use condition in entry 13 as the standard reaction conditions.

Table 1
Screening and optimization of the reaction conditions



Entry ^a	1a:2a	[Pd]	Ligand/Base	Solvent	Yield ^b (%)
1	1:2	Pd(OAc) ₂	—	Xylene	32
2	1:2	PdCl ₂	—	Xylene	trace
3	1:2	PdBr ₂	—	Xylene	NR
4	1:2	Pd(PPh ₃) ₂ (OAc) ₂	—	Xylene	34
5	1:2	PdSO ₄	—	Xylene	Trace
6	1:2	Pd(TFA) ₂	—	Xylene	45
7	1:2	Pd(TFA) ₂	—	DMSO	Trace
8	1:2	Pd(TFA) ₂	—	DMF	25
9	1:2	Pd(TFA) ₂	—	Dioxane	38
10	1:2	Pd(TFA) ₂	—	CH ₃ CN	Trace
11	1:4	Pd(TFA) ₂	—	Xylene	62
12	1:4	Pd(TFA) ₂	phen/ Cs_2CO_3	Xylene	Trace
13	1:4	Pd(TFA) ₂	PCy ₃ / K_2CO_3	Xylene	75
14	1:4	Pd(TFA) ₂	PPh ₃ / K_2CO_3	Xylene	51
15	1:4	Pd(TFA) ₂	PCy ₃ / Na_2CO_3	Xylene	66
16	1:4	Pd(TFA) ₂	PCy ₃ / K_3PO_4	Xylene	40
17	1:4	Pd(TFA) ₂	PCy ₃	Xylene	72
18 ^c	1:4	Pd(TFA) ₂	PCy ₃ / K_2CO_3	Xylene	58
19 ^d	1:4	Pd(TFA) ₂	PCy ₃ / K_2CO_3	Xylene	62

^a Reaction was performed with **1a** (0.25 mmol), **2a** (0.5 or 1 mmol), catalyst (10 mol %), ligand (20 mol %), base (0.5 mmol) in 2 mL solvent at 100 °C for 10 h.

^b Isolated yield.

^c The reaction was performed at 80 °C.

^d The reaction was performed at 120 °C.

After successfully identifying the optimal reaction conditions for the synthesis of 4-indolyl coumarins, we turned our attention to the substrate scope and generality. As summarized in Table 2, a broad range of coumarins were screened. The coupling of 1-methylindole or N-H indole **2** and coumarins **1** with electron-donating and electron-withdrawing groups (CH₃, OCH₃, Cl, Br, F) at the 6-position or 7-position were found to be favored in the reaction to afford the corresponding products **3a–3k** in moderate to good yields. Notably, the chloro and bromo moieties on the phenyl ring of coumarins were tolerated under these coupling conditions and offer versatile synthetic functionalization for further elaboration. It was gratifying to find that polycyclic triflate **1l** also reacted smoothly with N-H indole, leading to the corresponding product **3l** in 85% yield. Furthermore, we studied the scope and limitations by varying the indole component in the reaction with coumarins. Electronic effects in the indole structure turned out to be stronger, and sharp decrease yields were afforded when indoles with electron-withdrawing groups (CO₂Me) and electron-donating groups (Et, OCH₃) were employed. To our surprise, indole **1m** bearing –CH₃ at 2-position could be reacted under the typical conditions, and the desired product **3m** was obtained in 29% yield, albeit with certain steric hindrance. But, indole bearing –CH₃ group at 3-position was not tolerated, and the product **3q** was not observed.

With the established facile approach to the synthesis of 4-indolyl coumarins in hand, we wondered that this method might offer valuable 4-indolyl quinolinones¹² if 4-trifluoromethanesulfonyloxyquinolinones was employed instead of 4-coumarinyl triflates under similar conditions. As predicted, the palladium-catalyzed cross-coupling reactions of 4-trifluoromethanesulfonyloxyquinolinones with indoles worked well, giving the expected products **5a–5b** in moderate yields (Scheme 2).

To demonstration of this novel reaction, some control experiments were performed (Scheme 3). The reaction of 4-coumarinyl

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