# Direct Synthesis of Coumarins by Pd(II)-Catalyzed Reaction of Alkoxyphenols and Alkynoates

Juzo Oyamada, Chengguo Jia, Yuzo Fujiwara,† and Tsugio Kitamura*
*Department of Applied Chemistry, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka 812-8581*
†*Henkel Research Center of Advanced Technology, Molecular Engineering Institute, Kinki University, Kayanomori, Iizuka, Fukuoka 820-8555*

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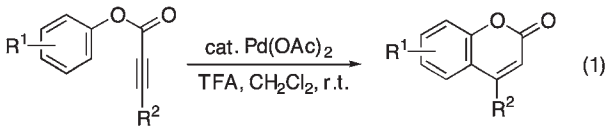
Reaction of alkoxyphenols and alkynoates in the presence of a catalytic amount of $Pd(OAc)_2$ in trifluoroacetic acid at room temperature gave coumarin derivatives in high yields. This procedure provides a convenient method for direct synthesis of coumarin derivatives under very mild conditions.

Coumarins attract a great deal of attention due to their wide biological activity[1] but the development of efficient and general method for the synthesis still remains unsolved.

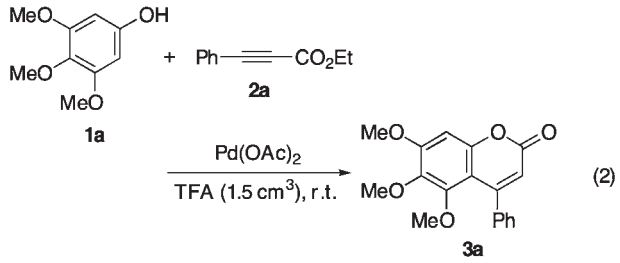
Recently, we have found the efficient Pd(II)-catalyzed inter- and intramolecular hydroarylations of alkynes by simple arenes at room temperature in a mixed solvent containing trifluoroacetic acid (TFA).[2] Although coumarins have been prepared by the intramolecular hydroarylation of aryl alkynoates by the above method (eq 1),[2] a direct synthesis from phenols and alkynoates is much more favorable.



(1)

Trost and Toste reported a Pd(0)-catalyzed addition of phenols to alkynoates in formic acid giving coumarins.[3] In their reaction, however, a Pd(0) species acts as the actual catalyst. The formic acid plays the important role in the catalytic cycle.

On the other hand, in our case, a Pd(II) species catalyzes the hydroarylation of alkynes by using TFA as the solvent without any additives.[2] Thus, we have examined the Pd(II)-catalyzed direct synthesis of coumarins from phenols and alkynoates. Here we wish to report our results concerning synthesis of coumarins by the reaction of phenols and alkynoates in the presence of a catalytic amount of $Pd(OAc)_2$ in TFA. In this paper, we focus on the synthesis of alkoxycoumarins because such alkoxycoumarins show biological activity and there exist anti-HIV active *Calophyllum* coumarins.[1b]



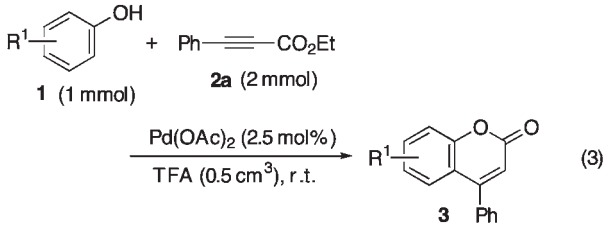
(2)

First, we examined the reaction of 3,4,5-trimethoxyphenol (**1a**) and ethyl phenylpropiolate (**2a**) to optimize the reaction conditions (eq 2). The results are given in Table 1. Exclusive formation of 4-phenyl-5,6,7-trimethoxycoumarin (**3a**) was observed in the reaction with a catalytic amount of $Pd(OAc)_2$ (Entries 2–8). No reaction occurred in the absence of $Pd(OAc)_2$ (Entry 1). The reaction using an excess amount of **2a** rather than **1a** gave the better yield of coumarin **3a** (Entries 2–4). Use of a less amount of TFA increased the yield to 91%, even though the amount of **2a** was reduced to 1.2 equivalent to **1a** (Entry 6). This result suggests that a higher concentration of the substrates promotes the reaction effectively.

**Table 1.** Pd(II)-Catalyzed reaction of **1a** and **2a**[a]

| Entry | $Pd(OAc)_2$/mol% | **1a**/mmol | **2a**/mmol | Time/h | Yield/%[b] |
|---|---|---|---|---|---|
| 1 | 0 | 2 | 1 | 6 | 0 |
| 2 | 2.5 | 2 | 1 | 6 | 76 |
| 3 | 2.5 | 1 | 1.5 | 6 | 76 |
| 4 | 2.5 | 1 | 2 | 6 | 87 |
| 5[c] | 1 | 1 | 2 | 18 | 93 |
| 6[d] | 1 | 1 | 1.2 | 18 | 91 |
| 7 | 1 | 1 | 2 | 6 | 64 |
| 8[e] | 1 | 1 | 1.2 | 6 | 80 |

[a]All reactions were carried out at room temperature using **1a**, **2a**, $Pd(OAc)_2$ and TFA (1.5 $cm^3$). [b]GC yield based on the least amount of substrates. [c]TFA (1.0 $cm^3$) was used. [d]TFA (0.6 $cm^3$) was used. [e]TFA (0.5 $cm^3$) was used.

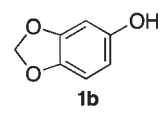
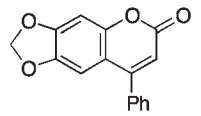
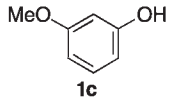
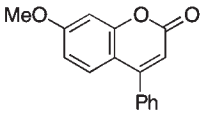
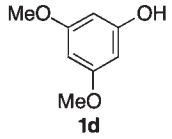
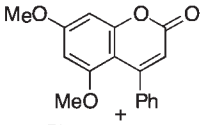
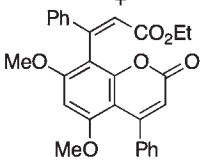


(3)

The Pd(II)-catalyzed reaction using trimethoxyphenol **1a** efficiently affords trimethoxycoumarin **3a**. Then, we investigated the reaction of some alkoxyphenols **1** with **2a** (eq 3). The results are summarized in Table 2. The Pd(II)-catalyzed reactions with alkoxyphenols **1** gave the corresponding coumarins **3** in high yields (Entries 1–3).

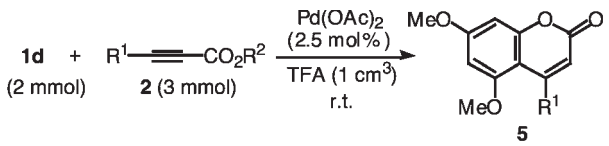
In the case of 3,5-dimethoxyphenol (**1d**) (Entry 3), 4-phenyl-5,7-dimethoxy-8-(1-phenyl-2-ethoxycarbonylethenyl)coumarin (**4**) was also formed in 18% yield together with 5,7-dimethoxy-4-phenylcoumarin (**3d**), suggesting further addition of **3d** to **2a**. The results obtained above indicate that the Pd(II)-catalyzed hydroarylation is very suitable for coumarin synthesis from phenols and alkynoates. Since the Pd(II)-catalyzed reaction proceeds via an electrophilic palladation of arenes, electron-rich alkoxyphenols

**Table 2.** Pd(II)-Catalyzed reaction of phenols **1** and **2a**

| Entry | Phenol **1** | Time/h | Product and isolated yield/% |
|---|---|---|---|
| 1[a] |  **1b** | 18 |  **3b:** 93[b] |
| 2[c] |  **1c** | 20 |  **3c:** 85 |
| 3[d] |  **1d** | 21 |  **3d:** 56 +  **4:** 18 |

[a]$Pd(OAc)_2$ (1.0 mol%) and **2a** (1.2 mmol). [b]GC yield. [c]TFA (1 $cm^3$) was used. [d]**1** (2 mmol), **2a** (4 mmol) and TFA (0.75 $cm^3$) were used.

**Table 3.** Pd(II)-Catalyzed reaction of **1d** and alkynoates **2**




| Entry | $R^1$ | $R^2$ | Time/h | Isolated yield/%[a] |
|---|---|---|---|---|
| 1 | H | Et | 18 | 59 |
| 2 | Me | Et | 20 | 97 |
| 3[b] | $n$-$C_5H_{11}$ | Me | 77 | 96 |

[a]Yield based on **1d**. [b]GC yield.

are the best choice of the arenes.

Furthermore, we examined the reaction of **1d** with some alkynoates **2**. Table 3 shows terminal and alkyl-substituted alkynoates **2** also undergo the intermolecular hydroarylation with **1d** to give the corresponding coumarins **5**. Therefore, the Pd(II)-catalyzed hydroarylation can be applied to the synthesis of coumarins bearing any substituent among hydrogen, alkyl and aryl groups at the 4 position.

In conclusion, we have applied the Pd(II)-catalyzed hydroarylation to the coumarin synthesis and found a convenient and direct synthesis of coumarins from phenols and alkynoates. This reaction proceeds under mild conditions and without any additives, and is useful for synthesis of biologically active alkoxycoumarin derivatives. This simple and convenient procedure will be applied to the synthesis of functionalized coumarins in near future. The detail study on the mechanism is now in progress.

## References and Notes

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