



A novel multicomponent reaction to synthesize substituted furo[3,2-c]chromenes via a Pd-catalyzed cascade process

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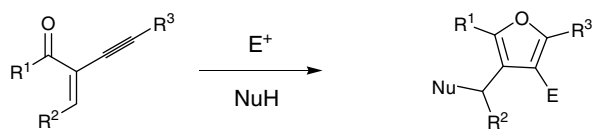
ABSTRACT

A novel one-pot three-component reaction for the synthesis of multisubstituted furo[3,2-c]chromenes using 3-(1-alkynyl)chromones, aryl iodides, and alcohols is developed via Pd-catalyzed cascade 1,4-addition and cyclization. This synthetic approach efficiently generates two C–O bonds and one C–C bond to construct diverse furo[3,2-c]chromenes structures.

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Domino and multicomponent reactions (MCRs) have attracted great interest among synthetic chemists as powerful tools for the rapid generation of molecular complexity and diversity.¹ In particular, the use of transition metal-catalyzed domino reactions is now recognized as an efficient synthetic strategy.² Much attention has been paid to the synthesis of highly substituted furans from 2-(1-alkynyl)-2-alken-1-ones, including 3-(1-alkynyl)chromones, by transition metal-catalyzed (using Au, Pt, or Cu catalysts)³ or electrophilic cyclization⁴ (Scheme 1).

Recently, our group has reported a one-pot synthesis of furocoumarins through cascade addition–cyclization–oxidation using 3-(1-alkynyl)chromone as the starting material and water as the nucleophile, in the presence of acid and without transition metal mediation.⁵ We report herein a novel three-component reaction



E = H(cat. AuCl₃); NuH = ROH, enol, ArH
 E = I; NuH = ROH, RCOOH, H₂O
 E = PhSe; NuH = ROH

Scheme 1. Synthesis of highly substituted furans from 2-(1-alkynyl)-2-alken-1-ones.

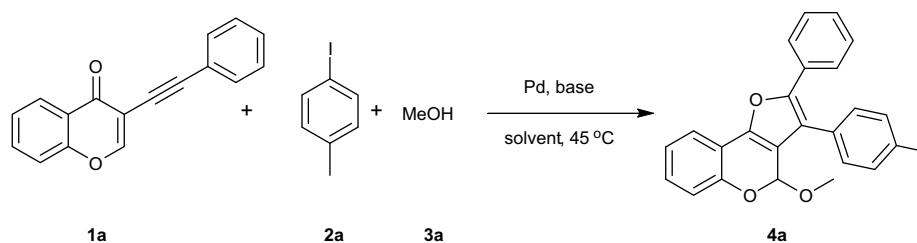
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for the synthesis of poly-substituted furo[3,2-c]chromenes via Pd-catalyzed cascade addition and cyclization.

Larock and co-workers had previously mentioned that Pd(OAc)₂ promoted the cyclization of 2-(1-alkynyl)-2-alken-1-ones in low yield only, because of the facile reduction of Pd(II) to Pd(0) in the presence of the alcohol.^{3a,4a} We suspected that introducing aryl halide by oxidative addition of Pd(0) could generate the Pd(II) species as a Lewis acid for 1,4-addition⁶ and the coordination reagent with a triple bond for cyclization.⁷ In this plausible approach, the carbonyl group of chromone could be activated by the palladium(II), which is formed in situ by oxidative addition of aryl halide with Pd(0). The activated **A** induces 1,4-addition by nucleophilic attack of the alcohol to generate intermediate **B**. Coordination of the triple bond of **B** with ArPdX induces cyclization to give intermediate **C**, which is followed by reductive elimination to furnish the product **D** and regenerate the Pd(0) species. In the meantime, 3-(1-alkynyl)-chromone **A** could be directly cyclized to generate product **E**. Recently, Xiao and Zhang also reported the similar mechanism to generate tetrasubstituted furans by a Pd-catalyzed three-component Michael addition/cyclization/cross-coupling reaction using 2-(1-alkynyl)-2-alken-1-ones, alcohols, and allyl chlorides.⁸

To test the feasibility of this possible mechanism, we started our investigation of the three-component reaction using 3-phenylethynyl chromone (**1a**), *p*-iodotoluene (**2a**), and methanol (**3a**) under different reaction conditions (Table 1). The reaction proceeded in DMF at 45 °C for 16 h, using DIPEA as the base and Pd(PPh₃)₄ as the catalyst, producing the desired compound **4a** in 30% yield and the direct cyclization product in 35% yield (entry 1). While Pd₂(dba)₃ (5 mol %) was employed as the catalyst instead of Pd(PPh₃)₄, the transformation was completed in 5 h in 37% yield

Table 1
Effect of catalyst, solvent, and base on MCR^a

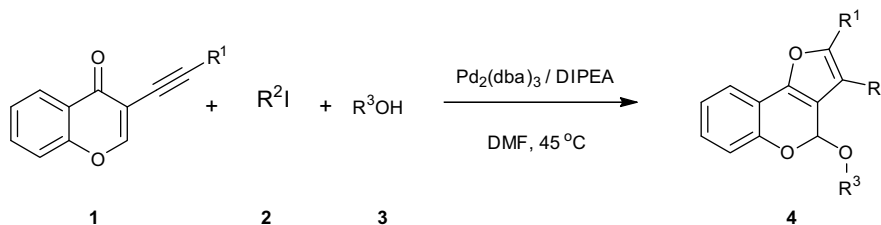


Entry	Solvent	Base	Catalyst	Time (h)	Yield ^b (%)
1	DMF	DIPEA	Pd(PPh ₃) ₄	16	30
2	DMF	DIPEA	Pd ₂ (dba) ₃	5	37
3	DMF	Cs ₂ CO ₃	Pd ₂ (dba) ₃	10	22
4	DMF	Ag ₂ CO ₃	Pd ₂ (dba) ₃	10	18
5	MeCN	DIPEA	Pd ₂ (dba) ₃	16	8
6	DCE	DIPEA	Pd ₂ (dba) ₃	8	23
7	Toluene	DIPEA	Pd ₂ (dba) ₃	6	35
8	DMF	DIPEA	Pd ₂ (dba) ₃ /PPh ₃	24	21
9	DMF	DIPEA	Pd ₂ (dba) ₃ / <i>t</i> -Bu ₃ P	6	10
10	DMF	DIPEA	Pd(OAc) ₂ /PPh ₃	20	Trace
11	DMF	DIPEA	PdCl ₂ (MeCN) ₂	5	32

^a All reactions were carried out with **1a** (0.20 mmol), **2a** (0.22 mmol), methanol **3a** (0.25 mL), base (0.8 mmol), and catalyst (0.02 mmol) in DMF (1 mL) at 45 °C for 5–24 h under a nitrogen atmosphere.

^b Isolated yields.

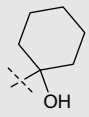

Table 2
Three-component one-pot reaction for the synthesis of substituted furo[3,2-*c*]chromenes^a



Entry	R ¹	R ²	R ³ OH	Yield ^b (%)
1	C ₆ H ₅		MeOH	4a (31)
2	C ₆ H ₅		MeOH	4b (66)
3	C ₆ H ₅		MeOH	4c (33)
4	C ₆ H ₅		MeOH	4d (25)
5	C ₆ H ₅		MeOH	4e (34)
6	C ₆ H ₅		MeOH	4f (62)
7	C ₆ H ₅		MeOH	4g (55)
8	4-MeO-C ₆ H ₄	2b	MeOH	4h (82)

(continued on next page)

Table 2 (continued)

Entry	R ¹	R ²	R ³ OH	Yield ^b (%)
9	2-F-C ₆ H ₄	2b	MeOH	4i (64)
10	4-CF ₃ C ₆ H ₄	2b	MeOH	4j (55)
11	(CH ₂) ₃ CN	2b	MeOH	4k (57)
12		2b	MeOH	4l (61)
13		2b	MeOH	4m (45)
14	C(CH ₃) ₃	2b	MeOH	4n (49)
15	(CH ₂) ₄ CH ₃	2b	MeOH	4o (55)
16	C ₆ H ₅	2b	<i>i</i> -PrOH	4p (45)
17	C ₆ H ₅	2b	<i>t</i> -BuOH	Complex
18	C ₆ H ₅	2b	BnOH	4q (48)
19	C ₆ H ₅	2b	<i>p</i> -NO ₂ C ₆ H ₄ OH	Complex

^a Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), and **3** (0.15 mL) in DMF (1.5 mL), using DIPEA (0.8 mmol) as the base and Pd₂(dba)₃ (10 mol %) as the catalyst, at 45 °C for 3–10 h.

^b Isolated yields.

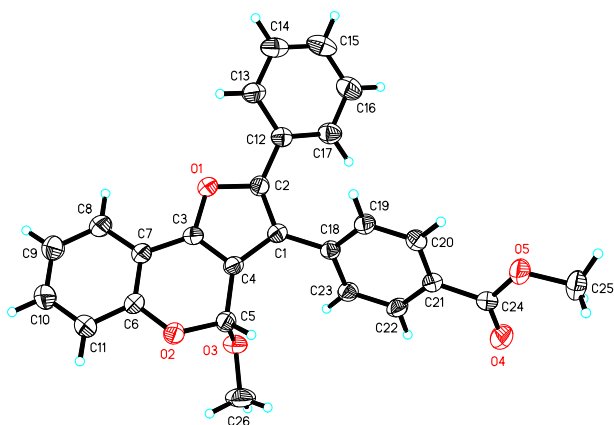
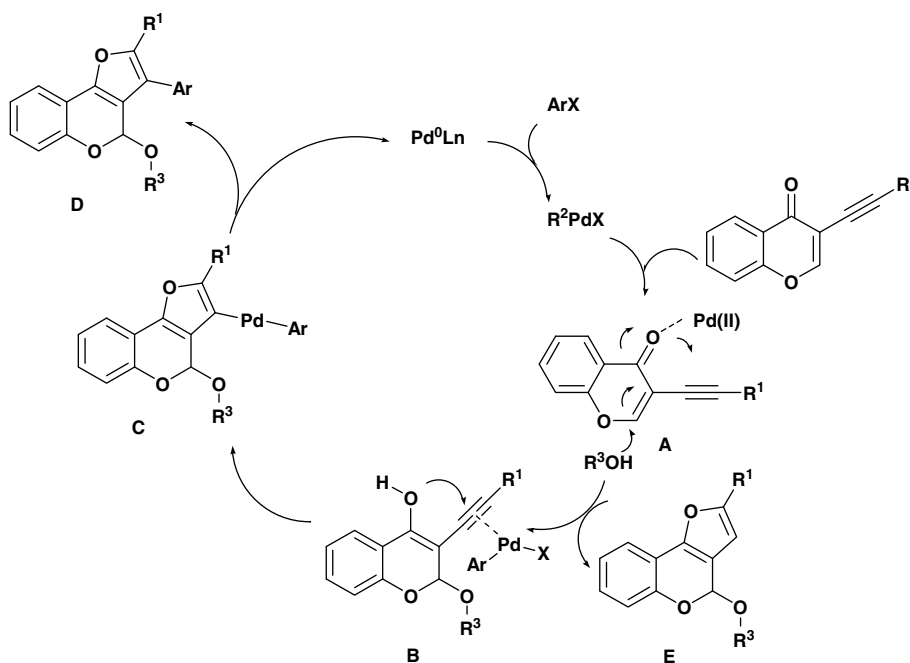


Figure 1. X-ray crystal structure of **4b**. Ellipsoid probability: 50%.

(entry 2). Among organic bases such as Et₃N and DBU and inorganic bases such as K₂CO₃, Cs₂CO₃, and Ag₂CO₃, only DIPEA gave the better result. After the different solvents were tested (entries 5–7), toluene exhibited the similar result as DMF. Surprisingly, Pd species with the phosphine ligands decreased the reaction efficiency (entries 8–10). The reported efficient catalyst PdCl₂(MeCN)₂⁸ did not improve the yield significantly. Furthermore, the additives such as Bu₄NCl or LiCl or increasing the amount of Pd₂(dba)₃ and *p*-iodotoluene did not effect the reaction.

Using the optimized conditions, we examined the scope of three-component one-pot cascade reactions using various substrates (Table 2). Among different aryl iodides, methyl 4-iodobenzoate **2b** gave the desired product **4b** in the best yield (66%, entry 2),⁹ which was obtained for X-ray crystal structure (Fig. 1).¹⁰ This indicates that aryl iodides bearing electron-withdrawing groups favor the cascade process due to the faster oxidative addition compared with other iodides. Comparing with entry 1, the meta-substi-



Scheme 2. Plausible mechanism for MCR.

tuted aryl iodide also gave the desired product **4e** in the reasonable yield. Iodothiophenes such as 2-iodothiophene and 3-iodothiophene afforded the corresponding products **4f** and **4g** in 62% and 55% yields, respectively (entries 6 and 7).

The arynyl moieties of chromones bearing different electronic groups exhibit different reactivity. When R¹ was the electron-donating group *p*-methoxyphenyl, the yield of **4h** improved dramatically (82%, entry 8). However, when R¹ was the electron-withdrawing group (*p*-trifluoromethyl) phenyl, yield of **4j** was decreased to 55% (entry 10). These results suggest that the fast oxidative addition of aryl iodide with the electron-withdrawing group by Pd(0) and the higher electronic density of the alkyne groups could stabilize the complex **B** (Scheme 2) to block the direct cyclized reaction in this process. Aliphatic ethynyls with hydroxy, CN, or sterically hindering parts also gave the desired products in moderate yields. The reaction of secondary alcohols *i*-PrOH and BnOH with **1a** and methyl 4-iodobenzoate **2b** under the standard condition proceeded smoothly, giving the corresponding products **4p** and **4q** in 45% and 48% yields, respectively (entries 16 and 18). However, *tert*-butyl alcohol and *p*-NO₂C₆H₄OH gave a complicated distribution of products each.

In conclusion, we have developed a novel three-component one-pot cascade reaction for the synthesis of multisubstituted furo[3,2-*c*]chromenes. This method rapidly increases the complexity and diversity of furo[3,2-*c*]chromene structures. Further studies of this methodology and biological evaluation of the compounds are under investigation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.025.

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- Synthesis of **4b**: To a stirred mixture of 3-(2-phenylethynyl)-4H-chromen-4-one (50 mg, 0.20 mmol), methyl 4-iodobenzoate (57.6 mg, 0.22 mmol), methanol (0.25 mL), and DIPEA (0.15 mL, 0.90 mmol) in dry DMF (1 mL) was added Pd₂(dba)₃ (18.6 mg, 0.02 mmol) under a N₂ balloon and the resulting solution was heated at 45 °C for 5 h. Then it was quenched with water (10 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography to afford 54.3 mg of the desired compound **4b** (66% isolated yield) as a white solid. Mp 137–139 °C. ¹H NMR (CDCl₃): δ = 3.54 (s, 3H), 3.95 (s, 3H), 6.05 (s, 1H), 7.05–7.15 (m, 2H), 7.25–7.35 (m, 4H), 7.50–7.60 (m, 4H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (CDCl₃): 52.2, 55.1, 97.3, 115.0, 115.6, 117.0, 119.6, 120.1, 122.0, 125.3, 126.4, 128.1, 128.3, 128.5, 128.9, 129.3, 130.1, 130.5, 134.7, 137.2, 143.3, 146.4, 149.8, 150.8, 166.8. HRMS calcd for C₂₆H₂₀O₅ 412.1311, found 412.1319.
- Crystallographic data: **4b**; CCDC 695854.