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Unexpected Domino Reaction via Pd-Catalyzed Sonogashira Coupling of Benzimidoyl Chlorides with 1,6-Enynes and Cyclization To Synthesize Quinoline Derivatives

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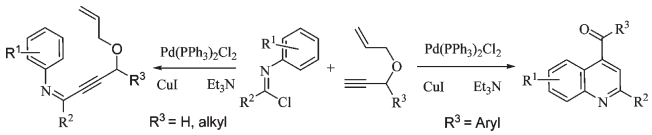

A domino reaction via palladium-catalyzed Sonogashira coupling of benzimidoyl chlorides with 1,6-enynes and then cyclization to form quinoline derivatives has been developed. The reaction conditions and the scope of the process are examined, and a plausible mechanism is proposed. The procedure is simple, rapid, and general, and the substrates are readily available.

Quinolines and their derivatives are well-known as important natural alkaloids which often endowed with many pharmacological properties.[1] They also occupied a central role in many medicinally relevant compounds.[2] The synthesis of quinolines and their derivatives has been extensively developed for more than 100 years since the discovery of quinoline by Gerhardt in 1842.[3] The Skraup,[4] the Doebner-Miller,[5] the Conrad-Limpach,[6] the Friedländer,[7] the Pfitzinger,[8] and other[9] reactions have been frequently employed in the synthesis of quinoline alkaloids. However, some of these methods usually suffered from relatively low yields, poor regioselectivity, and rather tedious reaction procedure. Therefore, the development of mild and simple approaches to quinoline derivatives is still desired because of their extreme significance. The cyclization of aryl-substituted alkynes via intramolecular hydroarylation has proven to be an efficient method for the construction of carbocycles and heterocycles.[10] Recently, considerable methods have been directed toward the synthesis of quinolines. For example, quinolines have been prepared via Rh,[11] Ni,[10b] Ru,[12] Au,[13] and other metals[14] catalyzed reactions. In our ongoing efforts to explore mild and efficient methodologies for the synthesis of heterocyclic compounds promoted by transition-metal catalysts,[15] we initially envisioned that reaction of benzimidoyl chlorides (**1a**) with (1-(allyloxy)prop-2-ynyl)-benzene (**2a**) via palladium-catalyzed Sonogashira coupling reaction could afford alkynyl amidine (**4a**). To our delight, more valuable functionalized quinoline (**3a**) was obtained rather than simple coupling product (Scheme 1). Herein, we wish to report this convenient synthetic approach to substituted quinolines by utilizing a Pd-catalyzed tandem process.

Our preliminary studies focused on the reaction of *N*-phenylbenzimidoyl chloride (**1a**) with (1-(allyloxy)prop-2-

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SCHEME 1

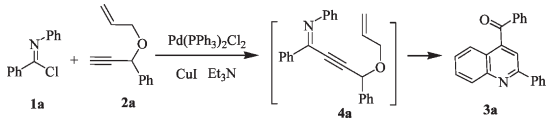
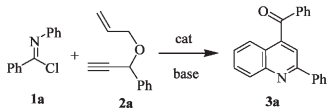


TABLE 1. Optimization of the Reaction Conditions Base on the Synthesis of 3a from 1a and 2a[a]

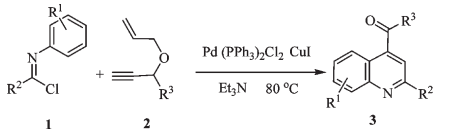


entry	catalyst	solvent	base	temp (°C)	time (h)	yield (%)
1	$PdCl_2$, CuI	Et_3N	Et_3N	80	7	52
2	$Pd_2(dba)_3$, CuI	Et_3N	Et_3N	80	7	63[b]
3	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N	80	7	85
4	$Pd(PPh_3)_4$, CuI	Et_3N	Et_3N	80	7	60
5	$Pd(PPh_3)_2Cl_2$, CuI	Et_2NH	Et_2NH	80	7	45
6	$Pd(PPh_3)_2Cl_2$, CuI	THF	Cs_2CO_3	80	7	49
7	$Pd(PPh_3)_2Cl_2$, CuI	THF	NaOAc	80	7	67
8	$Pd(PPh_3)_2Cl_2$, CuI	THF	Na_2CO_3	80	7	47
9	$Pd(PPh_3)_2Cl_2$, CuI	THF	K_3PO_4	80	7	70
10	$Pd(PPh_3)_2Cl_2$, CuI	THF	Et_3N	80	7	67
11	$Pd(PPh_3)_2Cl_2$, CuI	toluene	Et_3N	80	7	35
12	$Pd(PPh_3)_2Cl_2$, CuI	CH_3CN	Et_3N	80	7	52
13	$Pd(PPh_3)_2Cl_2$, CuI	DMF	Et_3N	80	7	29
14	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N	rt	10	52
15	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N	60	8	73
16	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N	100	5	58

[a]Unless otherwise specified, the reaction was carried out in Ar atmosphere using **1a** (0.30 mmol), **2a** (0.33 mmol), Pd catalysts (0.015 mmol), and CuI (0.0075 mmol). If the base is a solid, 0.9 mmol of the base and 3.0 mL of the solvent were added. If a liquid base is used, 1.0 mL of base and 2.0 mL of the solvents were added. DMF = dimethylformamide. dba = 1,5-diphenylpenta-1*E*,4*E*-dien-3-one. [b]0.0075 mmol of $Pd_2(dba)_3$ was used.

ynyl)benzene (**2a**) in the presence of 5 mol % of $PdCl_2$ and 2.5 mol % of CuI in Et_3N at 80 °C. The unexpected quinoline product **3a** was isolated in 52% yield after 7 h (Table 1, entry 1). This inspirited us to examine optimal reaction conditions for the coupling and cyclization of **1a** with **2a** in order to obtain more satisfied results. Subsequently, different palladium species such as $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, and $Pd(PPh_3)_4$ were also tested (Table1, entries 2−4). $Pd(PPh_3)_2Cl_2$ proved to be the more efficient catalyst in this reaction. Other common bases used in this reaction such as Et_2NH, Cs_2CO_3, NaOAc, Na_2CO_3, and K_3PO_4 were effective as well, although lower yields were obtained (Table 1, entries 5−9). This indicated that base played an important role in this process. The effect of the solvent was also investigated. Changing the solvent to THF, toluene, CH_3CN, and DMF failed to improve the yield of the product **3a** (Table 1, entries 10−13). Further investigation revealed that temperature was also a key factor in this domino reaction. When the reaction was run at room temperature, the product **3a** was obtained in 52% yield even though the reaction was prolonged to 10 h (Table 1, entry 14). When the temperature was increased to 60 °C, more satisfied result was obtained (Table 1, entry 15). Further increasing the temperature to 100 °C, a lower yield of 58% was observed (Table 1, entry 16). Thus, we chose the following reaction conditions as optimum for all subsequent cyclization: 0.3 mmol of **1a**, 0.33 mmol of **2a**, 0.015 mmol $Pd(PPh_3)_2Cl_2$, and 0.0075 mmol of CuI in 3.0 mL of Et_3N were stirred at 80 °C for 7 h.

TABLE 2. Pd-Catalyzed Synthesis of Substituted of Quinoline 3[a]



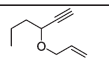
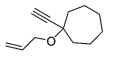
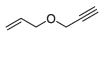
	substrate					
entry	**1**	R^1	R^2	**2**	R^3	yield (%)
1	**1a**	H	Ph	**2a**	Ph	85 (**3a**)
2	**1b**	4-OMe	Ph	**2a**	Ph	87 (**3b**)
3	**1c**	4-Me	Ph	**2a**	Ph	83 (**3c**)
4	**1d**	3-Me	Ph	**2a**	Ph	76 (**3d**) [b]
5	**1e**	2-Me	Ph	**2a**	Ph	76 (**3e**)
6	**1f**	4-Cl	Ph	**2a**	Ph	70 (**3f**)
7	**1g**	3-Cl	Ph	**2a**	Ph	68 (**3g**) [c]
8	**1h**	H	4-MeC_6H_4	**2a**	Ph	80 (**3h**)
9	**1i**	H	4-ClC_6H_4	**2a**	Ph	62 (**3i**)
10	**1a**	H	Ph	**2b**	5-benzo[*d*] [1,3]dioxole	90 (**3j**)
11	**1a**	H	Ph	**2c**	4-$OMeC_6H_4$	86 (**3k**)
12	**1a**	H	Ph	**2d**	2-$OMeC_6H_4$	70 (**3l**)
13	**1a**	H	Ph	**2e**	4-MeC_6H_4	83 (**3m**)
14	**1a**	H	Ph	**2f**	3-MeC_6H_4	63 (**3n**)
15	**1a**	H	Ph	**2g**	4-ClC_6H_4	mixture

[a]Unless indicated otherwise, all the reactions were carried out under Ar atmosphere using **1** (0.30 mmol), **2** (0.33 mmol), $Pd(PPh_3)Cl_2$ (0.015 mmol), CuI 0.0075 mmol in 3.0 mL of anhydrous Et_3N at 80 °C for 7 h. [b]Only one product (5-methyl-2-phenylquinolin-4-yl)-(phenyl)methanone was isolated. [c]Only one product (5-chloro-2-phenylquinolin-4-yl)(phenyl)methanone was isolated.

With the optimized conditions in hand, the scope of this Pd-catalyzed domino reaction was further investigated, and the results are summarized in Table 2. As depicted in Table 2, for all the tested substrates, good results have also been obtained. First of all, using (1-(allyloxy)prop-2-ynyl)benzene (**2a**), we examined the effect of various substituents on the *N*-aryl moiety. In contrast, introducing an electron-withdrawing −Cl group on the N-aromatic ring apparently lowered the yield, no matter substituents appeared in *para* or *meta* positions (Table 2, entries 6 and 7). It is noteworthy that when the imidoyl chloride **1d** and **1g** bearing *meta* substituents on the *N*-aryl fragment, were used as the starting substrates, only a unique product was isolated in each case in moderate yield, which were confirmed as (5-methyl-2-phenylquinolin-4-yl)(phenyl)methanone (**3d**) and (5-chloro-2-phenylquinolin-4-yl)(phenyl)methanone (**3g**), respectively (Table 2, entries 4 and 7). The presence of substituents at the *ortho* position of the *N*-aryl fragment did not hinder the reaction. Thus, quinoline **3e** could be synthesized in a moderate (76%) yield by the coupling and cyclization of imidoyl chloride **1e** with 1,6-enyne **2a** (Table 2, entry 5). The effect of R^2 substitution on the C=N double bond has also been examined. An evident electronic effect was observed. Substrates with an electron-donating R^2 group showed better results than those with an electron-withdrawing R^2 group (**1h** vs **1i**) (Table 2, entries 8 and 9).

We continued to elucidate the scope of the reaction by examining the effect of various R^3 substituents. When the phenyl is replaced with benzo[*d*][1,3]dioxole at the R^3 position, the reaction proceeds smoothly to give the corresponding products in excellent yield (Table 2, entry 10). When there is only one electron-donating substituent attached to the phenyl ring at the *para* position, the cyclization affords the corresponding quinoline derivatives in similar yields

TABLE 3. Pd-Catalyzed Coupling of 1a with Other 1,6-Enynes[a]

entry	1	2	product		yield (%)
1	**1a**	**2h**		**4b**	88
2	**1a**	**2i**		**4c**	75
3	**1a**	**2j**		**4d**	80

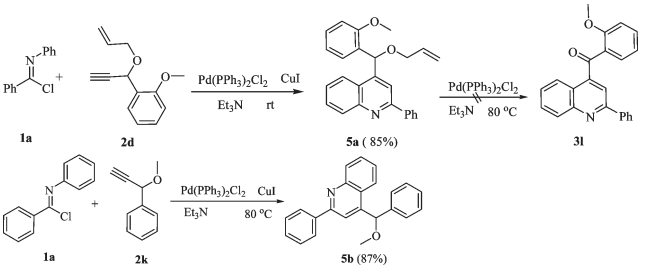
[a]All of the reactions were carried out in Ar atmosphere using **1** (0.30 mmol), **2** (0.33 mmol), $Pd(PPh_3)Cl_2$ (0.015 mmol), and CuI (0.0075 mmol) in 3.0 mL of anhydrous Et_3N at 80 °C for 7 h. Flash chromatography was carried out on Al_2O_3.

(Table 2, entries 11 and 13). However, the presence of substituents at both the *meta* and *ortho* positions of the phenyl ring clearly hampered the reaction (Table 2, entries 12 and 14). Further, when R^3 was phenyl with an electron-withdrawing group, a rather intractable complex reaction mixture was detected (Table 2, entry 15). The structures of all these products (**3**) were confirmed with the help of spectral and analytical data, and the structure of **3c** was further established by X-ray diffraction analysis (see the Supporting Information).

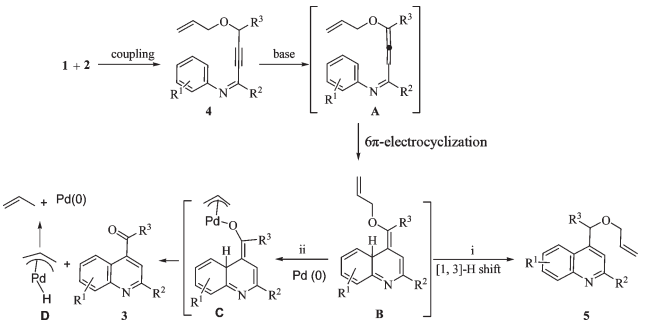
Furthermore, to expand the scope of this reaction, we also introduced hydrogen atom or alkyl group at the R^3 position (**2h**−**j**); no expected quinoline product was formed under the optimized conditions, and only the Sonogashira coupling product was isolated (Table 3, entries 1−3).

To have a more insight into the reaction, we also performed the following reactions as shown in Scheme 2. The reaction of **1a** with **2c** at room temperature gave **5a** in 85% yield. When **5a** was treated with 5 mol % of $Pd(PPh_3)Cl_2$ and 2.5 mol % of CuI in 3.0 mL of Et_3N at 80 °C, no desired product **3l** was observed. When the reaction temperature was further increased to 100 °C, the compound **5a** could be still recovered. We reasoned that the allyl in product **5a** is not a good leaving group in palladium-catalyzed allylations; thus, **5a** could not be transformed into **3l**. On the other hand, when **1a** and **2k** were also treated under the optimized conditions, no **3a** was observed, and only **5b** was isolated in 87% yield. When 1-phenylprop-2-yn-1-ol was used as substrate, neither quinoline nor Sonogashira coupling product was isolated, and the reaction led to a mixture. This revealed that allyl and the aryl as R^3 substituents on alkynes **2** played a vital role and are indispensable for the present method. Hence, based on the above results, we propose the following plausible mechanism for this reaction (Scheme 3): (i) benzimidoyl chlorides (**1**) and 1,6-enynes (**2**) react via Sonogashira coupling to afford intermediate alkynyl imine **4**;[16] (ii) the intermediate **4** undergoes a base-assisted propargyl−allenyl isomerization to form allene intermediate **A**;[17] (iii) that reaction is followed

SCHEME 2



SCHEME 3. Plausible Mechanism for the Formation of Quinolines



by a 6π-electrocyclization[18] to form quinoline intermediate **B**; (iv) subsequently, activation of the allyl moiety of quinoline **B** by Pd species generates intermediate **C**; (v) and removal of an allyl palladium complex **D** from **C** form the final product **3** and the complex **D** lost a molecule of propylene and regenerate the Pd(0) catalyst.[19] However, at lower temperature, we observed that the intermediate **B** underwent a [1, 3]-H shift to form the product **5**, which was in good agreement with the previous result.[10c] We assumed that at low temperature Pd species did not effectively activate allyl moiety of quinoline **B**. Because the allyl palladium intermediate was an excellent leaving group at moderate temperature, enol activated by Pd species lost an allyl group from the proposed intermediate **B** and consequently converted into the ketones **3**.

In summary, we have described a mild and efficient approach for the synthesis of substituted quinoline via Pd-catalyzed reaction of benzimidoyl chlorides with 1,6-enynes. This Pd-catalyzed reaction is simple, and the reaction proceeds smoothly in moderate to good yields. Further application of the methodology to synthesize some natural alkaloids and pharmaceutical compounds is in progress in our laboratory.

Experimental Section

General Proceduce for the preparation of Quinolines. An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with CuI (1.4 mg, 0.0075 mmol), $Pd(PPh_3)_2Cl_2$ (10.5 mg, 0.015 mmol), and **1** (0.30 mmol). The Schlenk tube was sealed and then evacuated and backfilled with argon (three cycles).

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A solution of **2** (0.33 mmol) in 3.0 mL of anhydrous Et_3N was subsequently added to the reaction system. The reaction was stirred at 80 °C for 7 h. After the reaction was completed (monitored by TCL), the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 5 mL), and the organic layers were combined, washed with saturated NaCl solution (2 × 5 mL), and dried over anhydrous Na_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluting with hexanes/EtOAc (15:1) to afford pure **3**.

Phenyl(2-phenylquinolin-4-yl)methanone (3a). Yield: 79 mg (85%). Yellowish solid: mp 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46−7.53 (m, 6 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.74−7.78 (m, 1 H), 7.84−7.91 (m, 4 H), 8.15−8.17 (m, 2 H), 8.26 (d, J = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 117.5, 123.9, 125.1, 127.2, 127.5, 128.8, 128.9, 129.7, 130.2, 130.2, 130.3, 134.2, 136.6, 138.9, 145.2, 148.7, 156.4, 196.3. IR (KBr): 695, 737, 767, 1070, 1252, 1347, 1449, 1592, 1668, 2924 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{16}NO^+$ (MH^+) 310.1226, found 310.1222.

(6-Methoxy-2-phenylquinolin-4-yl)(phenyl)methanone (3b). Yield: 89 mg (87%). Yellowish solid: mp 140−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3 H), 7.22 (d, J = 2.8 Hz, 1 H), 7.41−7.45 (m, 2 H), 7.48−7.52 (m, 4 H), 7.65 (t, J = 7.6 Hz, 1 H), 7.84 (s, 1 H), 7.92 (d, J = 7.2 Hz, 2 H), 8.11−8.14 (m, 2 H), 8.16 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.5, 102.8, 118.3, 123.1, 125.0, 127.2, 128.8, 128.9, 129.3, 130.4, 131.7, 134.0, 136.9, 139.0, 143.1, 145.2, 153.9, 158.5, 196.6. IR (KBr): 740, 1264, 1455, 2925 cm^{-1}. HRMS (ESI): calcd for $C_{23}H_{18}NO_2^+$ (MH^+) 340.1332, found 340.1328.

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Supporting Information Available: Experimental procedure, characterization details, and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.