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Palladium(II)-Catalyzed Cyclization Reaction of 2-(Alk-2′-ynyloxy)benzonitriles or 2-(Alk-2′-ynylamino)benzonitriles: A Facile Way to 2*H*-Chromene and 1,2-Dihydroquinoline Derivatives

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Abstract: An efficient synthesis of 2*H*-chromenes and 1,2-dihydroquinolines from palladium(II)-catalyzed tandem reactions of 2-(alk-2′-ynyloxy)benzonitriles or 2-(alk-2′-ynylamino)benzonitriles was developed. This tandem reaction involves an intermolecular *trans*-acetoxypalladation of an alkyne followed by an addition to the nitrile group to quench the carbon-palladium bond and complete the catalytic cycle without the necessity of a redox system.

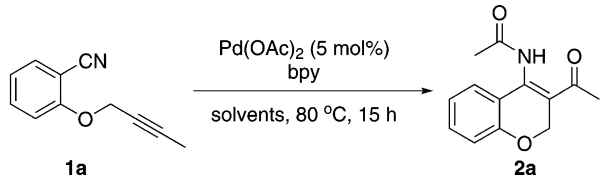
Keywords: cyclization; nitriles; oxypalladation; palladium; protonolysis

In recent years, the addition of carbon-transition metal bonds to carbon-heteroatom multiple bonds has become a new strategy in carbon-carbon bond formation.[1] Compared to the reactions using Grignard reagents and organolithium reagents, these reactions are generally catalytic, more tolerant for the functional groups, more atom economic and easier to handle. As to the carbon-heteroatom multiple bonds, the nitrile group is generally inert in organometallic reactions, and compounds such as CH_3CN or PhCN are usually used as solvents or ligands in many catalytic reactions. In the literature, rhodium and nickel complexes have already been exploited to catalyze addition reactions to the nitrile group, and many useful products can be synthesized by this strategy.[2,3]

Palladium-catalyzed nucleophilic addition reactions to polar carbon-heteroatom multiple bonds are an important development of the traditional palladium chemistry,[4] and nitrile groups have also been studied. Yang and Larock reported the Pd(0)-catalyzed intramolecular addition reactions of nitriles to form the carbocycles,[5a–d] and Vicente studied the insertion of a nitrile into the carbon-palladium bond.[5e] There are also a few examples of Pd(II)-catalyzed intermolecular additions to nitriles for the synthesis of aryl ketones and aryl ketimines.[6] Recently, our group explored some palladium(II)-catalyzed tandem reactions initiated by nucleopalladation of alkynes and quenching of the carbon-palladium bond by its addition to the carbon-heteroatom multiple bond followed by protonolysis.[7] In these reactions, palladium(II) complexes were used as catalysts and no redox system was required. As part of ongoing efforts in developing nucleophilic addition reactions of carbon-palladium bonds to carbon-heteroatom multiple bonds, we set out to explore the cyclization reactions of 2-(alk-2′-ynyloxy)benzonitriles or 2-(alk-2′-ynylamino)benzonitriles initiated by acetoxypalladation. If it works, some 2*H*-chromene and 1,2-dihydroquinoline derivatives will be obtained conveniently, and these kinds of substructures frequently exist in natural products and pharmaceuticals.[8]

In the initial investigation, 2-(but-2′-ynyloxy)benzonitrile (**1a**) was chosen as a substrate to test the reaction conditions under the catalysis of $Pd(OAc)_2$/bpy and the results are shown in Table 1. It was found that the cyclization of **1a** proceeded smoothly in moderate yield to produce 2*H*-chromene **2a** at 80 °C using dioxane/acetic acid as solvent, and the best amount of 2,2′-bipyridine was 10 mol% (Table 1, entries 1–3). No desired product was detected in the absence of $Pd(OAc)_2$ as the catalyst or 2,2′-bipyridine as the ligand (Table 1, entries 4 and 5). Other ligands such as substituted bipyridines, pyridine and dppp were also tested, but none of them could improve the yield (see the Supporting Information). The yield of **2a** decreased when raising up or lowering down the reaction temperature (Table 1, entries 6 and 7). It was worth noting that the yield was decreased significantly in the presence of 4 Å molecular sieve (Table 1, entry 8), indicating that water was crucial for the reaction. When some amount of water was added to the

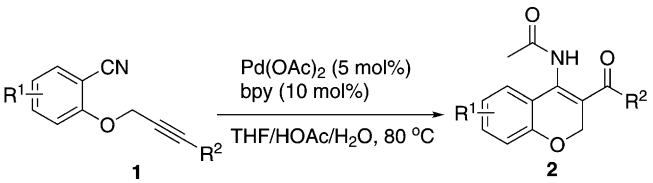
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvents	bpy [mol%]	Yield [%][b]
1	dioxane/HOAc (2/0.5)	6	50
2	dioxane/HOAc (2/0.5)	10	55
3	dioxane/HOAc (2/0.5)	20	41
4	dioxane/HOAc (2/0.5)	0	0
5[c]	dioxane/HOAc (2/0.5)	10	0
6[d]	dioxane/HOAc (2/0.5)	10	43
7[e]	dioxane/HOAc (2/0.5)	10	31
8[f]	dioxane/HOAc (2/0.5)	10	38
9	dioxane/HOAc/H_2O (2/0.5/0.1)	10	61
10	dioxane/HOAc/H_2O (2/0.5/0.05)	10	50
11	dioxane/HOAc/H_2O (2/0.5/0.25)	10	60
12	HOAc/H_2O (2/0.5)	10	13
13	THF/HOAc/H_2O (2/0.5/0.1)	10	64
14	toluene/HOAc/H_2O (2/0.5/0.1)	10	trace
15	DCE/HOAc/H_2O (2/0.5/0.1)	10	62
16	MeCN/HOAc/H_2O (2/0.5/0.1)	10	34

[a] *Reaction conditions*: **1a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%) and bpy (10 mol%) were dissolved in solvents as shown in the Table, then the mixture was stirred for 15 h at 80 °C.
[b] Isolated yield.
[c] Reaction was carried out in the absence of $Pd(OAc)_2$.
[d] The reaction was conducted at 60 °C.
[e] The reaction was conducted at 100 °C.
[f] 4 Å MS was added.

Table 2. Substrate scope for the cyclization of 2-(alk-2′-ynyloxy)benzonitriles.[a]



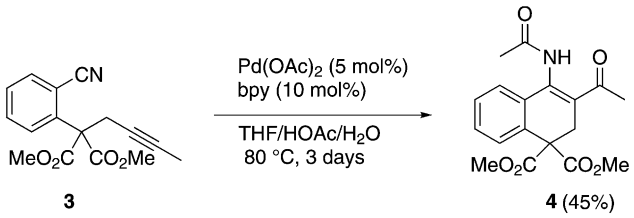
Entry	R^1	R^2	Yield [%][b]
1	H	Me (**1a**)	64 (**2a**)
2	4-OMe	Me (**1b**)	74 (**2b**)
3	3-OMe	Me (**1c**)	70 (**2c**)
4	5-Me	Me (**1d**)	54 (**2d**)
5	5-*t*-Bu	Me (**1e**)	58 (**2e**)
6	4-NEt_2	Me (**1f**)	54 (**2f**)
7	5-F	Me (**1g**)	62 (**2g**)
8	5-Cl	Me (**1h**)	57 (**2h**)
9	5-Br	Me (**1i**)	47 (**2i**)
10	4-NO_2	Me (**1j**)	23 (**2j**)
11	H	H (**1k**)	0
12	H	*n*-Pr (**1l**)	58 (**2l**)
13[c]	H	Ph (**1m**)	30 (**2m**)
14	4,5-di-Me	Me (**1n**)	61 (**2n**)
15	4,5-methylenedioxy	Me (**1o**)	72 (**2o**)
16	(**1p**)[d]		76 (**2p**)

[a] *Reaction conditions*: **1** (0.3 mmol), $Pd(OAc)_2$ (5 mol%) and bpy (10 mol%) were dissolved in THF (2 mL), HOAc (0.5 mL) and H_2O (0.1 mL), then the mixture was stirred at 80 °C for 15 h.
[b] Isolated yield.
[c] The reaction time was 3 days.
[d] **1p** = β-(but-2-ynyloxy)-α-naphthonitrile.

system, the yield did improve (Table 1, entry 9).[9] A solvent screening showed that THF was most effective, and other solvents such as MeCN, DCE and toluene were ineffective or gave a lower yield of **2a** (Table 1, entries 13–16). Then many kinds of additives such as LiOAc and acetic anhydride were tried to improve the reaction further, but the yield of **2a** was decreased dramatically. Many Brønsted acids and Lewis acids were also screened to activate the nitrile group (see the Supporting Information), but none of them gave a better result. Finally, the following conditions were chosen as being optimal for the reaction: **1a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), bpy (10 mol%) were dissolved in THF (2 mL), HOAc (0.5 mL), and H_2O (0.1 mL), then the mixture was stirred at 80 °C for 15 h.

Under the optimized conditions, a series of substituted 2-(alk-2′-ynyloxy)benzonitriles was tested as shown in Table 2. Substrates with electron-donating groups such as methoxy or methyl on the benzene ring provided good results (Table 2, entries 2–6, 14 and 15), while substrates with a strong electron-withdrawing group such as a nitro group gave a very poor yield (Table 2, entry 10). When the benzene ring was substituted with a halogen atom, the cyclization reactions can also proceed smoothly to get the corresponding products in moderate yields (Table 2, entries 7–9). Then β-(but-2-ynyloxy)-α-naphthonitrile (**1p**) was tested under the same reaction conditions, a good yield was obtained (76%, Table 2, entry 16), and the structure of product **2p** is the fundamental skeleton of a chromene antibiotic.[8a] There was little influence when the substituent R^2 was changed from Me to *n*-Pr, but for a phenyl-substituted one, the yield of the product was only 30% even on prolonging the reaction time to 3 days. Terminal alkynes gave no product in this reaction.

In the cyclization reaction of 2-(but-2′-ynyloxy)benzonitrile (**1a**), 2-hydroxybenzonitrile was found to be a side product, indicating the instability of the substrates under the reaction conditions. Thus, a relatively stable substrate **3** was used to test the reaction (Scheme 1). Unfortunately, the yield was far from satisfactory.



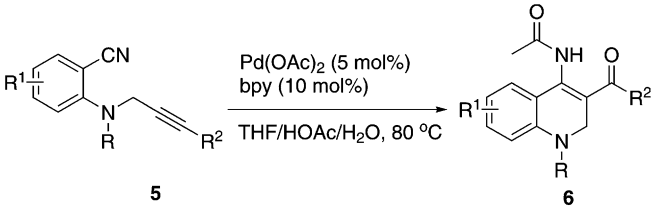
3 4 (45%)

Scheme 1. Cyclization of dimethyl 2-(but-2′-ynyl)-2-(*o*-cyanophenyl)malonate. *Reaction conditions*: **3** (0.3 mmol), $Pd(OAc)_2$ (5 mol%) and bpy (10 mol%) were dissolved in THF (2 mL), HOAc (0.5 mL) and H_2O (0.1 mL), then the mixture was stirred at 80 °C for 3 days.

Generally, a heteroatom in the substrate is supposed to coordinate with the palladium catalyst, which makes the reaction proceed smoothly. Then the substrate 2-(but-2′-ynylamino)benzonitrile (**5a**) which contains a nitrogen atom was tried. To our delight, under the same conditions as shown in Table 2, a 92% yield of product **6a** was obtained. Subsequent investigation of the substrate scope showed that a series of substituted 2-(alk-2′-ynylamino)benzonitriles could give the corresponding cyclization products in good to excellent yields (Table 3).

When the substituent on the nitrogen was a benzyl, the reaction rate was faster as compared with substrate **5a**, although the yield was slightly decreased (Table 3, entries 1 and 2). Chlorine or bromine atom on the benzene ring of the substrates had no influence on the yield of the reaction (Table 3, entries 5 and 6). It was obvious to see that the cyclization reactions of 2-(alkyl-2′-ynylamino)benzonitriles proceeded better as compared with their oxy-containing counterparts (compare Table 2 and Table 3).

Table 3. Substrate scope for the cyclization of 2-(alk-2′-ynylamino)benzonitriles.[a]



5 6

Entry	R	R^1	R^2	Time [h]	Yield [%][b]
1	Ts	H	Me (**5a**)	20	92 (**6a**)
2	Bn	H	Me (**5b**)	14	84 (**6b**)
3	Ts	H	*n*-Pr (**5c**)	48	86 (**6c**)
4	Ts	H	Ph (**5d**)	96	62 (**6d**)
5	Ts	4-Cl	Me (**5e**)	20	85 (**6e**)
6	Ts	4-Br	Me (**5f**)	16	74 (**6f**)

[a] *Reaction conditions*: **5** (0.2 mmol), $Pd(OAc)_2$ (5 mol%) and bpy (10 mol%) were dissolved in THF (2 mL), HOAc (0.5 mL) and H_2O (0.1 mL), then the mixture was stirred at 80 °C for the indicated time.

[b] Isolated yield.

A proposed mechanism is outlined in Scheme 2. First, the coordination of the palladium catalyst with the substrate generates complex **A**, then *trans*-acetoxypalladation of **A** occurs to form the vinyl palladium species **B**. The carbon-palladium bond in intermediate **B** adds to the nitrile group intramolecularly to produce the intermediate **C**. Protonolysis of **C** generates the imine **D** and Pd(II) catalyst. The attack of protonated imine **E** by water results in the formation of enamine **F**. Then, **F** undergoes an intermolecular acetyl migration with **E** to generate the final product **G** and regenerate another molecule of **F**. It is worth noting that the ligand bipyridine is crucial to the cyclization reaction, possibly for its ability in stabilizing the vinyl palladium intermediate that allows the catalytic reaction to proceed smoothly.[7a,10]

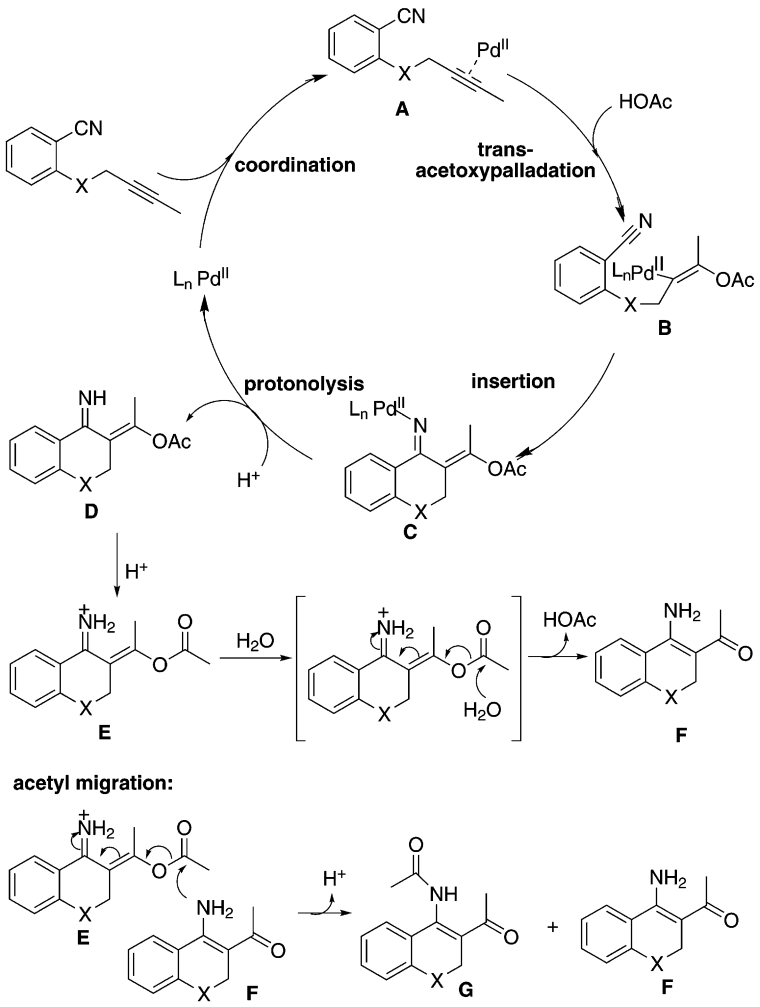
We have also tried this kind of cyclization reactions initiated by carbopalladation of alkynes using different kinds of arylboronic acids, but none of them worked. It seems that only vinyl C–Pd bonds generated by acetoxypalladation of alkynes can add to the nitrile groups successfully in our cyclization reactions. One possible explanation is the effect of the lone pair of electrons on the oxygen atom of the acetoxy group in intermediate **B** as shown in Scheme 2, which may make the C–Pd bond more nucleophilic to add to the nitrile group easily.

In conclusion, we have developed an efficient way for the synthesis of 2*H*-chromene and 1,2-dihydroquinoline derivatives. This is a Pd(II)-catalyzed intramolecular cyclization of 2-(alk-2′-ynyloxy)benzonitriles or 2-(alk-2′-ynylamino)benzonitriles initiated by *trans*-acetoxypalladation of the alkyne and quenching of the carbon-palladium bond by the addition to the nitrile group followed by protonolysis without the necessity of a redox system. This strategy may find further applications in the future for rapidly constructing other useful heterocyclic compounds.

Experimental Section

Representative Procedure for the Synthesis of 2*H*-Chromene 2a

A dried tube equipped with a condenser was charged with substrate **1a** (0.3 mmol), palladium acetate (3.4 mg, 5 mol%) and bipyridine (4.7 mg, 10 mol%), then 2 mL of THF, 0.5 mL of acetic acid and 0.1 mL of water were added sequentially, the resulting mixture was refluxed for 15 h. Then the solvents were evaporated under reduced pressure and the residue was purified by flash column chromatography to give the cyclization product **2a** as a white solid; yield: 64%; mp 190–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.94 (s, 1H), 7.34–7.27 (m, 2H), 6.99–6.92 (m, 2H), 4.88 (s, 2H), 2.30 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =



Scheme 2. A plausible mechanism for the palladium(II)-catalyzed tandem cyclization reaction.

197.9, 169.6, 156.5, 142.3, 132.4, 128.5, 121.2, 118.9, 116.8, 114.5, 65.2, 29.4, 24.8; IR (KBr): ν = 3271, 1671, 1652, 1600, 1500 cm^{-1}; MS (70 eV, EI): *m/z* (%) = 131 (M^+), 188, 146, 91, 77, 43 (100); anal. calcd. for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06; found: C 67.48, H 5.76, N 5.94.

Acknowledgements

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