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Efficient Synthesis of 5*H*-Cyclopenta[*c*]quinoline Derivatives via Palladium-Catalyzed Domino Reactions of *o*-Alkynylhalobenzene with Amine

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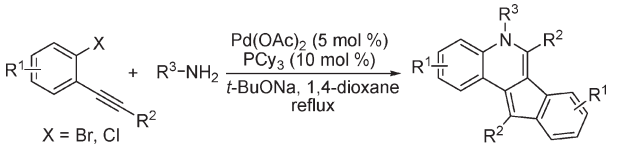
ABSTRACT



A novel and efficient route for the synthesis of 5*H*-cyclopenta[*c*]quinoline derivatives via a palladium-catalyzed domino reaction of *o*-alkynylhalobenzene with amine is described. The starting materials are easily available, and the reaction proceeds smoothly with high efficiency, which shows broad scope with good functional group tolerance.

Heterocyclic compounds hold a special place among pharmaceutically important natural products or synthetic materials. A variety of efficient and reliable methods have been developed for the synthesis of these compounds.[1] Among the strategies utilized, the domino reaction has been widely used to efficiently generate diverse heterocyclic compounds.[2] Additionally, this method is ideally suited for the construction of natural-product-like libraries with privileged scaffolds, which are prone to display different biological activities.[3] Recently, intense attention has been paid to cyclopenta[*c*]quinoline derivatives, due to their immense biological importance. For instance, compounds in Figure 1 with a 5*H*-cyclopenta[*c*]quinoline unit show moderate to high inhibitory activity against cancer cells.[4]

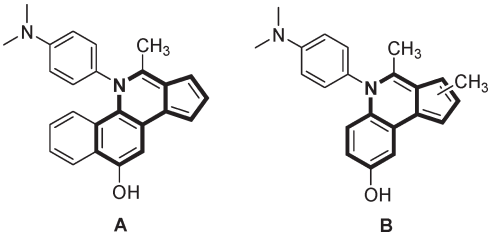


Figure 1. 5*H*-Cyclopenta[*c*]quinoline derivatives.

In addition, compound **A** exhibits high inhibitory activity against MCF7 and T-47D breast cancer cells. However, to the best of our knowledge, there are few efficient ways to access this skeleton.[4,5] As part of a continuing effort in our laboratory for accessing natural-product-like compounds,[6] we are interested in exploring efficient methods for the facile assembly of 5*H*-cyclopenta[*c*]quinoline derivatives.

(1) Recent reviews for the synthesis of heterocycles: (a) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (b) Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140. (d) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodrıguez-Garcıa, I. *Chem. Rev.* **2008**, *108*, 3174. (e) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

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(3) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266.

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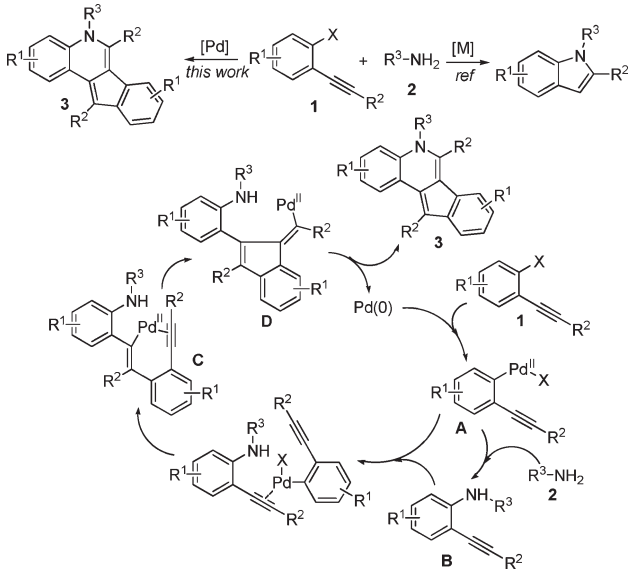
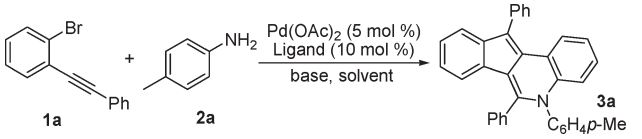
Amination of *o*-alkynylhalobenzene is a useful and widely used method for generation of N-heterocycles.[7] For example, 2-substituted indoles can be formed through palladium- or copper-catalyzed amination of *o*-alkynylhalobenzene and intramoleular cyclization.[7a,b] We hypothesized that the 5*H*-cyclopenta[*c*]quinoline **3** could be formed as well via a reaction of *o*-alkynylhalobenzene with amine.

Scheme 1. Proposed Synthetic Route to 5*H*-Cyclopenta[*c*]quinoline **3** via a Palladium-Catalyzed Reaction of *o*-Alkynylhalobenzene with Amine



The proposed synthetic route is described in Scheme 1. We reasoned that amination of *o*-alkynylhalobenzene would occur first to afford *o*-alkynylbenzeneamine **B**, which then reacted with intermediate **A** via intermolecular insertion of the triple bond, leading to the intermediate **C**. Intramolecular insertion of the triple bond and amination took place subsequently to furnish the expected compound **3** and Pd(0), which would re-enter the catalytic cycle. This route would allow a direct transformation of easily accessible *o*-alkynylhalobenzenes and amines to 5*H*-cyclopenta[*c*]quinoline derivatives. Additionally, diversity and complexity could be introduced easily. However, several challenges remained in this strategy: (1) the indole could be easily produced via Buchwald−Hartwig amination[8] and intramolecular cyclization,[9] as previously reported; (2) the control of insertion into the triple bond with high chemoselectivity and regioselectivity under such sterically hindered circumstances would be a major concern. Herein, we wish to report our recent efforts for the formation of 5*H*-cyclopenta[*c*]quinoline **3** via a palladium-catalyzed domino reaction of *o*-alkynylhalobenzene with amine.

Table 1. Initial Studies for the Palladium-Catalyzed Reaction of 1-Bromo-2-(phenylethynyl)benzene (**1a**) with *p*-Toluidine (**2a**)



entry	ligand	base	solvent	temp (°C)	yield (%)[a]
1		*t*-BuONa	1,4-dioxane	reflux	trace
2	PCy_3	*t*-BuONa	1,4-dioxane	80	11
3	PCy_3	K_2CO_3	1,4-dioxane	80	trace
4	PCy_3	K_2CO_3	1,4-dioxane	reflux	trace
5	PCy_3	*t*-BuOK	1,4-dioxane	reflux	trace
6	PCy_3	*t*-BuONa	1,4-dioxane	reflux	99
7	PCy_3	KOH	1,4-dioxane	reflux	95
8	PCy_3	K_3PO_4	1,4-dioxane	reflux	38
9	PCy_3	CH_3ONa	1,4-dioxane	reflux	61
10	PCy_3	*t*-BuONa	toluene	105	75
11	PCy_3	*t*-BuONa	DMF	105	trace
12	PPh_3	*t*-BuONa	DMSO	105	trace
13	DPPF	*t*-BuONa	1,4-dioxane	reflux	93
14	DPPP	*t*-BuONa	1,4-dioxane	reflux	80
15	PPh_3	*t*-BuONa	1,4-dioxane	reflux	90
16	XPhos	*t*-BuONa	1,4-dioxane	reflux	53

[a] Isolated yield based on *p*-toluidine (**2a**). XPhos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl.

To verify the feasibility of the hypothesis as shown in Scheme 1, 1-bromo-2-(phenylethynyl)benzene (**1a**) and *p*-toluidine (**2a**) were used as the model substrates (Table 1). The reaction was initially performed in the presence of 5 mol % of palladium acetate in 1,4-dioxane under reflux, using *t*-BuONa as the base (Table 1, entry 1). However, only a trace amount of product was detected. Gratifyingly, the expected product **3a** was isolated in 11% yield when the reaction occurred at 80 °C with tricyclohexylphosphine (PCy_3) added as the ligand (Table 1, entry 2). The structure

(6) For selected examples, see: (a) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (b) Qiu, G.; Ding, Q.; Ren, H.; Peng, Y.; Wu, J. *Org. Lett.* **2010**, *12*, 3975. (c) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (d) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 5238. (e) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950. (f) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746. (g) Yu, X.; Ye, S.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 2050. (h) Yu, X.; Chen, Z.; Yang, X.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 374. (i) Ye, S.; Ren, H.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 670. (j) Yu, X.; Ding, Q.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 743. (k) Yu, X.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 238.

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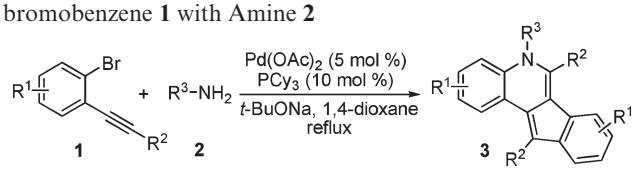
(8) For selected reviews, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Synlett* **1997**, 329. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (e) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(9) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

of compound **3a** was confirmed by X-ray diffraction analysis (see the Supporting Information). This result encouraged us to explore further. We found that the reactivity was diminished when the base was changed to *t*-BuOK or K_2CO_3 (Table 1, entries 3−5). To our delight, an almost quantitative yield was isolated when the reaction took place in 1,4-dioxane under reflux, in the presence of PCy_3 and *t*-BuONa (Table 1, entry 6). A similar yield was obtained when KOH was used as a replacement (95% yield, Table 1, entry 7). However, inferior results were displayed when other bases (such as K_3PO_4 and CH_3ONa) were utilized in the reaction (Table 1, entries 8 and 9). Different solvents and ligands were examined subsequently (Table 1, entries 10−16). However, no better results were generated.

Table 2. Generation of 5*H*-Cyclopenta[*c*]quinoline Derivatives via the Palladium-Catalyzed Domino Reaction of *o*-Alkynylbromobenzene **1** with Amine **2**



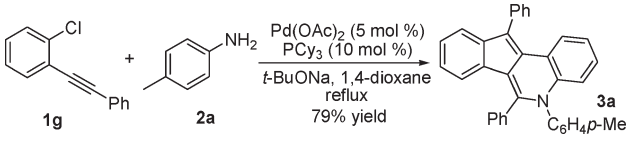
entry	R^1, R^2	R^3	product	yield (%)[a]
1	H, C_6H_5 (**1a**)	4-MeC_6H_4 (**2a**)	**3a**	99
2	H, C_6H_5 (**1a**)	4-$^iPrC_6H_4$ (**2b**)	**3b**	88
3	H, C_6H_5 (**1a**)	4-$OMeC_6H_4$ (**2c**)	**3c**	95
4	H, C_6H_5 (**1a**)	4-OHC_6H_4 (**2d**)	**3d**	98
5	H, C_6H_5 (**1a**)	4-ClC_6H_4 (**2e**)	**3e**	93
6	H, C_6H_5 (**1a**)	4-$CF_3C_6H_4$ (**2f**)	**3f**	77[b]
7	H, C_6H_5 (**1a**)	4-CNC_6H_4 (**2g**)	**3g**	87[b]
8	H, C_6H_5 (**1a**)	2-MeC_6H_4 (**2h**)	**3h**	95
9	H, C_6H_5 (**1a**)	2,4,6-$(Me)_3C_6H_2$ (**2i**)	**3i**	71
10	H, C_6H_5 (**1a**)	Cy (**2j**)	**3j**	85[c]
11	H, C_6H_5 (**1a**)	n-C_5H_{11} (**2k**)	**3k**	68[c]
12	H, n-C_4H_9 (**1b**)	4-MeC_6H_4 (**2a**)	**3l**	49[d]
13	H, 4-MeC_6H_4 (**1c**)	4-MeC_6H_4 (**2a**)	**3m**	61
14	H, 4-MeC_6H_4 (**1c**)	4-ClC_6H_4 (**2e**)	**3n**	92
15	H, 4-ClC_6H_4 (**1d**)	4-MeC_6H_4 (**2a**)	**3o**	91
16	H, 4-ClC_6H_4 (**1d**)	4-ClC_6H_4 (**2e**)	**3p**	83
17	4-Cl, C_6H_5 (**1e**)	4-MeC_6H_4 (**2a**)	**3q**	55
18	4-Cl, C_6H_5 (**1e**)	4-ClC_6H_4 (**2e**)	**3r**	36
19	4-Me, C_6H_5 (**1f**)	4-MeC_6H_4 (**2a**)	**3s**	38
20	4-Me, C_6H_5 (**1f**)	4-ClC_6H_4 (**2e**)	**3t**	54

[a] Reaction conditions: *o*-alkynylbromobenzene **1** (0.48 mmol), amine **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), *t*-BuONa (0.8 mmol), 1,4-dioxane (2.0 mL), reflux. [b] Cs_2CO_3 (0.8 mmol) was used as the base. [c] Bis(2-(diphenylphosphino)phenyl) ether (DPEphos, 5 mol %) and toluene (2.0 mL) were used as replacement. [d] The reaction was performed in the presence of $Pd(OAc)_2$ (10 mol %) and PCy_3 (20 mol %).

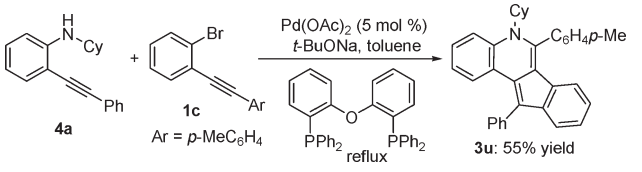
The scope of this palladium-catalyzed domino reaction of *o*-alkynylbromobenzene **1** with amine **2** was then examined under optimized conditions ($Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), *t*-BuONa, 1,4-dioxane, reflux). The results are summarized in Table 2. We noticed that all reactions worked well to generate the desired product in moderate to good yields. For instance, reactions of 1-bromo-2-(phenylethynyl)benzene (**1a**) and anilines **2b**−**d** with an electron-donating group attached to the aromatic ring gave rise to the corresponding 5*H*-cyclopenta[*c*]quinolines in excellent yields (Table 2, entries 2−4). It was noteworthy that the hydroxyl group in aniline **2d** could be tolerated in the reaction (Table 2, entry 4). 4-Chloroaniline was a good partner as well in the reaction of 1-bromo-2-(phenylethynyl)benzene (**1a**), which afforded the expected product **3e** in 93% yield (Table 2, entry 5). However, low yields were observed when 4-(trifluoromethyl)aniline or 4-cyanoaniline was employed in the above reaction. The results could be improved by using Cs_2CO_3 as the base, as a replacement for *t*-BuONa (Table 2, entries 6 and 7). Ortho-substituted anilines could be tolerated as well under the standard conditions. For example, 1-bromo-2-(phenylethynyl)benzene (**1a**) reacted with 2,4,6-trimethylaniline (**2i**), leading to the desired product **3i** in 71% yield (Table 2, entry 9). Reaction of substrate **1a** with aliphatic amine was explored in the meantime. It was found that good results could be obtained when the reaction occurred in toluene in the presence of bis(2-(diphenylphosphino)phenyl) ether (DPEphos) as the ligand (Table 2, entries 10 and 11). Next, reactions of various *o*-alkynylbromobenzenes with anilines were investigated. For the reaction of the *o*-alkynylbromobenzene **1b** with an alkyl group attached to the triple bond, an increased amount of catalyst had to be utilized in order to obtain a respectable yield (Table 2, entry 12). In addition, this reaction seemed to be sensitive for the *o*-alkynylbromobenzenes with substitution on the aromatic ring. Reactions of chloro- or methyl-substituted *o*-alkynylbromobenzene with anilines gave the corresponding products with poor to moderate yields (Table 2, entries 17−20).

We also explored the reaction of 1-chloro-2-(2-phenylethynyl)benzene (**1g**) with *p*-toluidine (**2a**) (Scheme 2). Under the standard conditions shown in Table 2, this reaction proceeded smoothly to generate the desired

Scheme 2. Palladium-Catalyzed Reaction of 1-Chloro-2-(phenylethynyl)benzene (**1a**) with *p*-Toluidine (**2a**)



Scheme 3. Palladium-Catalyzed Reaction of Substrate **1c** with *N*-Cyclohexyl-2-(2-phenylethynyl)benzenamine (**4a**)



5*H*-cyclopenta[*c*]quinoline **3a** in 79% yield. It seemed that aryl chloride was effective as well in this transformation. Moreover, to prove the proposed mechanism as illustrated in Scheme 1, *N*-cyclohexyl-2-(2-phenylethynyl)benzenamine (**4a**), which could be observed during the reaction of 1-bromo-2-(phenylethynyl)benzene **1a** with cyclohexylamine **2j** (Table 2, entry 10) was used to react with substrate **1c** (Scheme 3). As expected, the desirable product **3u** was obtained in 55% yield. This reaction also provided a protocol for the synthesis of diverse 5*H*-cyclopenta[*c*]quinoline compounds.

In conclusion, we have described a novel and efficient route for the synthesis of 5*H*-cyclopenta[*c*]quinoline derivatives via a palladium-catalyzed domino reaction of *o*-alkynylhalobenzene with amine. The starting materials are easily available, and the reaction shows broad scope with good functional group tolerance. Not only aryl bromide but also aryl chloride is effective in this transformation. Generation of diverse 5*H*-cyclopenta[*c*]quinoline compounds could be expected. Efforts toward its library construction and subsequent evaluation against various biological screens are currently under investigation.

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Supporting Information Available. Text, figures, and a CIF file giving experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, and X-ray crystal data of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.