ORGANIC LETTERS

2007
Vol. 9, No. 17
3413−3416

Palladium-Catalyzed Carbonylative Annulation Reaction of 2-(1-Alkynyl)benzenamines: Selective Synthesis of 3-(Halomethylene)indolin-2-ones

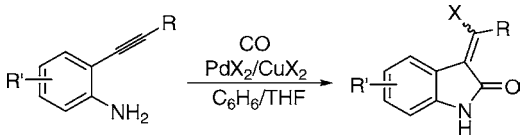
Shi Tang,[†,‡] Quan-Fu Yu,[‡] Peng Peng,[‡] Jin-Heng Li,*[,‡,¶] Ping Zhong,[¶] and Ri-Yuan Tang[¶]

College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China, Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research, Hunan Normal University, Changsha 410081, China, and Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100101, China

jhli@hunnu.edu.cn

Received June 20, 2007

ABSTRACT



A novel and selective palladium-catalyzed carbonylative annulation process for the synthesis of 3-(halomethylene)indolin-2-ones was demonstrated. In the presence of PdX_2 and CuX_2, 3-(halomethylene)indolin-2-ones were selectively obtained from the carbonylative annulations of 2-(1-alkynyl)benzenamines with CO in moderate to good yields.

The indolin-2-one system is presented in many naturally occurring and biologically active compounds and displays various pharmacological activities and potential utilizations in many major therapeutic areas, such as oncology, inflammation, CNS, immunology, and endocrinology.[1] The importance of indolin-2-ones has resulted in the development of several synthetic methods for their construction.[2−5] The traditional transformation utilizes intermolecular condensation of an oxindole with a diaryl ketone.[1,2] However, this methodology is limited because of its low selectivity. An alternative approach may involve a transition-metal-cata-

[†] Technical Institute of Physics and Chemistry.
[‡] Hunan Normal University.
[¶] Wenzhou University.

(1) (a) Mohammadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B. K.; Hubbard, S. R.; Schlessinger, J. *Science* **1997**, *276*, 955. (b) Smith, N. F.; Figg, W. D.; Sparreboom, A. *Drug Dev. Res.* **2004**, *62*, 233. (c) Hare, B. J.; Walters, W. P.; Caron, P. R.; Bemis, G. W. *J. Med. Chem.* **2004**, *47*, 4731. (d) Noble, M. E. M.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *203*, 1800. (e) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (f) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683 and references cited therein. (g) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099.

(2) (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *20*, 1133. (b) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem.* **1999**, *42*, 5120. (c) Fielding, M. R.; Grigg, R.; Urch, C. J. *Chem. Commun.* **2000**, 2239. (d) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. *J. Med. Chem.* **2003**, *46*, 1116. (e) Yang, T.-M.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 86.

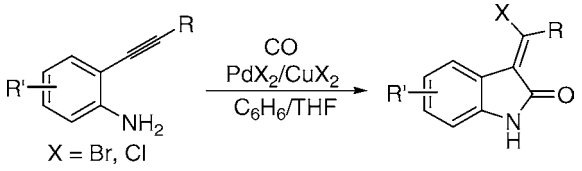
(3) (a) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972. (c) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (d) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (e) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (f) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153.

(4) For a paper on the selective synthesis of 3-alkylideneoxindoles using tandem In-mediated carbometalation and a Pd-catalyzed cross-coupling reaction, see: Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825.

10.1021/ol701450n CCC: $37.00
Published on Web 07/27/2007

lyzed, in particular palladium-catalyzed, domino reaction, which has been recently shown to be an efficient and selective tool for the construction of indolin-2-one frameworks.[3] Player and co-workers,[3a] for example, reported the preparation of (*E*)-3,3-(diarylmethylene)indolinones by the Heck carbocyclization/Suzuki coupling sequence of *N*-(2-iodophenyl)propiolamides using the $Pd(PPh_3)_4$ and CuTC (copper(I) thiophene-2-carboxylate) catalytic system. However, the selectivity of the protocol is still undesirable. Subsequently, Takemoto and co-workers[3b] have reported a selective protocol for the synthesis of 3-alkylideneoxindoles by $Pd(OAc)_2/PPh_3$-catalyzed Heck/Suzuki, Heck/Heck, and Heck/carbonylation/Suzuki domino reactions with *N*-(2-iodophenyl)propiolamides. Interestingly, Zhu and co-workers have demonstrated a $Pd(OAc)_2$-catalyzed domino carbopalladation/C−H activation/C−C bond-forming process for selectively synthesizing 3-(diarylmethylene)oxindoles.[3c,d] However, to the best of our knowledge, no report on the synthesis of 3-(disubstituted methylene)oxindoles via the Pd-catalyzed carbonylative annulations of 2-(1-alkynyl)benzenamines has been described. Here, we wish to report a novel and selective palladium-catalyzed carbonylative annulation route for the preparation of 3-(halo(substituted)methylene)-indolin-2-ones using 2-(1-alkynyl)benzenamines as the starting materials. Furthermore, the method affords products with a halomethylene (Cl or Br) at the 3-position, which provides an attractive and useful route to introduce new groups for the synthesis of new bioactive products (Scheme 1).

Scheme 1

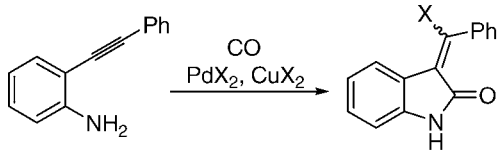


The reaction of 2-(2-phenylethynyl)benzenamine (**1a**) with carbon monoxide was first conducted to screen the optimal reaction conditions, and the results are summarized in Table 1. Initially, the solvent effect on the reaction was examined. After a series of trials, a mixture of benzene/THF (10:1) as the solvent provided the highest yield (entries 1−11). In the presence of $PdCl_2$ and $CuCl_2$, substrate **1a** was treated with CO in benzene/THF (10:1) to afford the corresponding 3-(chloro(phenyl)methylene)indolin-2-one (**2a**) in a 66% yield (*E*/*Z* = 1.7:1; entry 8). Some additives, including LiCl, benzoquinone, O_2, and Bu_4NCl, were also tested, and the results showed that they all disfavored the reaction to some extent (entries 12−15). Unfortunately, a rather low yield of 3-(bromo(phenyl)methylene)indolin-2-one (**3a**) was isolated from the reaction of substrate **1a** with CO, $PdBr_2$, and $CuBr_2$ (entry 16).

Prompted by these results, we decided to further explore the scope of this protocol.[6] As listed in Table 2, we initially

(5) For a paper on the use of $[RhCl(C_2H_4)_2]_2$/dppf system, see: Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799.

Table 1. Screening Reaction Conditions[a]



1a **2a:** X = Cl; **3a:** X = Br

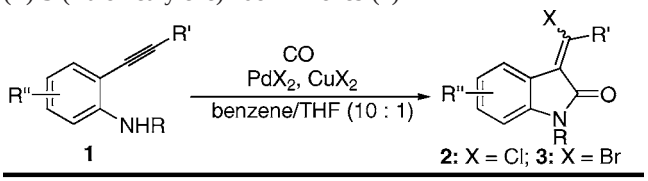
entry	additive	solvent	yield (%)[b]
1	–	DCE	9 (8:1)
2	–	benzene	<5 (ND)
3	–	MeCN	12 (ND)
4	–	THF	10 (ND)
5	–	benzene/DCE (20:1)	15 (ND)
6	–	benzene/MeCN (20:1)	31 (2:1)
7	–	benzene/THF (20:1)	39 (3:1)
8	–	***benzene/THF (10:1)***	***66 (1.7:1)***
9	–	benzene/THF (5:1)	23 (ND)
10	–	DCE/THF (20:1)	49 (2.5:1)
11	–	MeCN/THF (20:1)	21 (ND)
12	LiCl	benzene/THF (10:1)	31 (ND)
13	benzoquinone	benzene/THF (10:1)	11 (ND)
14[c]	O_2	benzene/THF (10:1)	65 (2:1)
15	Bu_4NCl	benzene/THF (10:1)	28 (ND)
16[d]	–	benzene/THF (10:1)	8 (**3a**) (ND)

[a] Reaction conditions: **1a** (0.5 mmol), $PdCl_2$ (5 mol %), $CuCl_2$ (3 equiv), CO (1 atm, bubbling), and additive (1 equiv) in solvent (5 mL) at room temperature for 12 h. [b] Isolated yield. Ratio of (*E*)-isomer vs (*Z*)-isomer determined by ^1H NMR spectroscopy is given in parenthesis. ND = Not determined. [c] O_2 (1 atm, bubbling). [d] $PdBr_2$ (5 mol %) and $CuBr_2$ (3 equiv) instead of $PdCl_2$ and $CuCl_2$. Other unidentified products were observed.

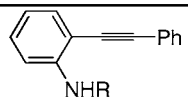
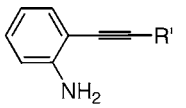
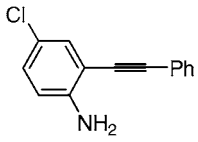
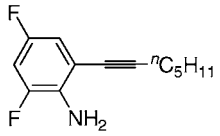
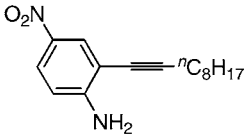
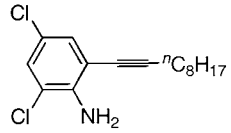
examined N-disubstituted substrates **1b**−**d**. Unfortunately, these substrates were not suitable for the Pd-catalyzed carbonylative annulation reactions with CO, $PdCl_2$, and $CuCl_2$ (entries 1−3). Subsequently, the reaction of 2-ethynylaniline (**1e**) was also tested, and only a trace amount of the target product **2e** was observed (entry 4). To our delight, this methodology allows for efficient annulations of the other N-monosubstituted 2-ethynylanilines **1f**−**o** with CO, PdX_2, and CuX_2 to synthesize the corresponding 3-(halomethylene)-indolin-2-ones in moderate to good yields (entries 5−15). In addition, many products were obtained stereospecifically. In the presence of $PdCl_2$, CuX_2, and CO, 2-ethynylanilines **1f**−**h**, bearing electron-deficient and electron-rich aryl groups at the terminal of alkyne, were reacted with CO, $PdCl_2$, and $CuCl_2$ smoothly to afford a mixture of (*E*)- and (*Z*)-isomers. 2-(2-*p*-Tolylethynyl)benzenamine (**1f**), for instance, affords a mixture of (*E*)- and (*Z*)-isomers (**2f**) in a 72% yield (*E*/*Z* = 2.7:1; entry 5). The configuration and structures of the products were determined according to the authoritative ^1H NMR spectroscopy data[3] and were unambiguously assigned by X-ray analysis.[7] Interestingly, substrates **1i**−**k** having alkyl groups at the terminal of alkyne were shown to undergo

(6) 2-(1-Alkynyl)benzenamines **1a**−**o** were readily prepared from the reactions of the corresponding 2-iodobenzenamines with terminal alkynes directly without simultaneous cyclization by the known procedures: (a) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, 749. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (c) Tang, S.; Li, J.-H.; Xie, Y.-X.; Wang, N.-X. *Synthesis* **2007**, 1535.

Table 2. Selective Synthesis of (*E*)-3-(Halomethylene)indolin-2-ones (2)[a]



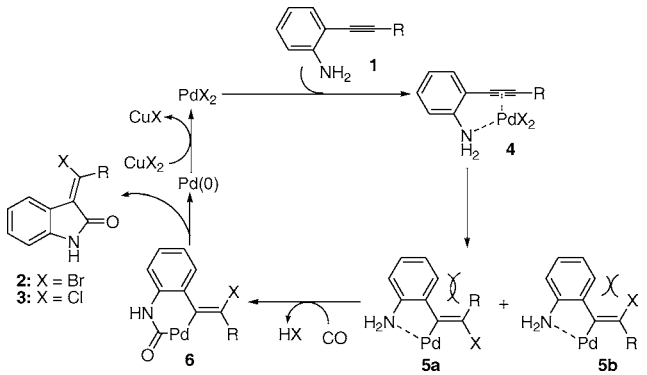
1 **2:** X = Cl; **3:** X = Br

entry	substrate	X	time (h)	*E*:Z ratio[b]	yield (%)[c]
1	 R = Me (**1b**)	Cl	48	ND	9 (**2b**)
2	R = Bn (**1c**)	Cl	48	ND	11 (**2c**)
3[d]	R = Ac (**1d**)	Cl	48	0	0 (**2d**)
4[e]	 R′ = H (**1e**)	Cl	24	ND	trace (**2e**)
5	R′ = *p*-MeC$_6$H$_4$ (**1f**)	Cl	24	2.7:1	72 (**2f**)
6	R′ = *p*-MeOC$_6$H$_4$ (**1g**)	Cl	24	4.9:1	32 (**2g**)
7	R′ = *p*-NO$_2$C$_6$H$_4$ (**1h**)	Cl	24	6.2:1	33 (**2h**)
8	R′ = *n*-C$_5$H$_{11}$ (**1i**)	Cl	7	>99:1	75 (**2i**)
9	R′ = *n*-C$_8$H$_{17}$ (**1j**)	Cl	5	>99:1	82 (**2j**)
10[f]	R′ = *n*-C$_8$H$_{17}$ (**1j**)	Br	4	>99:1	65 (**3j**)
11	R′ = *t*-Bu (**1k**)	Cl	15	>99:1	31 (**2k**)
12	 (**1l**)	Cl	30	>99:1	52 (**2l**)
13	 (**1m**)	Cl	4	>99:1	54 (**2m**)
14	 (**1n**)	Cl	15	>99:1	80 (**2n**)
15[g]	 (**1o**)	Cl	3	ND	trace (**2o**)

[a] Reaction conditions: **1** (0.5 mmol), $PdCl_2$ (5 mol %), CuX_2 (3 equiv), and CO (1 atm, bubbling) in benzene/THF (10:1, 5 mL) at room temperature. [b] The *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. ND = Not determined. [c] Isolated yield. [d] 1-(3-Chloro-2-phenyl-1*H*-indol-1-yl)ethanone was isolated in a 78% yield; see ref 10k. [e] Other unidentified products were observed. [f] $PdBr_2$ (5 mol %) instead $PdCl_2$. [g] 5,7-Dichloro-2-octyl-1*H*-indole (**4o**) was isolated in an 83% yield; see ref 10k.

the reaction selectively providing (*E*)-isomers alone (entries 8−11). For example, 2-(dec-1-ynyl)benzenamine (**1j**) underwent the reaction with CO stereoselectively to offer the corresponding (*E*)-3-(1-chlorononylidene)indolin-2-one (**2j**) alone in an 82% yield (entry 9). The *E*-configuration of the tetrasubstituted double bond was determined according to the authoritative ^{1}H NMR spectroscopy data.[8] Note that (*E*)-3-(1-bromononylidene)indolin-2-one (**3j**) can be obtained in a 65% yield using the $PdBr_2$/$CuBr_2$ system instead of the $PdCl_2$/$CuCl_2$ system (entries 10). Gratifyingly, the other 2-ethynylanilines **1l**−**n** bearing substitutes, such as chloro, fluoro, and nitro, on the aromatic ring were perfectly tolerated and gave the corresponding desired (*E*)-products exclusively in moderate yields (entries 12−14). However, the carbonylative annulation reaction of substrate **1o** was unsuccessful, and another product, 5,7-dichloro-2-octyl-1*H*-indole (**4o**), was isolated in an 83% yield (entry 15).[10k]

Scheme 2. A Working Mechanism



A working mechanism as outlined in Scheme 2 for the palladium-catalyzed selective carbonylative annulation reaction is proposed on the basis of the previously reported mechanisms.[9−11] First, the coordination of $PdCl_2$ with the triple bond and nitrogen affords intermediate **4**,[11] followed by *cis*- and *trans*-halopalladation to generate intermediates

(7) For X-ray analysis of (*Z*)-**1f**, see Figure S1 in Supporting Information. Interestingly, only a small crystal of (*Z*)-3-(chloro(*p*-tolyl)methylene)indolin-2-one (**2f**) was obtained from the product **1f** with a mixture of (*Z*)- and (*E*)-isomers, and the small crystal was further determined by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, COSY, and NOESY. Based on the results, the *E*- and *Z*-configurations of the tetrasubstituted double bond of the products **2a**, **2f**−**h**, and **2l** can be determined by chemical shift of hydrogen at the 4- and 7-positions of the products; also see refs 3a and 3b.

(8) The *E*-configuration of the tetrasubstituted double bond of the products **2i**, **2j**, **2m**−**o**, and **3j** can be determined by the allylic hydrogen chemical shift: (a) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1994**, *50*, 12697. (b) Beccalli, E. M.; Marchesini, A. *Tetrahedron* **1995**, *51*, 2353.

(9) For reviews on the halopalladation reaction, see: (a) Lu, X. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, pp 2267−2288. (b) Han, X. L.; Liu, G. X.; Lu, X. Y. *Chin. J. Org. Chem.* **2005**, *25*, 1182.

(10) For some representative papers on the halopalladation reaction using PdX_2/CuX_2 as a catalytic system, see: (a) Bäckvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 393. (b) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160. (c) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (d) Li, J.-H.; Jiang, H.-F.; Feng, A.-Q.; Jia, L.-Q. *J. Org. Chem.* **1999**, *64*, 5984. (e) Li, J.-H.; Jiang, H.-F.; Chen, M.-C. *J. Org. Chem.* **2001**, *66*, 3627. (f) Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2004**, *69*, 8125. (g) Li, J.-H.; Tang, S.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 477. (h) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429. (i) Ma, S.; Wu, B.; Jiang, X.; Zhao, S. *J. Org. Chem.* **2005**, *70*, 2568. (j) Ma, S.; Wu, B.; Jiang, X. *J. Org. Chem.* **2005**, *70*, 2588. (k) Tang, S.; Xie, Y.-X.; Li, J.-H.; Wang, N.-X. *Synthesis* **2007**, 1841.

5. The subsequent coordination and insertion of CO with intermediate **5** occurs to give intermediate **6**. Intermediate **6** undergoes the reductive elimination readily to form the desired products **2** and a Pd(0) species. The active Pd(II) species can be regenerated by the oxidation reaction of Pd(0) with CuX_2 to start a new catalytic cycle. The (*E*)-isomer obtained as the major product may be due to the presence of less steric hindrance (intermediate **5a** vs intermediate **5b**).

In summary, a novel and selective carbonylative annulation method for the synthesis of 3-(halo(substituted)methylene)-indolin-2-ones has been developed. In the presence of PdX_2 and CuX_2, a variety of 2-(1-alkynyl)anilines underwent the carbonylative annulation reaction with CO smoothly to afford the target products in moderate to good yields. Moreover, a halomethylene (Cl or Br) at the 3-position of these products provides an attractive and useful route to introduce new groups for the synthesis of new bioactive products. Efforts to study the mechanism and extend the application of the palladium-catalyzed transformations in organic synthesis are underway in our laboratory.

(11) (a) Yukawa, T.; Tsutsumi, S. *Inorg. Chem.* **1968**, *7*, 1458. (b) Dupont, J.; Basso, N. R.; Meneghetti, M. R. *Polyhedron* **1996**, *15*, 2299. (c) Dupont, J.; Basso, N. R.; Meneghetti, M. R.; Konrath, R. A. *Organometallics* **1997**, *16*, 2386.

Acknowledgment. We thank the Specialized Research Fund for the Doctoral Program of Higher Education (No. 20060542007), Hunan Provincial Natural Science Foundation of China (No. 05JJ1002), National Natural Science Foundation of China (No. 20572020), New Century Excellent Talents in University (No. NCET-06-0711), Fok Ying Tung Education Foundation (No. 101012), and the Key Project of Chinese Ministry of Education (No. 206102) for financial support.

Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **2**, **3j** and **4o**; typical procedure for the palladium-catalyzed annulation reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701450N