ORGANIC
LETTERS

2011
Vol. 13, No. 21
5858–5861

A New Insight into Palladium-Catalyzed Reaction of 2-Alkynylphenol with Carbon Monoxide

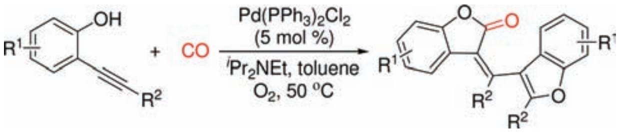
Yong Luo[†] and Jie Wu*[†,‡]

*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433,
China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute
of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road,
Shanghai 200032, China*

jie_wu@fudan.edu.cn

Received September 13, 2011

ABSTRACT



A novel and efficient pathway for the generation of 3-(benzofuran-3-ylmethylene)benzofuran-2(3*H*)-ones via a palladium-catalyzed carbonylative reaction of 2-alkynylphenol with carbon monoxide is described. The reaction proceeds through a double insertion of triple bonds during the reaction process. The products are obtained in good yields with high selectivity. A one-pot synthesis starting from 2-iodophenol and alkyne is presented as well.

Recently, we have disclosed a novel transformation for access to indeno[1,2-*c*]chromenes **A** via a Pd-catalyzed reaction of 2-alkynylhalobenzene with 2-alkynylphenol in the presence of PCy_3 (Scheme 1, eq 1).[1] In the reaction process, a double insertion of triple bonds was found crucial for the successful conversion.[2] Additionally, the effect of several side reactions such as Pd-catalyzed direct cyclization of 2-alkynylphenol and formation of 2,3-diarylbenzo[*b*]furan were minimized under the conditions.[3,4] Prompted by this result, we conceived that carbon monoxide might be involved in this transformation, which would afford benzo[*b*]oxepin-2(5*H*)-ones **B** (Scheme 1, eq 2) based on the mechanism we proposed previously.[1] Thus, the model reaction was explored by using 1-bromo-2-(2-phenylethynyl)benzene and 2-(2-phenylethynyl)phenol **1a** as the substrates in the presence of carbon monoxide (balloon, Scheme 1, eq 3). The reaction was initially catalyzed by 5 mol % of palladium acetate in the presence of $^iPr_2NEt$ and oxygen in toluene under reflux conditions. Interestingly, we did not observe the formation of **B**, and a small amount of product was isolated in 8% yield. After structural elucidation by X-ray diffraction analysis (see Supporting Information), the product was identified as 3-(benzofuran-3-ylmethylene)benzofuran-2(3*H*)-one **2a**. From this result, we noticed that 1-bromo-2-(2-phenylethynyl)benzene was not involved in the conversion, and **2a** was generated solely from the Pd-catalyzed reaction of 2-(2-phenylethynyl)phenol **1a** and carbon monoxide.

The Pd(II)-catalyzed/mediated cascade carbonylative annulation of 2-alkynylphenols has proven to be a highly efficient method for rapidly generating diverse

---

[†] Fudan University.

[‡] Chinese Academy of Sciences.

(1) Luo, Y.; Hong, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5298.

(2) (a) Luo, Y.; Pan, X.; Wu, J. *Org. Lett.* **2011**, *13*, 1150. (b) Pan, X.; Luo, Y.; Wu, J. *Chem. Commun.* **2011**, *47*, 8967. (c) Luo, Y.; Wu, J. *Chem. Commun.* **2011**, *47*, 11137.

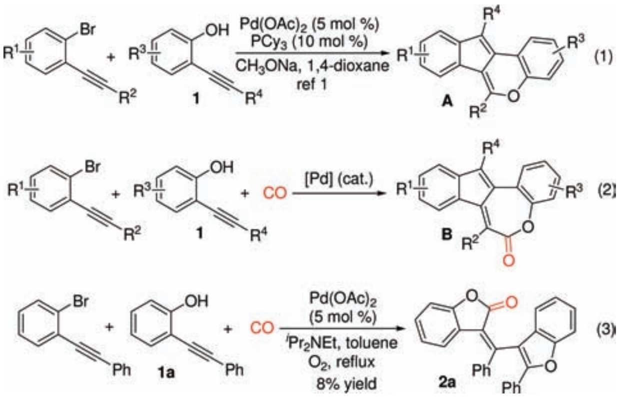
(3) For selected examples, see: (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, 1137. (b) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235. (c) Du, H.-A.; Zhang, X.-G.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 7844. (e) Liang, Y.; Tang, S.; Zhang, X.-D.; Mao, L.-Q.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2006**, *8*, 3017. (f) Martínez, C.; Álvarez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083. (g) Nakamura, M.; Ilies, L.; Otsubo, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 944.

(4) (a) Lütjens, H.; Scammells, P. J. *Tetrahedron Lett.* **1998**, *39*, 6581. (b) Lütjens, H.; Scammells, P. J. *Synett* **1999**, *7*, 1079. (c) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. (d) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607. (e) Liao, Y.; Smith, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2005**, *7*, 2707. (f) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387. (g) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365.

10.1021/ol202478u

benzo[*b*]furan-3-carbonyl compounds.[4] For instance, Yang et al.[4c−g] reported the synthesis of benzo[*b*]furan-3-carboxylic acids, esters, and ketones via a Pd(II)-catalyzed cascade carbonylative annulation of 2-alkynylphenols with carbon monoxide. In their protocol, the triple bond was activated by an acylpalladium species, which initiated an intramolecular cyclization to afford the corresponding benzo[*b*]furan compounds. From our result shown in Scheme 1, we conceived that a double insertion of triple bonds would occur in the reaction of 2-alkynylphenol and carbon monoxide since 2 equiv of 2-alkynylphenol were incorporated in the transformation.

Scheme 1. An Unexpected Result for the Palladium-Catalyzed Reaction of 2-Alkynylphenol **1a** with Carbon Monoxide



It is well-known that benzofuran is a very important heterocycle that is broadly found in natural[5] and biologically important molecules[6] and frequently used as a building block in materials science and in organic synthesis.[7] The benzofuran-2-one moiety can be found in many natural products as well. Compounds with this substructure usually display remarkable biological activities.[8] For instance, Calycin, extracted from the lichen *C. concolor*, shows significant antibacterial activity.[8a] A naturally occurring isoaurone (4′,6-dihydroxy-4-methoxyisoaurone) from *Trichosanthes kirilowii* seeds has been identified as an inhibitor of HIF-1 and NF-κB.[8b] Recently, compounds containing the 3-(furan-3-ylmethylene)furan-2(3*H*)-one skeleton[9] were shown to be an important class of photoswitches that complement diarylethenes and spiropyrans.[10] Upon wavelength-specific illumination, they undergo reversible color changes and ring-closing/opening reactions which are thus of great interest for a range of applications. Thus, generation of the related molecules in a novel and concise pathway would be of high interest.

With the above promising result in hand, we started to optimize conditions for the formation of 3-(benzofuran-3-ylmethylene)benzofuran-2(3*H*)-ones. The screening results are shown in Table 1. To our delight, the expected product **2a** was isolated in 54% yield when $PdCl_2(PPh_3)_2$ was used as a replacement (Table 1, entry 2). Only a trace amount of product was detected when the reaction occurred in the presence of K_2CO_3, Na_2CO_3, or KOAc (Table 1, entries 3−5). No reaction took place when ^{t}BuONa was employed as the base (Table 1, entry 6). A comparable yield of the desired product was obtained when DABCO was utilized (Table 1, entry 7). Neither $PdCl_2$ or $Pd(PPh_3)_4$ was successful in catalyzing the reaction of 2-(2-phenylethynyl)phenol **1a** with carbon monoxide (Table 1, entries 8 and 9). Adding extra ligands proved to be unhelpful for the outcome (Table 1, entries 10−15). Changing of the oxidant to benzoquinone (BQ) resulted in a lower yield (Table 1, entry 16). The solvent effect was studied as well. However, inferior results were obtained (Table 1, entries 17−20). In terms of temperature effects, the reaction was found to be more effective at 50 °C, which afforded the expected product **2a** in 62% yield

---

(5) For selected examples, see: (a) Máximo, P.; Lourenço, A.; Feio, S. S.; Roseiro, J. C. *J. Nat. Prod.* **2002**, *65*, 175. (b) Ohta, T.; Maruyama, T.; Nagahashi, M.; Miyamoto, Y.; Hosoi, S.; Kiuchi, F.; Yamazoe, Y.; Tsukamoto, S. *Tetrahedron* **2002**, *58*, 6631. (c) Song, K.-S.; Raskin, I. *J. Nat. Prod.* **2002**, *65*, 76. (d) Sritularak, B.; Likhitwitayawuid, K.; Conrad, J.; Vogler, B.; Reeb, S.; Klaiber, I.; Kraus, W. *J. Nat. Prod.* **2002**, *65*, 589. (e) Lin, Y.-L.; Chang, Y.-Y.; Kuo, Y.-H.; Shiao, M.-S. *J. Nat. Prod.* **2002**, *65*, 745. (f) Pacher, T.; Seger, C.; Engelmeier, D.; Vajrodaya, S.; Hofer, O.; Greger, H. *J. Nat. Prod.* **2002**, *65*, 820. (g) Muriithi, M. W.; Abraham, W.-R.; Addae-Kyereme, J.; Scowen, I.; Croft, S. L.; Gitu, P. M.; Kendrick, H.; Njagi, E. N. M.; Wright, C. W. *J. Nat. Prod.* **2002**, *65*, 956. (h) Weng, J. R.; Yen, M. H.; Lin, C. N. *Helv. Chim. Acta* **2002**, *85*, 847. (i) Iliya, I.; Tanaka, T.; Iinuma, M.; Furusawa, M.; Ali, Z.; Nakaya, J.; Darnaedi, D. *Helv. Chim. Acta* **2002**, *85*, 2394. (j) Yan, K.-X.; Terashima, K.; Takaya, Y.; Niwa, M. *Tetrahedron* **2002**, *58*, 6931. (k) Cagniant, P.; Carniant, D. *Adv. Heterocycl. Chem.* **1975**, *18*, 337. (l) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 657−712.

(6) (a) Felder, C. C.; Joyce, K. E.; Briley, E. M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291. (b) Yang, Z.; Hon, P. M.; Chui, K. Y.; Chang, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M. *Tetrahedron Lett.* **1991**, *32*, 2061. (c) Carter, G. A.; Chamberlain, K.; Wain, R. L. *Ann. Appl. Biol.* **1978**, *88*, 57. (d) Ingham, J. L.; Dewick, P. M. *Phytochemistry* **1978**, *17*, 535. (e) Takasugi, M.; Nagao, S.; Masamune, T. *Tetrahedron Lett.* **1979**, 4675. (f) Davies, W.; Middleton, S. *Chem. Ind. (London)* **1957**, 599. (g) Kawaguchi, T.; Akatsuka, H.; Morimoto, M.; Watanabe, T.; Iijima, T.; Murakami, J. PCT Int. Appl. (2005), 142 pp. (h) McGarry, D. G.; Regan, J. R.; Volz, F. A.; Hulme, C.; Moriarty, K. J.; Djuric, S. W.; Souness, J. E.; Miller, B. E.; Travis, J. J.; Sweeney, D. W. *Bioorg. Med. Chem.* **1999**, *7*, 1131. (i) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 455. (j) Fukai, T.; Oku, Y.; Hano, Y.; Terada, S. *Planta Medica* **2004**, *70*, 685. (k) Tsuji, E.; Ando, K.; Kunitomo, J.-i.; Yamashita, M.; Ohta, S.; Kohno, S.; Ohishi, Y. *Org. Biomol. Chem.* **2003**, *1*, 3139.

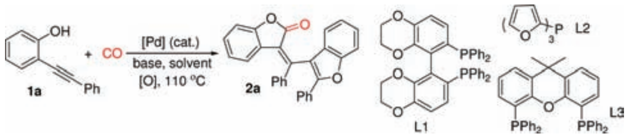
(7) Example in material science: Hwu, J. R.; Chuang, K.-S.; Chuang, S. H.; Tsay, S.-C. *Org. Lett.* **2005**, *7*, 1545. In organic synthesis: (a) Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, p 337. (b) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: U.K., 1984; Vol. 4, p 531. (c) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 259.

(8) For selected examples: (a) Dias, D. A.; Urban, S. *Nat. Prod. Res.* **2009**, *23*, 925. (b) Dat, N. T.; Jin, X.; Hong, Y.-S.; Lee, J. J. *J. Nat. Prod.* **2010**, *73*, 1167. (c) Lin, P.; Li, S.; Wang, S.; Yang, Y.; Shi, J. *J. Nat. Prod.* **2006**, *69*, 1629. (d) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (e) Pattenden, G. *Prog. Chem. Nat. Prod.* **1979**, *35*, 133. (f) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* **1987**, *51*, 1. (g) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287. (h) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707.

(9) (a) Strübe, F.; Siewertsen, R.; Sönichsen, F. D.; Renth, F.; Temps, F.; Mattay, J. *Eur. J. Org. Chem.* **2011**, 1947. (b) Heller, H. G.; Hughes, D. S.; Hursthouse, M. B.; Rowles, N. G. *Chem. Commun.* **2000**, 1397.

(10) (a) Irie, M. *Chem. Rev.* **2000**, *100*, 1685. (b) Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741.

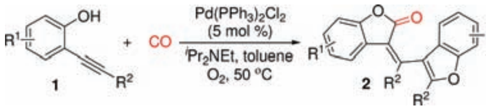
Table 1. Initial Studies for the Palladium-Catalyzed Reaction of 2-(2-Phenylethynyl)phenol **1a** and Carbon Monoxide

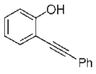
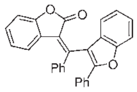
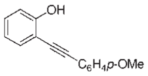
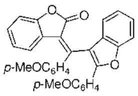
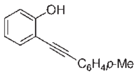
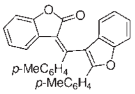
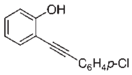
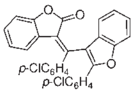
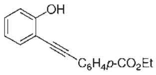
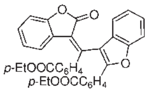
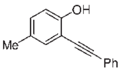
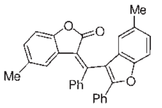
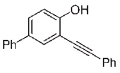
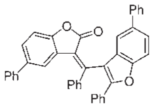
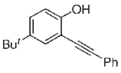
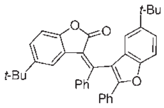
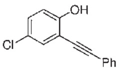
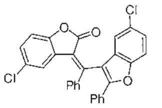
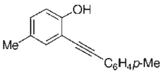
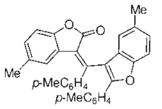
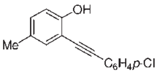
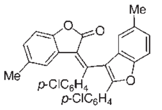
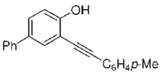
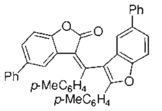
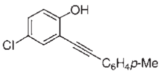
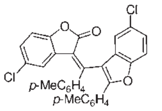


entry	[Pd]	ligand	base	[O]	solvent	yield (%)[a]
1	$Pd(OAc)_2$	-	$^{i}Pr_2NEt$	O_2	toluene	8
2	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	toluene	54
3	$PdCl_2(PPh_3)_2$	-	K_2CO_3	O_2	toluene	trace
4	$PdCl_2(PPh_3)_2$	-	Na_2CO_3	O_2	toluene	trace
5	$PdCl_2(PPh_3)_2$	-	KOAc	O_2	toluene	trace
6	$PdCl_2(PPh_3)_2$	-	$^{t}BuONa$	O_2	toluene	NR
7	$PdCl_2(PPh_3)_2$	-	DABCO	O_2	toluene	50
8	$PdCl_2$	-	$^{i}Pr_2NEt$	O_2	toluene	trace
9	$Pd(PPh_3)_4$	-	$^{i}Pr_2NEt$	O_2	toluene	trace
10	$PdCl_2(PPh_3)_2$	PCy_3	$^{i}Pr_2NEt$	O_2	toluene	trace
11	$PdCl_2(PPh_3)_2$	DPPF	$^{i}Pr_2NEt$	O_2	toluene	41
12	$PdCl_2(PPh_3)_2$	BINAP	$^{i}Pr_2NEt$	O_2	toluene	43
13	$PdCl_2(PPh_3)_2$	LI	$^{i}Pr_2NEt$	O_2	toluene	37
14	$PdCl_2(PPh_3)_2$	L2	$^{i}Pr_2NEt$	O_2	toluene	40
15	$PdCl_2(PPh_3)_2$	L3	$^{i}Pr_2NEt$	O_2	toluene	24
16	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	BQ	toluene	45
17	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	dioxane	trace
18	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	DMF	trace
19	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	DMSO	trace
20	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	NMP	trace
21[b]	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	toluene	54
22[c]	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	toluene	62
23[d]	$PdCl_2(PPh_3)_2$	-	$^{i}Pr_2NEt$	O_2	toluene	trace

[a] Isolated yield based on 2-(phenylethynyl)phenol **1a**. DPPF: 1,1′-bis(diphenylphosphino)ferrocene. [b] The reaction occurred at 70 °C. [c] The reaction was performed at 50 °C. [d] The reaction occurred at 25 °C.

Table 2. Palladium-Catalyzed Reaction of 2-Alkynylphenol **1** with Carbon Monoxide



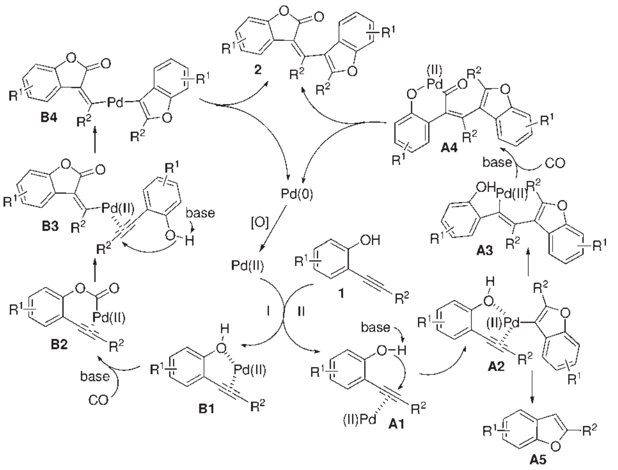
entry	2-alkynylphenol **1**	product	yield (%)[a]
1	 **1a**		62 (**2a**)
2	 **1b**		94 (**2b**)
3	 **1c**		92 (**2c**)
4	 **1d**		73 (**2d**)
5	 **1e**		40 (**2e**)
6	 **1f**		72 (**2f**)
7	 **1g**		80 (**2g**)
8	 **1h**		62 (**2h**)
9	 **1i**		47 (**2i**)
10	 **1j**		97 (**2j**)
11	 **1k**		66 (**2k**)
12	 **1l**		70 (**2l**)
13	 **1m**		50 (**2m**)

[a] Isolated yield based on 2-alkynylphenol **1**.

(Table 1, entry 22). The reaction was retarded when the reaction occurred at rt (Table 1, entry 23).

With the optimized conditions in hand [$PdCl_2(PPh_3)_2$ (5 mol %), $^{i}Pr_2NEt$ (2.0 equiv), toluene, 50 °C, CO/O_2 (v/v = 1:1)], we next focused on the generality of the Pd-catalyzed reaction of 2-alkynylphenol **1** with carbon monoxide. The results are summarized in Table 2. We noticed that these cascade reactions are effective to produce the expected 3-(benzofuran-3-ylmethylene)benzofuran-2(3*H*)-ones in moderate to excellent yields. For example, Pd-catalyzed carbonylative annulation of 2-alkynylphenol **1b** afforded the desired product **2b** in 94% yield (Table 2, entry 2). A similar outcome (92%) was obtained when substrate **1c** was used with the R^2 group replaced by 4-methylphenyl (Table 2, entry 3). A lower yield was obtained with 2-alkynylphenol containing an electron-withdrawing group at the R^2 position. For instance, **2e** was generated in 40% yield when 2-alkynylphenol **1e** was employed in the reaction (Table 2, entry 5). Further investigation revealed that the conditions were not suitable for substrates with an alkyl group attached to the triple bond (data not shown in Table 2). No desired product was generated when R^2 was an alkyl group (*n*-butyl or cyclopropyl group). Reactions of 2-alkynylphenols with different substitutions on the aromatic ring were examined subsequently. Good yields were obtained when methyl, phenyl, or *tert*-butyl substituted 2-alkynylphenol was utilized in the Pd-catalyzed carbonylative cascade reaction (Table 2, entries 6–8, 10–12). The yields were inferior with 2-alkynylphenols having a chloro group attached on the aromatic ring (Table 2, entries 9 and 13).

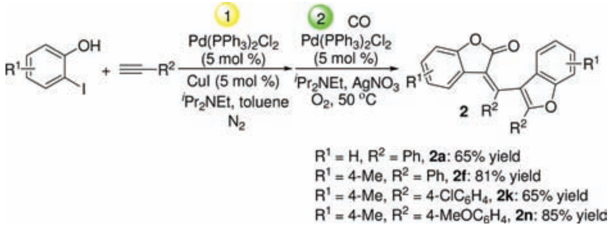
Scheme 2. A Plausible Mechanism for the Palladium-Catalyzed Reaction of 2-Alkynylphenols with Carbon Monoxide



As mentioned above, a double insertion of triple bonds is likely to occur in the reaction of 2-alkynylphenol and carbon monoxide since 2 equiv of 2-alkynylphenol are involved in the transformation. Thus, a possible mechanism is illustrated in Scheme 2. We envisioned that there might be two possible pathways for the final outcome. Takahashi[10] and Kuniyasu[11] reported the synthesis of benzofuran-2(3*H*)-ones in neutral conditions from 2-alkynylphenols and carbon monoxide (route I). We believe that route II cannot be excluded since 2-substituted benzofuran **A5** was the main byproduct in all reactions. Recently, Lautens reported an example for the synthesis of 2-(2-(2-butylbenzofuran-3-yl)hex-1-en-1-yl)phenols through a Rh-catalyzed reaction,[12] which illustrates that path II is also possible.

In the meantime, we noticed that the standard conditions shown in Table 2 are similar to those used in Sonogashira coupling reactions. Additionally, some 2-alkynylphenols are too unstable to be isolated during the purification process by flash chromatography on silica gel. Thus, a one-pot synthesis starting from 2-iodophenol and alkyne was investigated. After optimization of the reaction conditions, we found the reaction worked well when conducted in a two-step sequence. As presented in Scheme 3, after completion of the Sonogashira coupling, another 5 mol % of $PdCl_2(PPh_3)_2$, 2.0 equiv of $^i Pr_2NEt$, and 1.0 equiv of $AgNO_3$ were added to the reaction mixture. The atmosphere was changed to carbon monoxide and oxygen (v/v: 1/1). The addition of silver nitrate for removal of iodide was crucial for the successful one-pot reaction. Under the conditions, the reactions proceeded smoothly to afford the corresponding products in good yields.

Scheme 3. One-Pot Synthesis of 3-(Benzofuran-3-ylmethylene) benzofuran-2(3*H*)-ones Starting from 2-Iodophenol and Alkyne



In conclusion, we have described a novel and efficient pathway for the generation of 3-(benzofuran-3-ylmethylene)benzofuran-2(3*H*)-ones via a Pd-catalyzed carbonylative reaction of 2-alkynylphenol with carbon monoxide. The reaction proceeds in high yields with good selectivity. A one-pot synthesis starting from 2-iodophenol and alkyne is presented as well. During the reaction process, a double insertion of triple bonds is believed to be the key. Efforts for focused library construction and exploration of related transformations are under investigation currently.

Acknowledgment. Financial support from the National Natural Science Foundation of China (Nos. 21032007, 21172038) and Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science & Technology Normal University is gratefully acknowledged. We thank Dr. Jason Wong (Roche Pharma Research and Early Development, China) for English review.

Supporting Information Available. Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **2**, and a CIF file of compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[11] Kuniyasu, H.; Yoshizawa, T.; Kambe, N. *Tetrahedron Lett.* **2010**, *51*, 6818.

[12] Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. *Tetrahedron* **2010**, *66*, 6468.