JOC Note
pubs.acs.org/joc

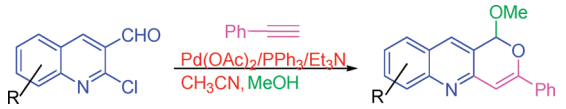
Copper-Free Palladium-Catalyzed Sonogashira Coupling−Annulation: Efficient One-Pot Synthesis of Functionalized Pyrano[4,3-*b*]quinolines from 2-Chloro-3-formylquinolines

Atish Chandra, Bhawana Singh, Ranjana S. Khanna, and Radhey M. Singh*

Department of Chemistry, Banaras Hindu University, Varanasi - 221 005, U.P., India

rmohan@bhu.ac.in

Received March 27, 2009



A convenient, one-pot, copper-free, Pd-catalyzed methodology has been described for the synthesis of 1,3-disubstituted pyrano[4,3−*b*]quinolines from 2-chloro-3-formylquinolines. Formation of annulated products **3** is attributed to the presence of $Pd(OAc)_2$ and PPh_3. Further, PPh_3 in the reaction mixture promotes the cyclization by reducing the reaction time and increasing the yield of cyclized product.

Over the past few years, palladium-catalyzed coupling/annulation reactions of alkynes mostly with vinyl/aryl halides containing preexisting nucleophiles have been studied for the synthesis of a variety of heterocycles/annulated heterocycles,[1] for example, α-pyrones,[2] pyridines,[3] indoles,[4] benzofurans,[5] benzopyrans,[6] isocoumarins,[2] and isoquinolines.[3] In contrast to internal alkynes, terminal alkynes require two-step reactions in most of these annulation processes, initially involving the formation of Sonogashira coupling products followed by transition-metal-catalyzed[7] or electrophile-catalyzed[8] cyclization of the resulting alkynes with their preexisting nucleophile in the subsequent step. Recently, a one-pot synthesis[9] involving Sonogashira coupling followed by cyclization of the resulting alkynes with suitable nucleophiles in proximity to the triple bond has emerged as an efficient route to the synthesis of variety of heterocycles. Generally, in these coupling−cyclization reactions, copper salts were used as cocatalysts along with palladium catalyst [e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, Pd/C−PPh_3] in the presence of amine base. However, one-pot Sonogashira coupling and cyclization reactions of *o*-chlorobenzaldehyde have not been explored. However, Yamamoto et al. have reported the $Pd(OAc)_2$-catalyzed cyclization of *o*-alkynylbenzaldehydes using methanol as nucleophile to the synthesis of the 1,3-disubstituted cyclic alkenyl ether moiety of isochromenes.[10]

In continuation of our interest in the synthesis of carbo-/heteroannulated quinolines,[11] we have recently reported the copper-free Sonogashira coupling of 2-chloroquinoline-3-carboxaldehydes with phenylacetylene followed by N-nucleophile cyclization of the resulting alkyne in the subsequent step to benzo[*b*][1,6]naphthyridines.[12] We realized from these observations that copper-free palladium-catalyzed reaction of *o*-haloaryl/heteroaryl aldehydes with terminal alkynes and methanol as nucleophile could lead to the synthesis of isochromenes/heteroanalogues in one pot via Sonogashira coupling and annulation. Because of our recent interest in palladium-catalyzed coupling−annulation, we report here the one-pot synthesis of 1,3-disubstituted 1*H*-pyrano[4,3-*b*]quinolines from 2-chloroquinoline-3-carboxaldehydes (**1**)[13] with phenylacetylene using $Pd(OAc)_2$ as a catalyst, PPh_3 as ligand, Et_3N as base, and methanol as nucleophile.

(1) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159.

(2) (a) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829–4837. (b) Wang, L.; Wang, S. *Tetrahedron Lett.* **1998**, *39*, 7625–7628.

(3) (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980–988. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5132–5138.

(4) (a) Terrason, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, *32*, 5332–5335. (b) Reboredo, F. J.; Treus, M.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Synlett* **2002**, 999–1001. (c) Larock, R. C.; Yum, E. K.; Doty, M. J.; Kelvin, K. C. S. *J. Org. Chem.* **1995**, *60*, 3270–3271.

(5) (a) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387–1390. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071–5075. (c) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620–1625. (d) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (e) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (f) Muniz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425–1428.

(6) (a) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522–524. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063–5064.

(7) (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *4*, 553–556. (b) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (e) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.

(8) (a) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* 2002, 622−628. (b) Gamila, M. M.; El-Taeb, Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945–5948. (c) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857–2870. (d) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193–7196.

(9) (a) Venkatraman, S.; Barange, D. K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 7317–7322. (b) Pal, M.; Venkatraman, S.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221–8225. (c) Venkatraman, S.; Batchu, V. R.; Barange, D. K.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778–4783.

(10) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765. (b) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139–5142. (c) Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496–9498.

(11) (a) Singh, R. M.; Singh, B.; Chandra, A.; Upadhyay, S. *Tetrahedron Lett.* **2008**, *49*, 6423–6425. (b) Singh, R. M.; Singh, M. K.; Chandra, A.; Singh, B. *Tetrahedron Lett.* **2007**, *48*, 5987–5990. (c) Singh, R. M.; Chandra, A.; Singh, M. K. *Synth. Commun.* **2007**, *37*, 1689–1695. (d) Singh, R. M.; Srivastava, A.; Chandra, A. *Indian J. Chem.* **2007**, *46B*, 303–307. (e) Singh, R. M.; Srivastava, A.; Singh, M. K. *Indian J. Chem.* **2006**, *45B*, 292–296. (f) Singh, R. M.; Srivastava, A.; Chandra, A. *Indian J. Chem.* **2005**, *44B*, 2077–2081.

(12) Singh, R. M.; Chandra, A.; Singh, B.; Upadhyay, S. *Tetrahedron* **2008**, *64*, 11680–11685.

(13) Singh, R. M.; Srivastava, A. *Indian J. Chem.* **2005**, *44B*, 1868–1875.

Published on Web 06/04/2009 DOI: 10.1021/jo900606j

SCHEME 1. One-Pot Synthesis of Pyrano[4,3-*b*]quinoline via Palladium Catalyst

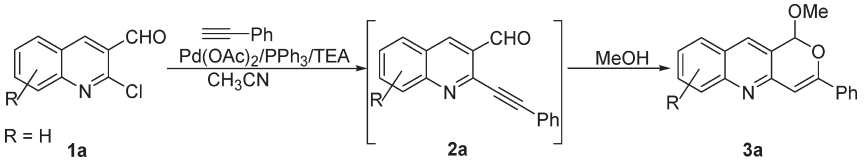


TABLE 1. Optimization of the Reaction Conditions for Cyclization of 1a to 3a and 2a to 3a

entry	reaction conditions	substrate	total time (h)	**3a**, yield (%)
1	5% $Pd(OAc)_2$, 10% PPh_3, 2 equiv TEA, MeOH (4 mL), 80 °C	**1a**	overnight	SM
2[a]	5% $Pd(OAc)_2$, 10% PPh_3, 2 equiv TEA, 80 °C	**1a**	overnight	28
3[a]	10% $Pd(OAc)_2$, 20% PPh_3, 2 equiv TEA, 80 °C	**1a**	6	76
4[a]	10% $Pd(OAc)_2$, 20% PPh_3, 3 equiv TEA, 80 °C	**1a**	6	76
5[a]	10% $PdCl_2$, 20% PPh_3, 2 equiv TEA, 80 °C	**1a**	7	68
6[b]	10% $Pd(OAc)_2$, 20% PPh_3, 80 °C	**2a**	2.5	80
7[b]	10% $Pd(OAc)_2$, 80 °C	**2a**	16	70

[a] Each reaction contained 2-chloro-3-formylquinoline **1a** (0.25 mmol), and excess methanol (4 mL) was added after consumption of substrate **1a**. [b] Each reaction contained **2a** (0.25 mmol) and excess methanol (4 mL), which is used as nucleophile and solvent.

The pyranoquinoline derivatives have wide applications, for example, as drugs, pharmaceuticals, and agrochemicals, and possess a significant range of biological activities, such as anti-inflammatory, antiallergic, psychotropic, and estrogenic.[14]

Initially, the reaction of 2-chloro-3-formylquinolines (**1**) with phenylacetylene under our optimized copper-free Sonogashira coupling conditions and using methanol as a nucleophile was examined for the desired cyclized products, 1-methoxy-3-phenyl-1*H*-pyrano[4,3-*b*]quinolines (**3**) (Scheme 1). Thus, the reaction of **1a** with phenylacetylene using 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 2 equiv of Et_3N in acetonitrile, and methanol (4.0 mL) as a nucleophile at 80 °C for overnight did not give the desired cyclized product **3a**[15] at all, and the starting material **1a** was recovered (Table 1, entry 1). On the other hand, methanol was added to the reaction mixture after the formation of the Sonogashira product **2a**, using optimized copper-free Songashira coupling conditions, to provide the cyclized product **3a** in 28% yield along with uncyclized **2a** (Table 1, entry 2). Encouraged by this result, we next attempted the reaction to explore the optimum reaction conditions by using various combinations of palladium source, ligand, and base for the best yield of **3a**. The combination of 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 2 equiv of Et_3N in acetonitrile at 80 °C for 3.5 h followed by addition of methanol (4.0 mL) at 80 °C and continued heating for a further 2.5 h not only gave the best yield of the cyclized product **3a** (76%) but also reduced the reaction time (Table 1, entry 3). An increase in the number of equivalents of Et_3N did not improve the yield of the cyclized product **3a** (Table 1, entry 4).[16] Thus, the increase in the yield of the cyclized product **3a** could be attributed to an increase in the mol % of $Pd(OAc)_2$ and PPh_3. However, the use of $PdCl_2$ under similar condition for 7 h did not improve the yield of cyclized product **3a** (Table 1, entry 5), although the use of $PdCl_2$ in place of $Pd(OAc)_2$ afforded a better yield of the Sonogashira products **2**.[12]

TABLE 2. One-Pot Synthesis of Pyrano[4,3-*b*]quinolines

entry	substrate	R	product	total time (h)	**3**, yield (%)
1	**1a**	H	**3a**	6	76
2	**1b**	6-Me	**3b**	5	74
3	**1c**	7-Me	**3c**	4.5	71
4	**1d**	7-OMe	**3d**	5	73
5	**1e**	8-Me	**3e**	5.5	69
6	**1f**	8-Et	**3f**	6	78
7	**1g**	6-OMe	**3g**	5	71

Encouraged by the establishment of the optimum reaction conditions (Table 1, entry 3), we tested the series of substituted 2-chloroquinoline-3-carboxaldehydes **1b**−**g** under our standard Sonogashira coupling−annulation conditions using 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 2 equiv of Et_3N in acetonitrile at 80 °C followed by addition of methanol (4.0 mL) at 80 °C and continued heating to afford the corresponding 1-methoxy-1*H*-pyrano[4,3-*b*]quinolines **3b**−**g** in good yields. The results are summarized in Table 2.

To explore the mechanism of the cyclization, we further examined the reaction of **2a** with various reagents such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2$, PPh_3, and Et_3N. Thus, the reaction of **2a** with 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 in methanol (4.0 mL) at 80 °C for 2.5 h afforded the cyclized product **3a** in 80% yield (Table 1, entry 6). However, when Yamamoto conditions were applied,[10] using only 10 mol % of $Pd(OAc)_2$ in methanol (4.0 mL) at 80 °C for 16 h afforded the cyclized product **3a** in 70% yield (Table 1, entry 7). In contrast, using PPh_3 (20 mol %) in the absence of Pd $(OAc)_2$ in methanol with **2a** at 80 °C for 4 h afforded the mixture of unidentified products. Further, Et_3N and Et_3N−HCl were also examined for cyclization and proved to be totally ineffective; none of the desired product was detected at all.[16] These observations clearly indicated that the PPh_3 ligand with the $Pd(OAc)_2$ facilitated the cyclization reaction and increased the yield of the product **3a**.

In conclusion, we have developed a new, one-pot palladium-catalyzed methodology for the synthesis of

(14) (a) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213. (b) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177–1181. (c) Johnson, J. V.; Rauckmann, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949. (d) Mohmed, E. A. *Chem. Pap.* 1994, *48*, 261−267; *Chem. Abstr.* 1995, *123*, 9315x

(15) Godet, T.; Bosson, J.; Belmont, P. *Synlett* **2005**, 2786–2790.

(16) Yue, D.; Ca, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381–3388.

1,3-disubstituted pyrano[4,3-*b*]quinolines without copper as a cocatalyst and avoiding column purification steps. Further, the presence of the PPh_3 ligand with $Pd(OAc)_2$ facilitates the cyclization reaction by reducing the reaction time and increasing the yield of cyclized product.

Experimental Section

General Procedure for the Pd-Catalyzed One-Pot Synthesis of Pyrano[4,3-*b*]quinolines 3. A mixture of 2-chloro-3-formylquinolines (**1**) (0.25 mmol), phenylacetylene (0.26 mmol), $Pd(OAc)_2$ (10 mol %), and PPh_3 (20 mol %) in CH_3CN (4.0 mL) and TEA (2 equiv) was stirred under N_2 at 80 °C for 3.5 h (as monitored by TLC) followed by addition of methanol (4.0 mL) at the same temperature for 2.5 h. After completion of the reaction, mixture was concentrated in vacuo and residue was purified by column chromatography on silica gel (silica gel was neutralized by TEA) using 10:90 EtOAc/hexane as eluent.

1-Methoxy-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline (3a):. yellow solid; yield 76%; mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.36 (s, 1H), 6.98 (s, 1H), 7.44−7.49 (m, 4H), 7.70 (t, J = 7.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.89 (m, 2H), 8.03−8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1, 98.9, 99.6, 122.5, 125.9, 126.4, 126.7, 128.0, 128.3, 128.7, 130.0, 130.8, 131.7, 133.3, 135.7, 148.7, 158.7; IR (KBr) 1022, 1376, 1445, 1615 cm^{-1}; MS m/z = 290 $[M + H]^+$; HRMS calcd for $C_{19}H_{16}NO_2$ $[M + H]^+$ 290.1181, found 290.1175.

1-Methoxy-8-methyl-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline (3b):. light yellow solid; yield 74%; mp 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.69 (s, 3H), 6.35 (s, 1H), 6.97 (s, 1H), 7.43−7.56 (m, 5H), 7.88−7.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 55.8, 100.2, 102.0, 113.9, 122.5, 125.3, 126.8, 128.2, 128.6, 129.7, 132.1, 132.6, 133.8, 135.5, 147.2, 148.6, 155.4; IR (KBr) 1021, 1465, 1621 cm^{-1}; HRMS calcd for $C_{20}H_{18}NO_2$ $[M + H]^+$ 304.1338, found 304.1335.

Acknowledgment. We acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, India, and the University Grant Comission (UGC), New Delhi, India, for financial support. A.C. and B.S. are thankful to CSIR, New Delhi, for the award of Senior Research Fellowship. We also thank Prof. S. Baskaran, Department of Chemistry, IIT Madras, Chennai, India, Director and SAIF, CDRI, Lucknow, India, for HRMS data.

Supporting Information Available: Experimental details, spectroscopic and analytical data, and ^{1}H and ^{13}C NMR spectra of the products **3a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.