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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

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A convenient, one-pot, copper-free, Pd-catalyzed methodology has been described for the synthesis of 1,3disubstituted pyrano[4,3-b]quinolines from 2-chloro-3formylquinolines. Formation of annulated products 3 is attributed to the presence of $Pd(OAc)_2$ and PPh_3 . Further, PPh₃ 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

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5664 J. Org. Chem. 2009, 74, 5664–5666

processes, initially involving the formation of Sonogashira coupling products followed by transition-metal-catalyzed⁷ or electrophile-catalyzed⁸ cyclization of the resulting alkynes with their preexisting nucleophile in the subsequent step. Recently, a one-pot synthesis⁹ 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(PPh₃)₄, PdCl₂(PPh₃)₂, Pd/C-PPh₃] 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-3carboxaldehydes 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 1Hpyrano[4,3-b]quinolines from 2-chloroquinoline-3-carboxaldehydes $(1)^{13}$ with phenylacetylene using Pd(OAc)₂ as a catalyst, PPh₃ as ligand, Et₃N as base, and methanol as nucleophile.

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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 ^{<i>a</i>}	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.

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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-1H-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 PPh₃, 2 equiv of Et₃N 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 PPh₃, and 2 equiv of Et₃N 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 Et₃N 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 PPh₃. However, the use of PdCl₂ under similar condition for 7 h did not improve the yield of cyclized

ABLE 2.	One-Pot S	ynthesis of	Pyrano[4,3-	<i>b</i>]quinolines

TABLE 2. One-1 of Synthesis of 1 yrano[4,5-0]quinonnes								
entry	substrate	R	product	total time (h)	3, yield (%)			
1	1a	Н	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			

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

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 PPh₃, and 2 equiv of Et₃N 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/PPh₃, Pd(OAc)₂, PPh₃, and Et₃N. Thus, the reaction of 2a with 10 mol % of Pd(OAc)₂ and 20 mol % of PPh₃ 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 PPh₃ (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, Et₃N and Et₃N-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 PPh₃ 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

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JOCNote

1,3-disubstituted pyrano[4,3-b]quinolines without copper as a cocatalyst and avoiding column purification steps. Further, the presence of the PPh₃ 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 PPh₃ (20 mol %) in CH₃CN (4.0 mL) and TEA (2 equiv) was stirred under N₂ 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; ¹H NMR (300 MHz, CDCl₃) \delta 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); ¹³C NMR (75 MHz, CDCl₃) \delta 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;**

 $MSm/z = 290[M + H]^+$; 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₀H₁₈NO₂ [M + H]⁺ 304.1338, found 304.1335.

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