Palladium-Catalyzed Three-Component Tethering: Synthesis of 1-Alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones

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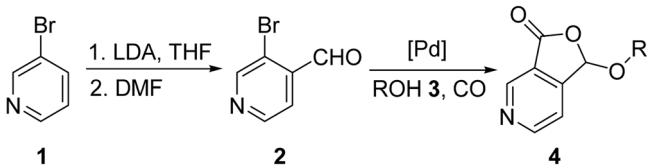
Received March 20, 2006

Key Words : Alcohol, Carbon monoxide, Cyclization, Palladium catalyst, 1-Alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones

Palladium-catalyzed carbonylative annulation technology has been recognized as a useful synthetic tool for heterocyles, which play an important role as a basic unit for the design of many pharmacologically and biologically active compounds.[1] As part of our continuing studies directed towards transition metal-catalyzed cyclization reactions, we also recently reported on the synthesis of various heterocycles such as isoindolinones,[2] β-lactams,[3] and phthalides[4] *via* palladium-catalyzed carbonylative cyclization. Among them, in connection with this report, 2-bromobenzaldehyde was found to be cyclized with primary alcohols in the presence of a palladium catalyst and a base under carbon monoxide pressure to afford 3-alkoxy-3*H*-isobenzofuran-1-ones.[5] Such a similar annulation using 2-bromobenzaldehydes leading to carbo- and heterocycles was also exemplified by us[6,7] and others.[8] Under these circumstances, the present work was disclosed during the course of the extension of this protocol to the reaction with 3-bromopyridine-4-carbaldehyde (**2**), which is readily prepared from 3-bromopyridine (**1**) *via* reported method (Scheme 1).[9] Herein this report describes a new entry for 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones **4** *via* intrinsic palladium-catalyzed three-component tethering.

The present reaction was intrinsically carried out with similar catalytic system based on our recent report on palladium-catalyzed synthesis of 3-alkoxy-3*H*-isobenzofuran-1-ones from 2-bromobenzaldehyde and primary or secondary alcohols under carbon monoxide pressure. Generally, 3-bromopyridine-4-carbaldehyde (**2**) was subjected to react with 5 equiv. of a primary or secondary alcohol **3** in THF at 100 °C in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (2 mol% based on **2**) and $NaHCO_3$ under carbon monoxide pressure to afford 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones **4** (Scheme 1). The reaction was monitored until **2** had disappeared on TLC, which occurred within 20 h. The reaction of **2** with various primary or secondary



1 **2** **4**

Scheme 1

alcohols **3** was screened in order to investigate the reaction scope and several representative results are summarized in Table 1. As shown in Table 1, **2** was readily tethered with an array of primary alcohols **3a-g** having straight and branched alkyl chains and carbon monoxide to give the corresponding 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones **4a-g** in the range of 40-71% yields. The product yield was increased with the chain length of straight primary alcohols, whereas the position of branching of branched primary alcohols had no relevance to the product yield. In the reaction with 2-methylbutan-1-ol (**3g**), the product **4g** was obtained as a diastereoisomeric mixture. As is the case for the cyclization with 2-bromobenzaldehyde,[5] in the reaction with benzyl alcohol (**3h**), a lower product yield was observed when compared with **3a-g**. The reaction proceeds likewise with secondary alcohols (**3i** and **3j**) to afford the corresponding 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones (**4i** and **4j**[10]) and the product yield was generally lower than that when primary alcohols were used.

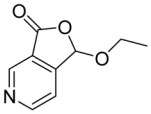
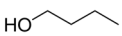
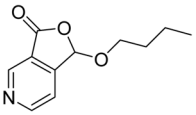
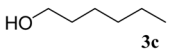
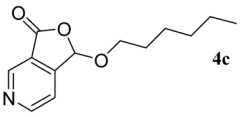
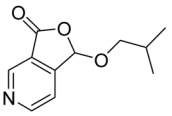
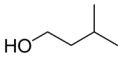
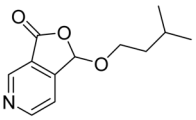
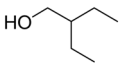
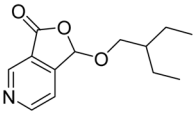
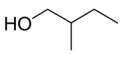
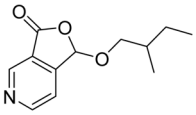
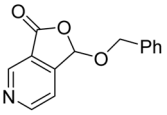
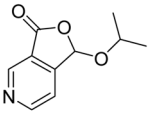
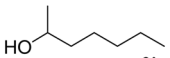
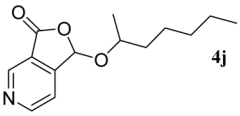
In summary, it has been shown that 3-bromopyridine-4-carbaldehyde undergoes tethering with primary alcohols as well as secondary alcohols under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst along with a base to afford 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones in moderate to good yields. The present reaction provides a new entry for phthalide analogue, 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones.

Experimental Section

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. IR spectra were recorded on Mattson Instruments, Inc., Galaxy 7020A spectrophotometer. Melting points (m.p.) were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out *via* thin layer chromatography (silica gel 60 GF_{254}, Merck). 3-Bromopyridine-4-carbaldehyde (**2**) was synthesized from 3-bromopyridine (**1**) by treatment of LDA and DMF.[9] Commercially available organic and inorganic compounds were used without further purification.

General experimental procedure. A mixture of 3-bromopyridine-4-carbaldehyde (0.093 g, 0.5 mmol), primary

Table 1. Palladium-catalyzed synthesis of 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones[a]

Primary alcohols **3**	Products **4**	Yield (%)
 **3a**	 **4a**	45
 **3b**	 **4b**	58
 **3c**	 **4c**	68
 **3d**	 **4d**	45
 **3e**	 **4e**	71
 **3f**	 **4f**	70
 **3g**	 **4g**	40
 **3h**	 **4h**	31
 **3i**	 **4i**	43
 **3j**	 **4j**	31

[a]Reaction conditions: **2** (0.5 mmol), **3** (2.5 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), $NaHCO_3$ (2 mmol), CO (10 atm), THF (5 mL), 100 °C, for 20 h.

or secondary alcohol (2.5 mmol), $PdCl_2(PPh_3)_2$ (0.007 g, 0.01 mmol) and $NaHCO_3$ (0.168 g, 2 mmol) in THF (5 mL) was placed in a 50 mL pressure vessel. After the system was flushed and then pressurized with CO (10 atm), the reaction mixture was allowed to react at 100 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give 1-alkoxy-1*H*-furo[3,4-*c*]pyridine-3-ones **4**. All products prepared by the above procedure were characterized spectroscopically as shown below.

1-Ethoxy-1*H*-furo[3,4-*c*]pyridine-3-one (4a). Solid (hexane-chloroform); mp 77-78 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 3.88-3.96 (m, 1H), 4.02-4.09 (m, 1H), 6.40 (s, 1H), 7.59 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.43, 67.26, 102.16, 118.68, 123.51, 148.20, 153.26, 154.59, 167.35.

1-Buthoxy-1*H*-furo[3,4-*c*]pyridine-3-one (4b). Pale yellow oil; IR (neat) 1774 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.38-1.47 (m, 2H), 1.65-1.72 (m, 2H), 3.81-3.87 (m, 1H), 3.95-4.01 (m, 1H), 6.41 (s, 1H), 7.59 (d, J = 5.0 Hz, 1H), 8.94 (d, J = 5.0 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 19.41, 31.76, 71.33, 102.39, 118.66, 123.52, 148.11, 153.28, 154.54, 167.31. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.88; H, 6.51; N, 6.94.

1-Hexyloxy-1*H*-furo[3,4-*c*]pyridine-3-one (4c). Pale yellow oil; IR (neat) 1774 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.3 Hz, 3H), 1.26-1.41 (m, 6H), 1.66-1.73 (m, 2H), 3.80-3.86 (m, 1H), 3.94-4.00 (m, 1H), 6.40 (s, 1H), 7.59 (d, J = 5.0 Hz, 1H), 8.94 (d, J = 5.0 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.38, 22.89, 25.86, 29.72, 31.81, 71.66, 102.39, 118.67, 123.52, 148.13, 153.27, 154.55, 167.33.

1-Isobutoxy-1*H*-furo[3,4-*c*]pyridine-3-one (4d). Pale yellow oil; IR (neat) 1778 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.93-2.03 (m, 1H), 3.58 (dd, J = 7.0 and 9.0 Hz, 1H), 3.75 (dd, J = 6.5 and 9.0 Hz, 1H), 6.39 (s, 1H), 7.58 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.40, 19.47, 28.80, 77.86, 102.50, 118.65, 123.59, 148.18, 153.28, 154.55, 167.32.

1-(3-Methylbutoxy)-1*H*-furo[3,4-*c*]pyridine-3-one (4e). Pale yellow oil; IR (neat) 1773 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 1.56-1.61 (m, 2H), 1.69-1.79 (m, 1H), 3.84-3.90 (m, 1H), 3.98-4.04 (m, 1H), 6.40 (s, 1H), 7.59 (d, J = 5.0 Hz, 1H), 8.94 (d, J = 5.0 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.80, 22.86, 25.23, 38.42, 70.05, 102.38, 118.66, 123.50, 148.11, 153.26, 154.55, 167.31.

1-(2-Ethylbutoxy)-1*H*-furo[3,4-*c*]pyridine-3-one (4f). Pale yellow oil; IR (neat) 1773 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 6H), 1.34-1.44 (m, 4H), 1.51-1.60 (m, 1H), 3.72 (dd, J = 5.5 and 9.0 Hz, 1H), 3.90 (dd, J = 5.5 and 9.0 Hz, 1H), 6.40 (s, 1H), 7.58 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.37, 11.39, 23.48, 23.50, 41.34, 73.61, 102.59, 118.63, 123.57, 148.15, 153.30, 154.53, 167.32. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.55; H, 7.64; N, 5.89.

1-(2-Methylbutoxy)-1*H*-furo[3,4-*c*]pyridine-3-one (4g). Pale yellow oil as an isomeric mixture; ^{1}H NMR ($CDCl_3$) δ 0.90-0.97 (m, 6H), 1.15-1.26 (m, 1H), 1.41-1.52 (m, 1H), 1.71-1.80 (m, 1H), 3.58-3.87 (m, 2H), 6.39 (s, 1H), 7.58 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.56 (11.59), 16.70 (16.75), 26.27 (26.30), 35.18 (35.22), 76.28 (76.42), 102.49 (102.60), 118.64, 123.59, 148.17, 153.29, 154.54, 167.32.

1-Benzyloxy-1*H*-furo[3,4-*c*]pyridine-3-one (4h). Solid (hexane-chloroform); mp 96-97 °C; ^{1}H NMR ($CDCl_3$) δ

4.87 (d, J = 11.5 Hz, 1H), 5.02 (d, J = 11.5 Hz, 1H), 6.43 (s, 1H), 7.39-7.55 (m, 6H), 8.92 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 72.67, 100.70, 118.67, 123.44, 128.90, 129.10, 129.16, 135.78, 148.22, 153.25, 154.54, 167.23. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.46; H, 4.68; N, 5.76.

1-Isopropoxy)-1*H*-furo[3,4-*c*]pyridine-3-one (4i). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 6.0 Hz, 3H), 1.38 (d, J = 6.0 Hz, 3H), 4.23-4.32 (m, 1H), 6.47 (s, 1H), 7.56 (d, J = 5.0 Hz, 1H), 8.93 (d, J = 5.0 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.37, 23.54, 74.96, 101.17, 118.63, 123.55, 148.11, 153.78, 154.50, 167.47.

1-(1-Methylhexyloxy)-1*H*-furo[3,4-*c*]pyridine-3-one (4j). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25-1.33 (m, 6H), 1.37 (d, J = 6.0 Hz, 3H), 1.48-1.56 (m, 1H), 1.62-1.70 (m, 1H), 4.06-4.14 (m, 1H), 6.46 (s, 1H), 7.53 (d, J = 5.0 Hz, 1H), 8.93 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.42, 20.07, 22.92, 25.30, 32.03, 37.14, 78.05, 100.71, 118.61, 123.68, 148.15, 153.81, 154.46, 167.48.

Acknowledgements. The present work was supported by the Korea Research Foundation Grant funded by Korea Government (MOEHRD, Basic Research Promotion Fund) (KRF-2005-015-C00264). C.S.C. gratefully acknowledges a Research Professor Grant of Kyungpook National University (2005).

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10. Although **4j**, as is the case for **4g**, was expected to be isolated as a diastereoisomeric mixture, however, the ^{1}H and ^{13}C NMR spectra revealed a feature of single product.