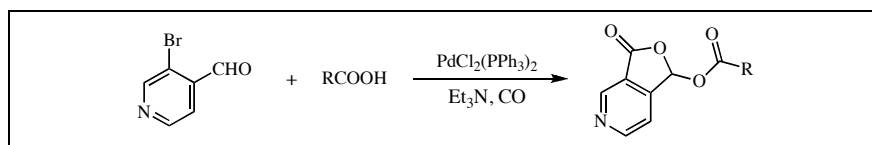


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Received February 28, 2008



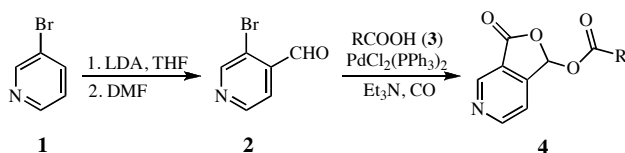
3-Bromopyridine-4-carbaldehyde is cyclized with carboxylic acids in acetonitrile at 100° under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst along with a base to afford the corresponding 3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-1-yl alkanooates in moderate to good yields.

J. Heterocyclic Chem., **45**, 1397 (2008).

INTRODUCTION

It is well known that many heterocyclic compounds play an important role as a basic unit for the design of many pharmacologically and biologically active compounds. Palladium-catalyzed carbonylation followed by cyclization process has been recognized as a useful straightforward synthetic tool for heterocycles containing carbonyl moiety [1]. As part of our continuing studies directed towards transition metal-catalyzed cyclization reactions, we also reported on the synthesis of several heterocycles such as isoindolinones [2], β -lactams [3] and phthalides [4] using such an intrinsic palladium-catalyzed carbonylation followed by cyclization [5,6]. Among them, in connection with this report, 2-bromobenzaldehyde was found to be cyclized with carboxylic acids in the presence of a palladium catalyst under carbon monoxide pressure to afford 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanooates [7]. This protocol led us to extend to the reaction with 3-bromopyridine-4-carbaldehyde, which is readily prepared from 3-bromopyridine *via* reported method (Scheme 1) [8]. Herein, this report describes a palladium-catalyzed cyclization of 3-bromopyridine-4-carbaldehyde with carbon monoxide and carboxylic acids leading to 1,3-dihydro-3-oxofuro[3,4-*c*]pyridine-1-yl alkanooates [9].

Scheme 1



RESULTS AND DISCUSSION

The present reaction was intrinsically carried out with similar catalytic system based on our recent report on palladium-catalyzed synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanooates from 2-bromobenzaldehyde


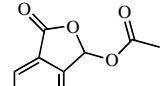

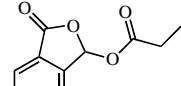
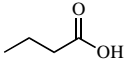
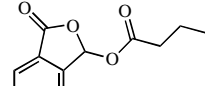
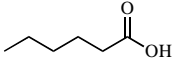
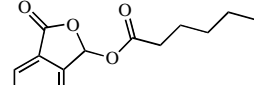
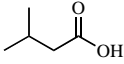
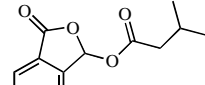
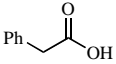
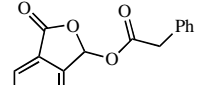
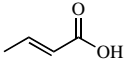
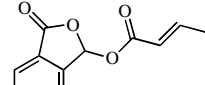

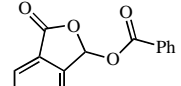
and carboxylic acids under carbon monoxide pressure. The starting 3-bromopyridine-4-carbaldehyde (**2**) was prepared by the treatment of 3-bromopyridine (**1**) with LDA and DMF by known method (Scheme 1) [8]. Generally, **2** was subjected to the reaction with two equivalents of a carboxylic acid **3** in acetonitrile at 100° in the presence of dichlorobis(triphenylphosphine)-palladium(II) along with triethylamine under carbon monoxide pressure (10 atm) to afford 3-oxo-1,3-dihydrofuro[3,4-*c*]pyridin-1-yl alkanooates **4**. The reaction was monitored until **2** had disappeared on TLC, which occurred within 1 hour.

The reaction of **2** with various carboxylic acids **3** was screened in order to investigate the reaction scope and several representative results are summarized in Table 1. Compound **2** was cyclized with an array of aliphatic carboxylic acids **3a-e** having straight and branched alkyl chains to give the corresponding 3-oxo-1,3-dihydrofuro[3,4-*c*]pyridin-1-yl alkanooates **4a-e** in the range of 51-73% isolated yields without any identifiable side products. The straight chain length and branching of aliphatic carboxylic acids had no relevance to the product yield. Lower reaction rate and yield were observed with phenylacetic acid (**3f**). From the reactions between **2** and α,β -unsaturated carboxylic acid **3g**, the corresponding cyclized product **4g** was also formed and the product yield was lower than that when compared to the reaction with aliphatic carboxylic acids. The reaction proceeds likewise with aromatic carboxylic acid **3h** to give 3-oxo-1,3-dihydrofuro[3,4-*c*]pyridin-1-yl benzoate (**4h**) in 59% yield.

The present reaction, consistent with the product formed, seems to proceed *via* a pathway shown in Scheme 2. Oxidative addition of a carbon-bromide bond of **2** to palladium(0) produces an arylpalladium(II) intermediate **5** where carbon monoxide coordination to palladium and then aryl migration from palladium to the carbon of carbon monoxide occurs to give an aroylpalladium(II)

Table 1

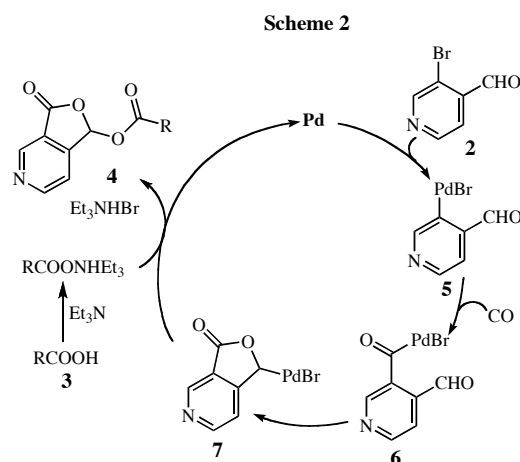
Palladium-Catalyzed Cyclization of **2** with Carbon Monoxide and **3** Leading to **4** [a]

Carboxylic acid 3	Product 4	Yield
		73
3a	4a	
		72
3b	4b	
		51
3c	4c	
		71
3d	4d	
		69
3e	4e	
		30
3f	4f	
		46
3g	4g	
		59
3h	4h	

[a] Reaction conditions: **2** (0.5 mmol), **3** (1 mmol), PdCl₂(PPh₃)₂ (0.025 mmol), Et₃N (2.5 mmol), MeCN (5 mL), CO (10 atm), 100°, for 1 hour. [b] Isolated yield.

intermediate **6**. Subsequent intramolecular addition of aroylpalladium bond of **6** to neighboring formyl C=O produces cyclized alkylpalladium species **7**. This is followed by the reaction with ammonium alkanolate to give **4**. A similar catalytic process has already been proposed in palladium-catalyzed cyclization of 2-bromobenzaldehyde with carbon monoxide and nucleophiles [4]. The mechanistic acylpalladium addition to ketones is

known on palladium-catalyzed cyclization of (*Z*)- β -iodoenones with carbon monoxide leading to γ -lactones [10,11].



In summary, it has been shown that 3-bromopyridine-4-carbaldehyde undergoes palladium-catalyzed cyclization with carboxylic acids under carbon monoxide pressure to afford 3-oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl alkanates in moderate to good yields. The present reaction provides a new entry for phthalide analogue exhibiting biological activity.

EXPERIMENTAL

¹H and ¹³C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me₄Si as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting points apparatus and are uncorrected. The isolation of pure products was carried out *via* thin layer (silica gel 60 GF₂₅₄, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled by standard methods before use.

General Procedure for Palladium-Catalyzed Cyclization of 3-Bromopyridine-4-carbaldehyde (2**) with Carbon Monoxide and Carboxylic Acids **3**.** To a 50 mL stainless steel autoclave were added 3-bromopyridine-4-carbaldehyde **2** (93 mg, 0.5 mmol), carboxylic acid **3** (1 mmol), PdCl₂(PPh₃)₂ (18 mg, 0.025 mmol), Et₃N (253 mg, 2.5 mmol) and MeCN (5 mL). After the system was flushed and then pressurized with carbon monoxide to 10 atm, the reaction mixture was allowed to react at 100° for 1 hour. 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 cyclized product **4**. All products prepared by the above procedure were characterized spectroscopically as shown below.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl acetate (4a**).** This compound was obtained as an oil; ¹H nmr (CDCl₃): δ 2.23 (s, 3H), 7.45 (s, 1H), 7.62 (d, J = 5.0 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 9.23 (s, 1H); ¹³C nmr (CDCl₃): δ 21.05, 92.35, 118.71,

122.81, 148.42, 152.76, 154.93, 166.42, 169.35. *Anal.* Calcd. For $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.75; H, 3.60; N, 7.27.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl propionate (4b).

This compound was obtained as a solid, mp 64–65° (hexane-chloroform); 1H nmr ($CDCl_3$): δ 1.22 (t, $J = 7.5$ Hz, 3H), 2.49 (q, $J = 7.5$ Hz, 2H), 7.47 (s, 1H), 7.60 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.23 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 9.00, 27.69, 92.34, 118.69, 122.86, 148.45, 152.89, 154.92, 166.48, 172.91. *Anal.* Calcd. For $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.80; H, 4.29; N, 6.75.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl butyrate (4c).

This compound was obtained as an oil; 1H nmr ($CDCl_3$): δ 1.00 (t, $J = 7.5$ Hz, 3H), 1.68–1.77 (m, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 7.47 (s, 1H), 7.60 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.23 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 13.88, 18.39, 36.04, 92.29, 118.67, 122.87, 148.45, 152.92, 154.92, 166.49, 172.06. *Anal.* Calcd. For $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.59; H, 4.88; N, 6.27.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl hexanoate (4d).

This compound was obtained as an oil; 1H nmr ($CDCl_3$): δ 0.91 (t, $J = 7.0$ Hz, 3H), 1.31–1.36 (m, 4H), 1.65–1.73 (m, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 7.46 (s, 1H), 7.58 (d, $J = 5.0$ Hz, 1H), 8.98 (d, $J = 5.0$ Hz, 1H), 9.23 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 14.24, 22.60, 24.53, 31.45, 34.22, 92.31, 118.63, 122.88, 148.48, 152.93, 154.90, 166.46, 172.24. *Anal.* Calcd. For $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.34; H, 6.00; N, 5.65.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl 3-methylbutanoate (4e).

This compound was obtained as an oil; 1H nmr ($CDCl_3$): δ 1.00 (d, $J = 7.0$ Hz, 6H), 2.10–2.21 (m, 1H), 2.34 (d, $J = 7.0$ Hz, 2H), 7.48 (s, 1H), 7.60 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.23 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 22.66, 25.94, 43.10, 92.25, 118.64, 122.86, 148.44, 152.94, 154.92, 166.50, 171.44. *Anal.* Calcd. For $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.02; H, 5.48; N, 5.94.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl 2-phenylacetate (4f).

This compound was obtained as a solid, mp 127–128° (hexane-chloroform); 1H nmr ($CDCl_3$): δ 3.73 (d, $J = 15.6$ Hz, 1H), 3.78 (d, $J = 15.6$ Hz, 1H), 7.26–7.36 (m, 5H), 7.43 (s, 1H), 7.51 (d, $J = 5.0$ Hz, 1H), 8.96 (d, $J = 5.0$ Hz, 1H), 9.23 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 41.16, 92.63, 118.64, 122.80, 128.12, 129.25, 129.66, 132.56, 148.51, 152.68, 155.00, 166.37, 170.15. *Anal.* Calcd. For $C_{15}H_{13}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.68; H, 4.04; N, 5.19.

(E)-3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl but-2-enoate (4g).

This compound was obtained as a solid, mp 89–90° (hexane-chloroform); 1H nmr ($CDCl_3$): δ 1.95 (dd, $J = 2.0$ and 7.0 Hz, 3H), 5.90 (dq, $J = 15.6$ and 2.0 Hz, 1H), 7.17 (dq, $J = 15.6$ and 7.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, $J = 5.0$ Hz, 1H), 8.98 (d, $J = 5.0$ Hz, 1H), 9.24 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 18.83, 92.47, 118.78, 120.92, 122.93, 148.44, 149.81, 153.06, 154.89, 164.44, 166.53. *Anal.* Calcd. For $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.01; H, 4.08; N, 6.35.

3-Oxo-1,3-dihydrofuro[3,4-c]pyridin-1-yl benzoate (4h).

This compound was obtained as a solid, mp 147–148° (hexane-chloroform); 1H nmr ($CDCl_3$): δ 7.46–7.50 (m, 2H), 7.65 (t, $J =$

7.5 Hz, 1H), 7.69 (d, $J = 5.0$ Hz, 1H), 7.70 (s, 1H), 8.05 (d, $J = 7.5$ Hz, 2H), 9.01 (d, $J = 5.0$ Hz, 1H), 9.27 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 93.01, 118.91, 122.93, 128.16, 129.14, 130.63, 134.85, 148.53, 152.97, 155.05, 165.04, 166.51. *Anal.* Calcd. For $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.78; H, 3.45; N, 5.44.

Acknowledgement. This work was supported by the Korea Research Foundation Grant funded by the Korea Government (MOEHRD, Basic Research Promotion Fund) (KRF-2007-359-C00021).

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