Note

Synthesis of alkyl 2,5-dihydro-5-oxofuran-2-carboxylates via palladium-catalyzed carbonylative cyclization of β-bromovinyl aldehydes in alcohols

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ABSTRACT

β-Bromovinyl aldehydes reacts with carbon monoxide and alcohols at 125 °C in the presence of a catalytic amount of a palladium catalyst along with a base to give the corresponding carbonylative cyclized alkyl 2,5-dihydro-5-oxofuran-2-carboxylates in good yields. A reaction pathway involving intramolecular addition of acylpalladium to formyl group is proposed as a key step of this catalytic process.

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1. Introduction

Palladium-catalyzed annulation reaction has been widely used as a convenient tool for the synthesis of many carbo- and hetero-cyclic compounds [1]. As part of our continuing studies directed towards transition metal-catalyzed cyclization reactions, we recently reported on the synthesis of several cyclic compounds using such a palladium-catalyzed cyclization protocol. Among them, several aldehydes such as β-bromovinyl aldehydes, 2-bromobenzaldehydes and 3-bromopyridine-4-carbaldehydes were found to be coupled and cyclized with suitably functionalized alkenes in the presence of a palladium catalyst to give benzenes, naphthalenes and isoquinolines, respectively, via tandem Heck and aldol reactions [2–4]. It is also reported by us that indazoles and pyrazoles can be synthesized by palladium-catalyzed intramolecular carbon–nitrogen bond forming reaction of 2-bromobenzaldehydes and β-bromovinyl aldehydes with arylhydrazines [5,6]. 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-alkoxyisobenzofuran-1(3H)-ones [7]. The present work was disclosed during the course of the extension of this carbonylative cyclization protocol to the reaction with β-bromovinyl aldehydes, which are readily prepared from ketones via the bromo analogue of Vilsmeier reaction (Scheme 1) [8]. Herein this report describes

a palladium-catalyzed cyclization of β-bromovinyl aldehydes with carbon monoxide and alcohols leading to alkyl 2,5-dihydro-5-oxofuran-2-carboxylates [9,10].

2. Results and discussion

The results of several attempted carbonylative cyclization of 2-bromocyclohex-1-enecarbaldehyde (**1a**) under various conditions are listed in Table 1. In contrast to the report on palladium-catalyzed synthesis of 3-alkoxy phthalides from 2-bromobenzaldehyde via carbonylative cyclization [7], treatment of **1a** in EtOH in the presence of PdCl$_2$(PPh$_3$)$_2$ along with Et$_3$N under carbon monoxide pressure (20 atm) afforded ethyl 1,3,4,5,6,7-hexahydro-3-oxoisobenzofuran-1-carboxylate (**2a**) in 66% yield with concomitant formation of 4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (**3**) (9% yield), no ethoxy substituted carbonylative cyclized product **4** being formed (entry 1). The reaction was monitored until **1a** had disappeared on TLC, which occurred within 1 h. In a separate experiment, we confirmed that similar treatment of 2-bromobenzaldehyde (**5**) under the employed reaction conditions afforded 3-ethoxyisobenzofuran-1(3H)-one (**6**) in 59% isolated yield as sole carbonylative cyclized product with 89% conversion of 2-bromobenzaldehyde (Scheme 2). This result indicates that **1a** is more susceptible to further carbonylation than 2-bromobenzaldehyde. All examined palladium precursors such as PdCl$_2$, Pd(OAc)$_2$ and Pd(dba)$_2$ combined with PPh$_3$ and Pd(PPh$_3$)$_4$ under the employment of Et$_3$N as base were revealed to be as similarly effective as that using PdCl$_2$(PPh$_3$)$_2$ (entries 1–5). The product yield and

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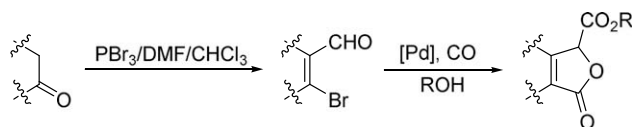
Scheme 1.

distribution were not significantly affected by the kind of palladium precursor. However, when the reaction was performed with other bases K_2CO_3 and NaOAc combined with $PdCl_2(PPh_3)_2$, the cyclization did not occur effectively towards **2a**, whereas **3** was produced as main carbonylative cyclized product (entries 6 and 7).

Having reaction conditions being established, various β-bromovinyl aldehydes were subjected to react with carbon monoxide and alcohols in order to investigate the reaction scope and several representative results are summarized in Table 2. β-Bromovinyl aldehyde **1a** was readily tethered with an array of straight and branched primary alcohols and carbon monoxide to give the corresponding alkyl 1,3,4,5,6,7-hexahydro-3-oxoisobenzofuran-1-carboxylates (**2a–c**) in the range of 61–80% yields. Here again, simple carbonylative cyclized product **3** was produced in 5–9% yields. Higher reaction rate and yield were observed with branched primary alcohol. However, when the reaction of **1a** was carried out in other alcohols such as MeOH and $(CF_3)_2CHOH$ under the employed conditions, no carbonylative cyclized esters like **2** were produced. With cyclic β-bromovinyl aldehydes (**1a–d**) having various ring sizes, the carbonylative cyclized esters (**2a, d–f**) were also formed in similar yields and the ring size of **1a–d** had no relevance to the product yield. In the reaction with 2-bromo-5-methylcyclohex-1-enecarbaldehyde (**1e**) and 2-bromo-5-pheylcyclohex-1-enecarbaldehyde (**1f**), the carbonylative cyclized products **2g** and **h** were obtained as diastereomeric mixtures. However, similar treatment of 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde scarcely afforded the corresponding carbonylative cyclized ester,
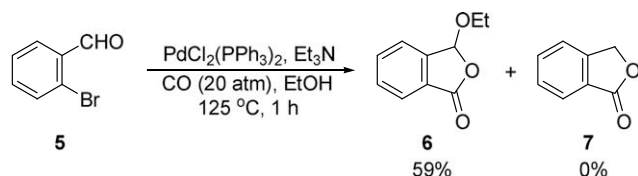

Scheme 2.

Table 2
Palladium-catalyzed synthesis of lactones **2**[a]

β-Bromovinyl aldehydes **1**	Lactones **2**	Isolated yield (%)
1a	**2a** R = Et **2b** R = Bu **2c** R = iBu	66 61 80
1b	**2d**	58
1c	**2e**	59
1d	**2f**	63
1e	**2g**	73[b]
1f	**2h**	62[b]

[a] Reaction conditions: **1** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), Et_3N (4 mmol), CO (20 atm), alcohol (10 mL), 125 °C, for 1 h.
[b] Mixture of diastereomers (1:1).

Table 1
Optimization of conditions for the reaction with **1a**[a]
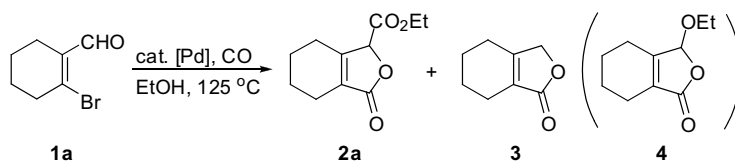
Entry	Pd catalysts	Bases	Isolated yield (%)	
			2a	**3**
1	$PdCl_2(PPh_3)_2$	Et_3N	66	9
2	$PdCl_2/2PPh_3$	Et_3N	54	9
3	$Pd(OAc)_2/2PPh_3$	Et_3N	54	9
4	$Pd(dba)_2/2PPh_3$	Et_3N	63	12
5	$Pd(PPh_3)_4$	Et_3N	64	16
6	$PdCl_2(PPh_3)_2$	K_2CO_3	0	17
7	$PdCl_2(PPh_3)_2$	NaOAc	16	33

[a] Reaction conditions: **1a** (0.5 mmol), palladium catalyst (0.02 mmol), base (4 mmol), EtOH (10 mL), CO (20 atm), 125 °C, for 1 h.

instead, simple carbonylative cyclized product like **3** was produced in 20% yield.

The present reaction, consistent with the product formed, seems to proceed via a pathway shown in Scheme 3. Oxidative addition of a carbon–bromide bond of **1a** to palladium(0) produces vinylpalladium(II) intermediate **8**, which is followed by the insertion of carbon monoxide into a carbon–palladium bond of **8** to give acylpalladium species **9**. Subsequent intramolecular addition of acylpalladium bond of **9** to neighboring formyl C=O produces cyclized alkylpalladium species **10**, which triggers further carbon monoxide insertion to produce acylpalladium **11** and ethanolysis to give **2a**. The mechanistic acylpalladium addition to ketones is known on palladium-catalyzed carbonylative cyclization of (Z)-β-iodoenones leading to γ-lactones [11,12].

For the formation of lactone **3**, adventitious water was suspected as the source of hydrogen. It seems that intermediate **10** undergoes a metallotropic shift to give a furanyl contributor **13** via an alkylpalladium intermediate **12**, which is trapped by H_2O to afford enol **14** (Scheme 4). We confirmed in a separate experiment that similar treatment of **1a** in EtOH along with the addition of H_2O (0.1 mL) afforded an increased yield of **3** (25%) with an decreased yield of **2a** (46% yield) compared with the result shown in entry 1 of Table 1 [13]. These results clearly indicate that H_2O works as a hydrogen source for the formation of **3**. It appears that adventitious water is also a hydrogen source in the synthesis of lactones like **3** via palladium-catalyzed carbonylative cyclization of β-bromovinyl aldehydes in an aprotic solvent [14]. As shown in Scheme 2, no observation of lactone **7** in the reaction with **5**

seems to be due to temporary destruction of the aromatic o-phenylene group for such a metallotropic process [12,15].

3. Conclusion

In summary, it has been shown that β-bromovinyl aldehydes undergoes carbonylative cyclization with carbon monoxide and alcohols in the presence of a catalytic amount of a palladium catalyst along with a base to give alkyl 2,5-dihydro-5-oxofuran-2-carboxylates in good yields. We believe that the present reaction will work as a useful two-step procedure for the construction of a lactone framework from ketones. Synthetic applications using the mechanistic metallotropic process are currently under investigation.

4. Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF$_{254}$, Merck). β-Bromovinyl aldehydes **1** were synthesized from the corresponding ketones by treatment of PBr$_3$/DMF/CHCl$_3$ [8]. Commercially available organic and inorganic compounds were used without further purification.

4.1. General procedure for palladium-catalyzed carbonylative cyclization of β-bromovinyl aldehydes with carbon monoxide and alcohols

To a 50 mL stainless steel autoclave were added β-bromovinyl aldehyde **1** (0.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.014 g, 0.02 mmol), Et$_3$N (0.405 g, 4 mmol) and alcohol (10 mL). After the system was flushed and then pressurized with carbon monoxide to 20 atm, the reaction mixture was allowed to react at 125 °C for 1 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 carbonylative cyclized product **2**. All products prepared by the above procedure were characterized spectroscopically as shown below.

### 4.1.1. Ethyl 1,3,4,5,6,7-hexahydro-3-oxoisobenzofuran-1-carboxylate (2a)

Oil; ^{1}H NMR (CDCl$_3$) δ 1.32 (t, J = 7.5 Hz, 3H), 1.69–1.81 (m, 4H), 2.24–2.26 (m, 2H), 2.28–2.42 (m, 2H), 4.22–4.34 (m, 2H), 5.25 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 14.50, 20.47, 21.63, 21.81, 23.71, 62.68, 80.47, 128.07, 158.79, 166.57, 173.00. Anal. Calc. for C$_{11}$H$_{14}$O$_4$: C 62.85; H 6.71. Found: C 62.58; H 6.62%.

### 4.1.2. Butyl 1,3,4,5,6,7-hexahydro-3-oxoisobenzofuran-1-carboxylate (2b)

Oil; ^{1}H NMR (CDCl$_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.34–1.43 (m, 2H), 1.62–1.78 (m, 6H), 2.24–2.26 (m, 2H), 2.34–2.37 (m, 2H), 4.22 (t, J = 6.8 Hz, 2H), 5.25 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 13.97, 19.34, 20.47, 21.64, 21.82, 23.70, 30.81, 66.47, 80.52, 128.06, 158.79, 166.66, 173.00. Anal. Calc. for C$_{13}$H$_{18}$O$_4$: C 65.53; H 7.61. Found: C 65.27; H 7.47%.

4.1.3. Isobutyl 1,3,4,5,6,7-hexahydro-3-oxoisobenzofuran-1-carboxylate (2c)

Oil; ^{1}H NMR (CDCl$_3$) δ 0.94 (d, J = 7.0 Hz, 6H), 1.69–1.81 (m, 4H), 1.93–2.03 (m, 1H), 2.25–2.31 (m, 2H), 2.33–2.42 (m, 2H), 3.95–4.04 (m, 2H), 5.26 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.28, 20.49, 21.66, 21.84,
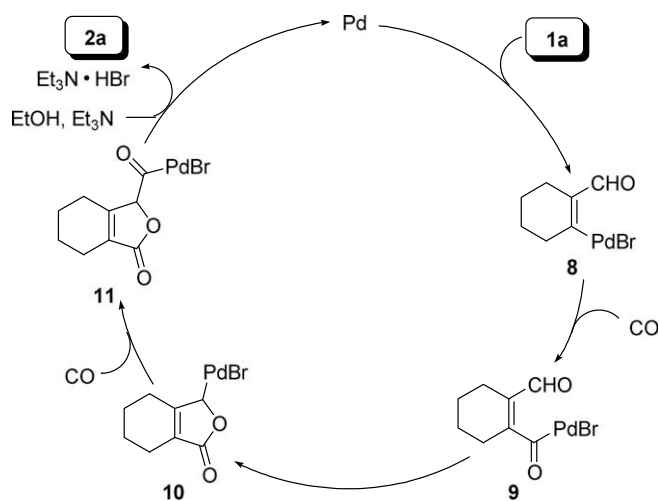
Scheme 3.
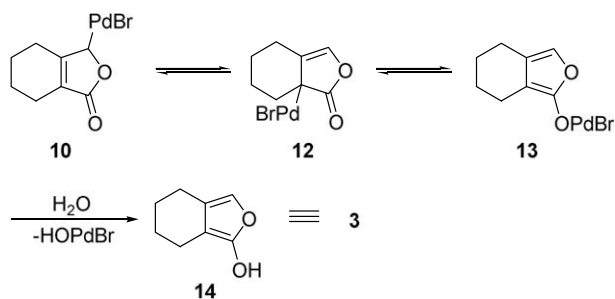
Scheme 4.

23.72, 28.02, 72.49, 80.54, 128.13, 158.72, 166.64, 172.95. Anal. Calc. for $C_{13}H_{18}O_4$: C 65.53; H 7.61. Found: C 65.36; H 7.48%.

4.1.4. Ethyl 3,4,5,6,7,8-hexahydro-3-oxo-1H-cyclohepta[c]furan-1-carboxylate (2d)

Oil; ^{1}H NMR (CDCl$_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 1.61–1.70 (m, 4H), 1.78–1.84 (m, 2H), 2.43–2.50 (m, 4H), 4.23–4.31 (m, 2H), 5.15 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 14.51, 25.52, 26.94, 26.96, 28.33, 30.84, 62.70, 80.27, 130.70, 160.21, 166.90, 174.07. Anal. Calc. for $C_{12}H_{16}O_4$: C 64.27; H 7.19. Found: C 64.22; H 7.14%.

4.1.5. Ethyl 1,3,4,5,6,7,8,9-octahydro-3-oxocyclooct a[c]furan-1-carboxylate (2e)

Oil; ^{1}H NMR (CDCl$_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 1.56–1.60 (m, 4H), 1.71–1.76 (m, 3H), 1.83–1.89 (m, 1H), 2.29–2.36 (m, 1H), 2.47–2.55 (m, 3H), 4.24–4.39 (m, 2H), 5.03 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 14.29, 22.48, 25.06, 25.20, 26.16, 26.25, 26.78, 64.33, 100.49, 131.34, 158.39, 168.57, 171.94. Anal. Calc. for $C_{13}H_{18}O_4$: C 65.53; H 7.61. Found: C 65.33; H 7.54%.

4.1.6. Ethyl 1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-3-oxocyclododeca[c]furan-1-carboxylate (2f)

Oil; ^{1}H NMR (CDCl$_3$) δ 1.25–1.50 (m, 15H), 1.57–1.64 (m, 2H), 1.69–1.75 (m, 2H), 2.33–2.41 (m, 4H), 4.23–4.36 (m, 2H), 5.04 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 13.80, 20.99, 21.79, 22.10, 22.72, 23.99, 24.21, 24.53, 24.59, 24.94, 25.00, 63.93, 99.97, 132.37, 157.27, 168.66, 171.22. Anal. Calc. for $C_{17}H_{26}O_4$: C 69.36; H 8.90. Found: C 69.18; H 8.81%.

4.1.7. Ethyl 1,3,4,5,6,7-hexahydro-6-methyl-3-oxoisobenzofuran-1-carboxylate (2g)

Oil; diastereoisomeric mixture; ^{1}H NMR (CDCl$_3$) δ 1.06 (d, J = 6.5 Hz, 3/2H), 1.07 (d, J = 6.5 Hz, 3/2H), 1.31 (t, J = 7.0 Hz, 3/2H), 1.32 (t, J = 7.0 Hz, 3/2H), 1.80–2.00 (m, 4H), 2.16–2.26 (m, 1H), 2.34–2.50 (m, 2H), 4.23–4.32 (m, 2H), 5.22 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 14.53 (x2), 20.14 (20.32), 21.31 (21.35), 28.51 (28.54), 29.91 (29.96), 31.54 (31.87), 62.68 (62.72), 80.25 (80.38), 127.91 (127.98), 158.57 (158.67), 166.57 (x2), 172.74 (x2). Anal. Calc. for $C_{12}H_{16}O_4$: C 64.27; H 7.19. Found: C 64.21; H 7.05%.

4.1.8. Ethyl 1,3,4,5,6,7-hexahydro-3-oxo-6-phenylisobenzofuran-1-carboxylate (2h)

Oil; diastereoisomeric mixture; ^{1}H NMR (CDCl$_3$) δ 1.30 (t, J = 7.0 Hz, 3/2H), 1.31 (t, J = 7.0 Hz, 3/2H), 1.76–1.90 (m, 1H), 2.09–2.13 (m, 1H), 2.30–2.54 (m, 3H), 2.67–2.75 (m, 1H), 2.90–3.00 (m, 1H), 4.28 (q, J = 7.0 Hz, 2H), 5.28–5.30 (m, 1H), 7.20–7.27 (m, 3H), 7.32–7.36 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 14.16 (x2), 20.58 (x2), 28.85 (29.09), 30.79 (31.29), 39.46 (39.57), 62.41 (62.44), 79.69 (79.91), 126.75 (126.76), 126.85 (x2), 127.75 (127.82), 128.76 (x2), 144.35 (x2), 158.04 (158.12), 166.07 (x2),

172.04 (172.11). Anal. Calc. for $C_{17}H_{18}O_4$: C 71.31; H 6.34. Found: C 71.14; H 6.25%.

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[15] A reviewer suggested that observation of oxidation products derived from β-hydrogen elimination of alcohol should be described. However, GLC analysis attempt to detect an aldehyde from crude mixture met with failure.