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An unusual palladium-catalyzed carbonylative cyclization of β-bromovinyl aldehydes leading to lactones

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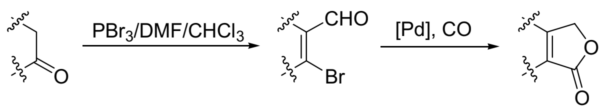
Abstract—β-Bromovinyl aldehydes are carbonylatively cyclized under carbon monoxide pressure in MeCN at 100 °C in the presence of a catalytic amount of a palladium catalyst along with a base to give the corresponding lactones in high yields.

Palladium-catalyzed carbonylative cyclization process 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] Many methods for such a palladium-catalyzed version have also been attempted for the construction of lactones because of the facility and efficiency of reaction and the wide availability of substrate.[2] During the course of our ongoing studies on palladium-catalyzed cyclization reactions, we also recently reported on the synthesis of various heterocycles such as isoindolinones,[3] β-lactams[4] and phthalides[5] via a carbonylative cyclization. Among them, in connection with this report, 2-bromobenzaldehyde was found to be cyclized with carboxylic acids in the presence of a palladium catalyst and a base under carbon monoxide pressure to afford 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates.[6] The present work was disclosed during the course of the extension of this protocol to the reaction with β-bromovinyl aldehydes, which are readily prepared from ketones via the bromo analogue of Vilsmeier reaction (Scheme 1).[7] Herein, we describe an unusual palladium-catalyzed lactonization of β-bromovinyl aldehydes via intrinsic carbonylative cyclization.[8]

The results of several attempted carbonylative cyclizations of 2-bromocyclohex-1-enecarbaldehyde (**1a**) under various conditions are listed in Table 1. In contrast to our recent report on palladium-catalyzed synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates from 2-bromobenzaldehyde and carboxylic acids,[6] treatment of **1a** with 4 equiv of acetic acid in MeCN in the presence of $PdCl_2/4PPh_3$ along with Et_3N under carbon monoxide pressure (20 atm) afforded 4,5,6,7-tetrahydro-3*H*-isobenzofuran-1-one (**2a**) in 53% yield, no cyclized product **3** incorporated with acetic acid being produced (entry 1).[9] This result indicates that the present cyclization proceeds irrespective of acetic acid. Thus, when the reaction was carried out in the absence of acetic acid, **2a** was also obtained as a sole cyclized product with complete conversion of **1a** on TLC (entry 2).[10] However, the present reaction did not proceed at all under atmospheric pressure of CO. The reaction was monitored until **1a** had disappeared on TLC, which occurred within 3 h. From the activity of several palladium precursors examined under the employment of Et_3N as base, $PdCl_2(PPh_3)_2$ is revealed to be the catalyst of choice (entries 2–7). Other palladium catalytic systems such as $PdCl_2/4PPh_3$, $Pd(OAc)_2/4PPh_3$ and $Pd(PPh_3)_4$ were moderately effective for the formation of **2a**. With other bases such as K_2CO_3 and NaOAc combined with $PdCl_2(PPh_3)_2$, the yield of **2a** was lower than that when Et_3N was employed (entries 8 and 9).



Scheme 1.

Keywords: β-Bromovinyl aldehydes; Carbon monoxide; Carbonylative cyclization; Lactones; Palladium catalyst.

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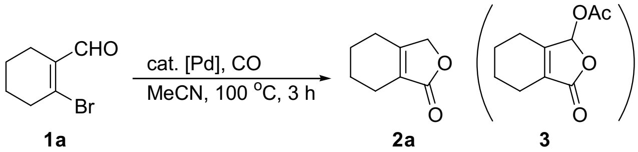
Table 1. Palladium-catalyzed carbonylative cyclization of **1a** under various conditions[a]



Entry	Palladium catalysts	Bases	Isolated yield (%)
1[b]	PdCl$_2$/4PPh$_3$	Et$_3$N	53
2	PdCl$_2$/4PPh$_3$	Et$_3$N	62
3	Pd(OAc)$_2$/4PPh$_3$	Et$_3$N	65
4	PdCl$_2$(PhCN)$_2$	Et$_3$N	52
5	Pd(dba)$_2$	Et$_3$N	47
6	Pd(PPh$_3$)$_4$	Et$_3$N	66
7	PdCl$_2$(PPh$_3$)$_2$	Et$_3$N	85
8	PdCl$_2$(PPh$_3$)$_2$	K$_2$CO$_3$	34
9	PdCl$_2$(PPh$_3$)$_2$	NaOAc	59

[a] Reaction conditions: **1a** (0.5 mmol), palladium catalyst (0.025 mmol), base (2 mmol), CO (20 atm), MeCN (5 mL), 100 °C, for 3 h.

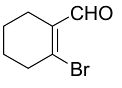
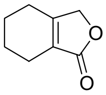
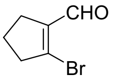
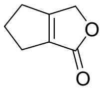
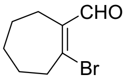
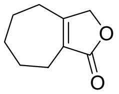
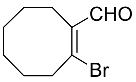
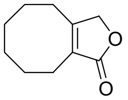
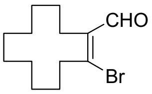
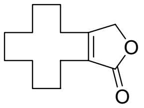
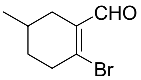
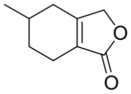
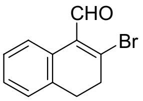
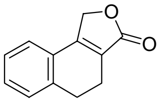
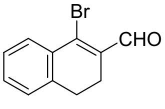
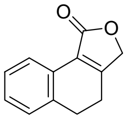
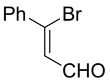
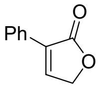
[b] Acetic acid (2 mmol) was added.

Having the established reaction conditions, various β-bromovinyl aldehydes were subjected to cyclize with carbon monoxide in order to investigate the reaction scope and several representative results are summarized in Table 2. With cyclic β-bromovinyl aldehydes (**1a**–**e**), the carbonylative cyclized α,β-butenolides (**2a**–**e**) were formed in the range of 79–89% yields without any identifiable side product. Here again, the starting substrates completely disappeared within 3 h. The product yield was not significantly affected by the ring size of **1a**–**e**. Bromo-5-methylcyclohex-1-enecarbaldehyde (**1f**) was also cyclized under the employed conditions to give 5-methyl-4,5,6,7-tetrahydro-3*H*-isobenzofuran-1-one (**2f**) in 78% yield. To test for the effect of the position of formyl group and bromide on cyclic β-bromovinyl aldehydes, **1g** and **1h** were employed. However, the carbonylative cyclization took place similarly irrespective of the position. Lower reaction rate and yield were observed with acyclic β-bromovinyl aldehyde **1i**,[11] the carbonylative cyclized product 3-phenyl-5*H*-furan-2-one (**2i**) being obtained in only 23% yield (24% yield for 20 h).

As to the reaction pathway, it seems to proceed via the initial carbonyl reduction of β-bromovinyl aldehyde to bromoallyl alcohol, which in turn triggers carbonylative cyclization to give α,β-butenolide. However, unfortunately, we confirmed in a separate experiment that 2-bromocyclohex-1-enylmethanol did not undergo carbonylative cyclization under the employed conditions. Thus, this result indicates that the present reaction excludes the initial carbonyl reduction pathway.

General experimental procedure: To a 50 mL stainless steel autoclave were added β-bromovinyl aldehyde **1** (0.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.025 mmol), Et$_3$N (2 mmol) and MeCN (5 mL). After the system was flushed and then pressurized with carbon monoxide to 20 atm, the mixture was stirred at 100 °C for 3 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–hexane) 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 α,β-butenolides **2**.

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

β-Bromovinyl aldehydes **1**	Lactones **2**	Yield (%)
 **1a**	 **2a**	85
 **1b**	 **2b**	79
 **1c**	 **2c**	86
 **1d**	 **2d**	80
 **1e**	 **2e**	89
 **1f**	 **2f**	78
 **1g**	 **2g**	61
 **1h**	 **2h**	73
 **1i**	 **2i**	23

[a] Reaction conditions: **1** (0.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.025 mmol), Et$_3$N (2 mmol), CO (20 atm), MeCN (5 mL), 100 °C, for 3 h.

In summary, we have demonstrated that β-bromovinyl aldehydes undergo an unusual carbonylative cyclization under carbon monoxide pressure in the presence of a palladium catalyst and a base to afford α,β-butenolides. The mechanistic rationale and synthetic applications are currently under investigation.

Acknowledgement

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