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Palladium-catalyzed carbonylative cyclization of 3-bromoallyl alcohols leading to furan-2(5*H*)-ones

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3-Bromoallyl alcohols are carbonylatively cyclized under carbon monoxide pressure in toluene in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 along with Na_2CO_3 to give furan-2(5*H*)-ones in good yields. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: 3-bromoallyl alcohol; carbon monoxide; cyclization; furan-2(5*H*)-one; palladium catalyst

Introduction

Transition metal-catalyzed carbonylation followed by cyclization (carbonylative cyclization) has been widely explored and used as a promising synthetic tool for the construction of the structural core of many pharmacologically and biologically active lactones and lactams.[1–7] During the course of our ongoing studies on palladium-catalyzed cyclization reactions using β-bromo-α, β-unsaturated aldehydes and their derivatives,[8–11] which are readily prepared from the corresponding ketones by Vilsmeier–Haack reaction[12,13] and subsequent transformation and used as a building block for the construction of versatile cyclic compounds,[14–36] we recently reported on the synthesis of several heterocycles via such a carbonylative cyclization. For example, β-bromovinyl aldehydes were found to be cyclized under carbon monoxide pressure in MeCN and alcohols in the presence of a palladium catalyst to give furan-2(5*H*)-ones.[37,38] Such a similar palladium-catalyzed carbonylative cyclization was also exemplified by the reaction of β-bromo-α, β-unsaturated ketones under carbon monoxide pressure to give (*Z*)-alkylidenefuranones.[39] It is also disclosed that 2-bromocyclohex-1-enecarbaldehydes react with anilines under carbon monoxide pressure in the presence of a palladium catalyst to afford hydroisoindol-1-ones.[40] Prompted by these findings, such an intrinsic palladium-catalyzed carbonylative cyclization protocol led us to seek for a promising route for other heterocyclic compounds using β-bromovinyl aldehyde and its derivatives. Herein, this report describes palladium-catalyzed carbonylative cyclization of 3-bromoallyl alcohols leading to furan-2(5*H*)-ones.

Results and Discussion

The starting 3-bromoallyl alcohols **3** were synthesized by initial conversion of the corresponding α-methylene containing cyclic and acyclic ketones **1** into β-bromovinyl aldehydes **2** under bromination conditions of Vilsmeier–Haack reaction (PBr_3/DMF/$CHCl_3$) (Scheme 1).[12,13] This is followed by the reaction with organomagnesium bromides in THF and subsequent quenching with saturated aqueous ammonium chloride solution to afford 3-bromoallyl alcohols **3**.[41]

To investigate the effect of reaction variants such as CO pressure, reaction temperature and time for the carbonylative cyclization, 1-(2-bromocyclohex-1-enyl)pentan-1-ol (**3a**) was chosen as a model substrate. Treatment of **3a** in toluene at 150°C in the presence of $Pd(OAc)_2$ and PPh_3 along with Na_2CO_3 under carbon monoxide pressure (10 atm) afforded **4a** in 28% isolated yield with 51% conversion of **3a** (entry 1). Either higher carbon monoxide pressure or longer reaction time resulted in an increased yield of **4a** with increased conversion of **3a** (entries 2 and 3). However, no significant synergic effect was observed with both conditions (entry 4). Performing the reaction at lower reaction temperature produced a slightly decreased yield of **4a** (entry 5). In spite of further elaboration for the optimization of reaction conditions, the best result in terms of the conversion of **3a** and the yield of **4a** is best accomplished under the standard set of condition shown in entry 4 of Table 1.

After the reaction conditions have been established, various 3-bromoallyl alcohols **3** were subjected to carbonylative cyclization in order to investigate the reaction scope and several representative results are summarized in Table 2. 3-Bromoallyl alcohol **3b** having phenyl group at allylic position was also cyclized under the employed conditions to give 3-phenyl-4,5,6,7-tetrahydroisobenzofuran-1(3*H*)-one (**4b**) in 47% yield. With cyclic 3-bromoallyl alcohols (**3a, 3c–f**) having various ring sizes, the carbonylative cyclized products (**4a, 4c–f**) were formed in the range of 31–85% yields and the product yield was considerably affected by the ring size of **3a** and **3c–f**. Lower reaction rate and yield were observed with **3e** and **3f**, having larger ring size. To test for the effect of the position of bromide and carbinol group on 3-bromoallyl alcohols, **3g** and **3h** were

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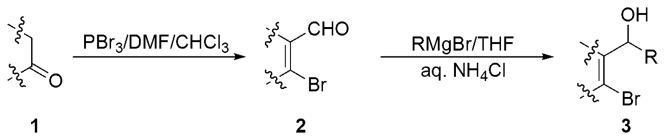
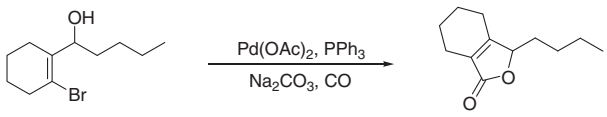


Scheme 1. Synthesis of 3-bromoallyl alcohols

Table 1. Optimization of conditions for the carbonylative cyclization of **3a**[a]



3a **4a**

Entry	Pressure of CO (atm)	Temp. (°C)	Time (h)	Conv. of **3a** (%)	Yield (%)
1	10	150	20	51	28
2	10	150	40	83	72
3	20	150	22	75	64
4	20	150	40	86	77
5	20	120	20	69	57

[a]Reaction conditions: **3a** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Na_2CO_3 (2 mmol), toluene (5 ml).

employed. The present carbonylative cyclization readily took place with both **3g** and **3h** irrespective of their position. Similar treatment of acyclic 3-bromoallyl alcohols (**3i** and **3j**) under the employed conditions also afforded the carbonylative cyclized products (**4i** and **4j**), however, the yield was lower than that when previously described cyclic 3-bromoallyl alcohols were used, except for **3e** and **3f**. In the reaction of **3j**, since the product **4j** was not possible to separate from the reaction mixture using column or thin-layer chromatography, the yield was analyzed from the intensity of the clearly separated allylic proton signal of **4j** based on anisole as an internal standard in ^{1}H NMR spectrum.[42]

The reaction seems to proceed as shown in Scheme 2. Oxidative addition of the carbon–bromide bond of 3-bromoallyl alcohol **3** to palladium(0) produces a vinylpalladium(II) complex **5**, where carbon monoxide coordination to palladium and then vinyl migration from palladium to the carbon of carbon monoxide occurs to give an acylpalladium(II) intermediate **6**. The elimination of HBr by a base occurs in intermediate **6** to produce a palladacycle intermediate **7**, which can reductively eliminate to give **4**.

Conclusion

In summary, we have demonstrated that 3-bromoallyl alcohols, which are readily prepared from α-methylene containing ketones in two steps, are carbonylatively cyclized to furan-3(5*H*)-ones in the presence of a palladium catalyst along with a base. The present reaction provides a promising route for the synthesis of valuable heterocycles from readily available starting ketones. Further study of synthetic applications to heterocycles by using this ketone as starting compound is in progress.

Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. The isolation of pure products was carried out via column (silica gel 60, 70–230 mesh, Merck) chromatography. 3-Bromoallyl alcohols **3** were synthesized in two steps: initial treatment of ketones **1** with PBr_3/DMF/$CHCl_3$[12,13] to produce β-bromovinyl aldehydes **2** and subsequent conversion of **2** into **3** by Grignard addition.[41] Commercially available organic and inorganic compounds were used without further purification.

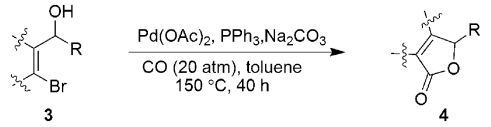
General Experimental Procedure

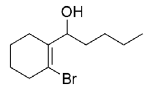
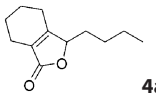
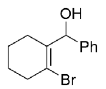
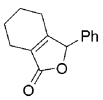
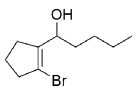
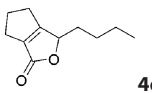
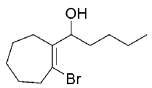
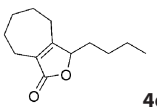
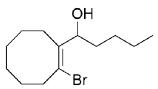
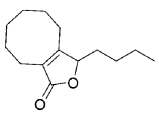
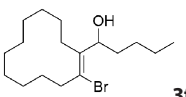
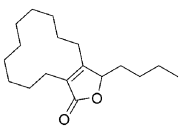
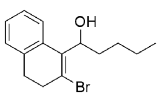
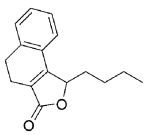
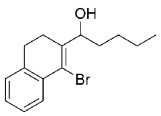
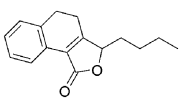
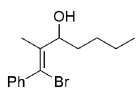
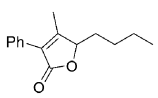
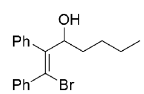
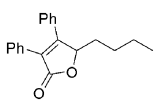
To a 50 ml stainless steel autoclave were added 3-bromoallyl alcohol (0.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol), Na_2CO_3 (0.212 g, 2 mmol), and toluene (5 ml). After the system was flushed and then pressurized with carbon monoxide to 10–20 atm, the reaction mixture was allowed to react at 120–150°C for 20–40 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate the precipitate. Removal of the solvent left a crude mixture, which was separated by column chromatography (hexane/ethyl acetate = 10/1) to give furan-3(5*H*)-ones. Except for known **4a**,[43] **4b**,[44] **4g**,[45]**4h**[46] and **4i**,[47] all new products prepared by the above procedure were characterized spectroscopically as shown below.

3-Butyl-5,6-dihydro-3H-cyclopenta[*c*]furan-1(4*H*)-one (**4c**)

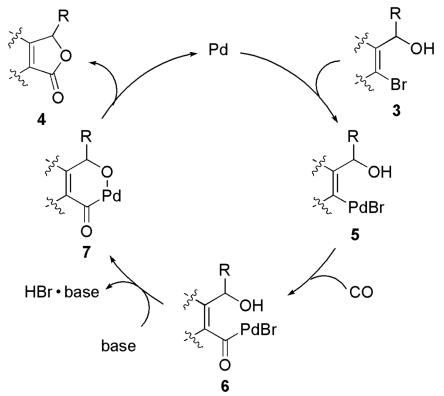
Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J_{HH} = 6.9 Hz, 3H, CH_3), 1.31–1.45 (m, 4H, $2CH_2$), 1.58–1.67 (m, 1H, $1/2CH_2$), 1.75–1.83 (m, 1H, $1/2CH_2$), 2.42–2.54 (m, 4H, $2CH_2$), 2.56–2.61 (m, 2H, CH_2), 4.92–4.95 (m, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02

Table 2. Palladium-catalyzed carbonylative cyclization of 3-bromoallyl alcohols **3** leading to furan-3(5*H*)-ones **4**[a]



3-bromoallyl alcohols **3**		furan-3(5*H*)-ones **4**		Isolated yield (%)
	**3a**		**4a**	37
	**3b**		**4b**	47
	**3c**		**4c**	80
	**3d**		**4d**	85
	**3e**		**4e**	36
	**3f**		**4f**	31
	**3g**		**4g**	94
	**3h**		**4h**	84
	**3i**		**4i**	52
	**3j**		**4j**	48

[a]Reaction conditions: 3 (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Na_2CO_3 (2 mmol), CO (20 atm), toluene (5 ml), 150°C, for 40 h.
[b]Determined by ^1H NMR.



Scheme 2. A catalytic cycle

(CH_3), 22.57 (CH_2), 25.13 (CH_2), 27.02 (CH_2), 28.84 (CH_2), 28.95 (CH_2), 32.54 (CH_2), 80.74 (OCH), 137.41 (=CCO), 169.78 (=*C*), 177.30 (*C*=O). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.10; H, 8.87.

3-Butyl-5,6,7,8-tetrahydro-3H-cyclohepta[*c*]furan-1(4*H*)-one (**4d**)

Solid; m.p. 38–39°C (from hexane–ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J_{HH} = 7.1 Hz, 3H, CH_3), 1.24–1.50 (m, 6H, $3CH_2$), 1.53–1.94(m, 8H, $4CH_2$), 2.34–2.37 (m, 2H, CH_2), 4.70–4.72 (m, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.07 (CH_3), 22.63 (CH_2), 25.06 (CH_2), 26.92 (CH_2), 26.95 (CH_2), 27.09 (CH_2), 28.44 (CH_2), 30.80 (CH_2), 31.78 (CH_2), 82.66 (OCH), 129.30 (=*C*CO), 165.77 (=*C*), 174.81 (*C*=O). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.04; H, 9.73.

*3-Butyl-4,5,6,7,8,9-hexahydrocycloocta[c]*furan-1(3*H*)-one (**4e**)

Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J_{HH} = 7.1 Hz, 3H, CH_3), 1.28–1.62 (m, 9H, 9/2CH_2), 1.63–1.74 (m, 2H, CH_2), 1.76–1.83 (m, 2H, CH_2), 1.85–1.95 (m, 1H, 1/2CH_2), 2.43–2.48 (m, 4H, $2CH_2$), 4.72–4.74 (m, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.08 (CH_3), 22.14 (CH_2), 22.64 (CH_2), 25.43 (CH_2), 25.94 (CH_2), 26.13 (CH_2), 26.71 (CH_2), 27.08 (CH_2), 27.23 (CH_2), 32.19 (CH_2), 82.83 (OCH), 127.25 (=*C*CO), 164.37 (=*C*), 174.74 (*C*=O). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.45; H, 9.97.

*3-Butyl-4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[c]*furan-1(3*H*)-one (**4f**)

Solid; m.p. 88–89°C (from hexane–ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J_{HH} = 6.9 Hz, 3H, CH_3), 1.12–1.70 (m, 20H, $10CH_2$), 1.76–1.81(m, 1H, 1/2CH_2), 1.87–1.91 (m, 1H, 1/2CH_2), 2.05–2.13 (m, 1H, 1/2CH_2), 2.25–2.36 (m, 2H, CH_2), 2.64–2.71 (m, 1H, 1/2CH_2), 4.83–4.85 (m, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09 (CH_3), 21.00 (CH_2), 21.77 (CH_2), 22.64 (CH_2), 22.87 (CH_2), 23.49 (CH_2), 23.52 (CH_2), 24.49 (CH_2), 25.30 (CH_2), 25.34 (CH_2), 25.38 (CH_2), 26.77 (CH_2), 32.10 (CH_2), 81.69 (OCH), 127.19 (=*C*CO), 164.43 (=*C*), 174.64 (*C*=O). Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.66; H, 10.96.

Acknowledgments

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