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Palladium-Catalyzed Carbonylative Cyclization of β-Bromo-α,β-Unsaturated Ketones Leading to Alkylidenefuranones

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Abstract β-Bromo-α,β-unsaturated ketones are carbonylatively cyclized to (*Z*)-alkylidenefuranones in good yields under carbon monoxide pressure in DMF in the presence of a catalytic amount of a palladium catalyst along with Et_3N.

Keywords Alkylidenefuranones · β-Bromo-α,β-unsaturated ketones · Carbon monoxide · Cyclization · Palladium catalyst

1 Introduction

Transition metal-catalyzed carbonylation followed by cyclization (carbonylative cyclization) has been used as convenient and efficient synthetic tool for the construction of the structural core of many pharmacologically and biologically active lactones and lactams [1–6]. During the course of our ongoing studies on palladium-catalyzed cyclization reactions [7–12], we also developed on the synthetic methods for several lactones and lactams via such an intrinsic palladium-catalyzed carbonylative cyclization [13–16]. Among them, in connection with this report, 2-bromobenzaldehyde and 2-bromocyclohex-1-enecarbaldehydes were found to be carbonylatively cyclized with primary amines in the presence of a palladium catalyst under carbon monoxide pressure to afford isoindol-1-ones and hydroisoindol-1-ones, respectively [17, 18]. A reaction pathway involving initial condensation to form an imine, carbonylation and subsequent intramolecular acylpalladation to carbon–nitrogen double bond and reduction was proposed for these catalytic processes (Scheme 1). The present work was disclosed during the course of the extension of this carbonylative cyclization protocol to the reaction with β-bromo-α,β-unsaturated ketones in order to synthesize 3-substituted lactams. Herein, as an example for the application of β-bromovinyl aldehydes to the construction of versatile cyclic compounds [9, 10, 15, 16, 18–38], this report describes a palladium-catalyzed carbonylative cyclization of β-bromo-α,β-unsaturated ketones leading to alkylidenefuranones.

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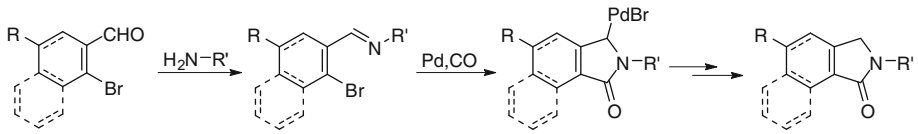
2 Results and Discussion

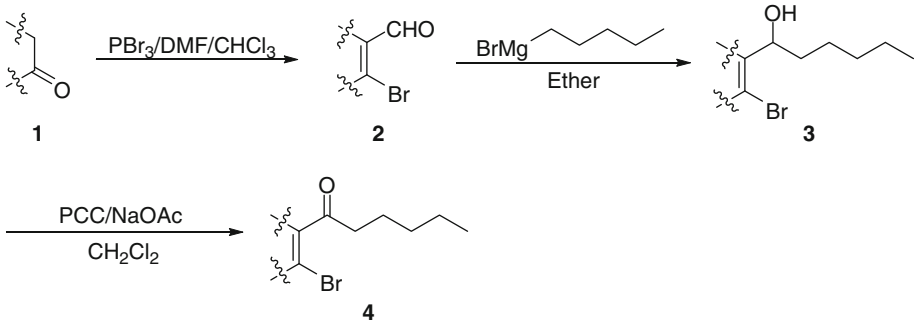
The substrates **4** were synthesized by three steps from the corresponding α-methylene containing cyclic and acyclic ketones **1** (Scheme 2). β-Bromovinyl aldehydes **2** were prepared by treating **1** under the reaction condition of the bromo analogue of Vilsmeier reaction (PBr_3/DMF/$CHCl_3$) [39]. Allyl alcohols **3** synthesized by the reaction with pentylmagnesium bromide in THF and subsequent quenching with saturated aqueous ammonium chloride solution were easily oxidized to β-bromo-α,β-unsaturated ketones **4** under PCC (pyridinium chlorochromate) [40].

Based on our recent report on palladium-catalyzed synthesis of isoindol-1-ones and hydroisoindol-1-ones by the reaction of 2-bromobenzaldehyde and 2-bromocyclohex-1-enecarbaldehydes with primary amines [17, 18], we attempted similar carbonylative cyclization of β-bromo-α,β-unsaturated ketone **4a** with aniline (**5**) in order to produce 3-alkyl substituted hydroisoindol-1-one **6** (Scheme 3). However, when **4a** was treated with equimolar amount of **5** under the reaction condition used for synthesis of isoindol-1-ones and hydroisoindol-1-ones [$PdCl_2(PhCN)_2$ (4 mol%), CO (10 atm), DMF, 100 °C, 20 h], the desired carbonylative

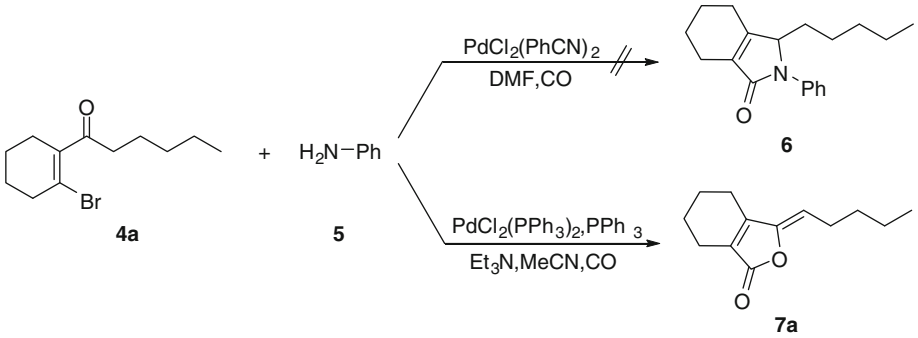
Scheme 1 A reaction pathway for the synthesis of isoindol-1-ones and hydroisoindol-1-ones



Scheme 2 Synthesis of β-bromo-α,β-unsaturated ketones



Scheme 3 Palladium-catalyzed reactions of **4a** with **5**



cyclized product **6** was not formed at all. The present reaction was found during the course of continuous attempts to realize the carbonylative cyclization toward **6**. For an example, treatment of **4a** with 2 equiv. of **5** under carbon monoxide pressure (15 atm) in acetonitrile at 120 °C for 20 h in the presence of $PdCl_2(PPh_3)_2$ (4 mol%), PPh_3 (10 mol%) and Et_3N (6 equiv.) afforded pentylidenefuranone **7a**, rather than **6**, in 52% isolated yield with 69% conversion of **4a**. The configuration of the product was determined by comparing the chemical shift of vinyl proton signal in ^{1}H NMR with that of a compound having a similar structural backbone. It is known that the chemical shift of vinyl proton of naturally occurring 6,7-dihydroligustilide (*Z*)-butylidene analogue of **7a** appears at δ 5.11 ppm [41]. It appears that the configuration of the product is (*Z*)-isomer as this chemical shift is exactly in accordance with that of the vinyl proton of **7a** and it is also known that the chemical shift of vinyl proton of (*E*)-isomer is shifted downfield from that of (*Z*)-isomer [42].

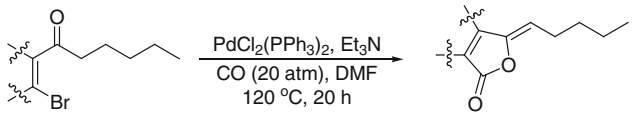
After further elaborated tuning on reaction conditions, the best result in terms of both product **7a** yield and effective conversion of **4a** was best accomplished by the standard set of reaction conditions shown in footnote of Table 1. Various cyclic and acyclic β-bromo-α,β-unsaturated ketones **4** were subjected to the reaction under the optimized conditions in order to investigate the reaction scope and several representative results are summarized in Table 1. With cyclic β-bromo-α,β-unsaturated ketones (**4a**–**g**), the carbonylative cyclized pentylidenefuranones (**7a**–**g**) were formed in the range of 38–70% yields without any identifiable side product. Here again, all pentylidenefuranones were produced with (*Z*)-configuration. The ring size of **4a**–**g** had some relevance to the product yield. Lower reaction rate and yield were observed with five and twelve membered cyclic β-bromo-α,β-unsaturated ketones (**4b** and **4g**). The reaction proceeds likewise with benzo-fused cyclic β-bromo-α,β-unsaturated ketone **4h** to give the corresponding carbonylative cyclized product **7h** in similar yield. Similar treatment of acyclic β-bromo-α,β-unsaturated ketone **4i** under the employed conditions also afforded the carbonylative cyclized product **7i**, however, the yield was lower than that when previously described β-bromo-α,β-unsaturated ketones were used except for **4g**.

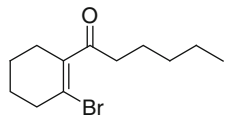
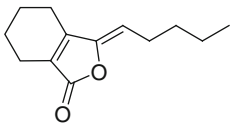
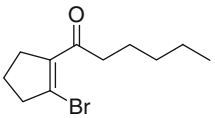
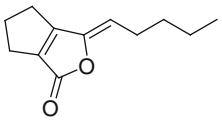
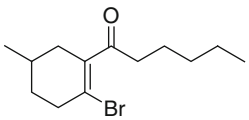
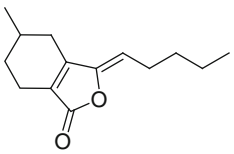
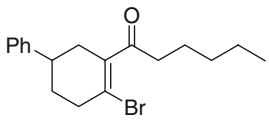
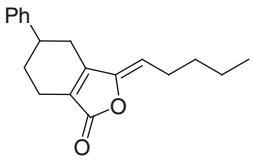
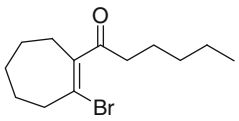
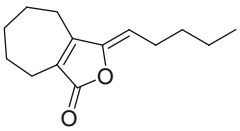
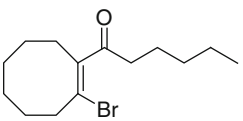
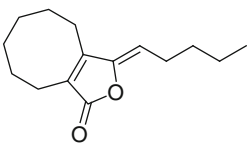
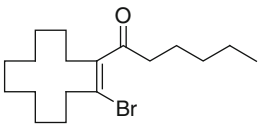
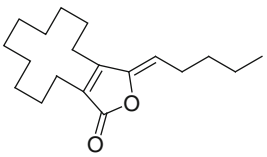
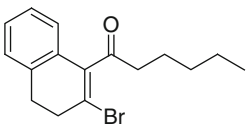
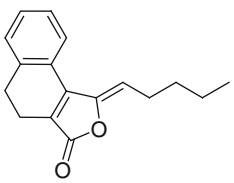
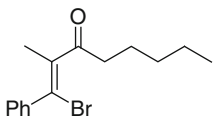
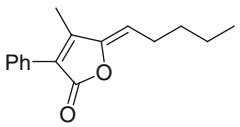
3 Experimental

3.1 General

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer

Table 1 Palladium-catalyzed carbonylative cyclization of β-bromo-α,β-unsaturated ketones



β-Bromo-α,β-unsaturated ketones **4**		Alkylidenefuranones **7**		Yield (%)
	4a		7a	66
	4b		7b	49
	4c		7c	66
	4d		7d	70
	4e		7e	70
	4f		7f	66
	4g		7g	38
	4h		7h	65
	4i		7i	43

Reaction conditions: **4** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol), Et_3N (1 mmol), DMF (5 mL)
CO (20 atm), at 120 °C, for 20 h

using TMS as an internal standard. IR spectra were measured on a Shimadzu FT IR-8400S spectrophotometer. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). β-Bromovinyl aldehydes **2** were synthesized from the corresponding ketones by treatment of PBr_3/DMF/$CHCl_3$ [39]. The aldehydes **2** were transformed to β-bromo-α,β-unsaturated ketones **4** through Grignard addition followed by oxidation with PCC [40]. Commercially available organic and inorganic compounds were used without further purification.

3.2 General Experimental Procedure

To a 50 mL stainless steel autoclave were added β-bromo-α,β-unsaturated ketone (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.018 g, 0.025 mmol), Et_3N (0.101 g, 1 mmol) and DMF (5 mL). After the system was flushed and then pressurized with carbon monoxide to 20 atm, the reaction mixture was allowed to react at 120 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate–hexane mixture) to eliminate black precipitate. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give (*Z*)-alkylidenefuranones **7**. All products prepared by the above procedure were characterized spectroscopically as shown below.

3.3 Characterization Data

(3*Z*)-4,5,6,7-Tetrahydro-3-pentylideneisobenzofuran-1(3*H*)-one (**7a**): Oil; IR (neat) 2932, 2862, 1759, 1674, 1643, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.31–1.47 (m, 4H), 1.75–1.76 (m, 4H), 2.30–2.39 (m, 6H), 5.11 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.04, 20.17, 21.23, 21.62, 21.89, 22.56, 25.73, 31.51, 110.93, 126.98, 149.28, 151.32, 170.26. Anal. ($C_{13}H_{18}O_2$) calcd: C, 75.69; H, 8.80. Found: C, 75.48; H, 8.75.

(3*Z*)-5,6-Dihydro-3-pentylidene-3*H*-cyclopenta[*c*]furan-1(4*H*)-one (**7b**): Oil; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.31–1.48 (m, 4H), 2.32–2.38 (m, 2H), 2.43–2.50 (m, 2H), 2.57–2.60 (m, 2H), 2.63–2.67 (m, 2H), 5.09 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.04, 22.56, 25.56, 25.94, 26.74, 28.97, 31.40, 113.64, 137.53, 146.05, 164.68, 166.06. Anal. ($C_{12}H_{16}O_2$) calcd: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.30.

(3*Z*)-4,5,6,7-Tetrahydro-5-methyl-3-pentylideneisobenzofuran-1(3H)-one (**7c**): Oil; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.31–1.46 (m, 5H), 1.79–2.00 (m, 3H), 2.21–2.30 (m, 1H), 2.33–2.53 (m, 4H), 5.11 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.03, 19.96, 21.35, 22.55, 25.72, 28.28, 29.33, 30.19, 31.50, 110.95, 126.74, 149.13, 151.36, 170.08. Anal. ($C_{14}H_{20}O_2$) calcd: C, 76.33; H, 9.15. Found: C, 76.13; H, 9.14.

(3*Z*)-4,5,6,7-Tetrahydro-3-pentylidene-5-phenylisobenzofuran-1(3*H*)-one (**7d**): Solid; MP 72.8–73.3 °C (from hexane-EtOAc); ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.31–1.47 (m, 4H), 1.80–1.90 (m, 1H), 2.09–2.15 (m, 1H), 2.35–2.57 (m, 5H), 2.70–2.76 (m, 1H), 2.90–2.97 (m, 1H), 5.12 (t, J = 7.8 Hz, 1H), 7.23–7.28 (m, 3H), 7.33–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.02, 20.73, 22.54, 25.76, 29.20, 29.51, 31.47, 39.73, 111.37, 126.78, 126.97, 126.98, 128.92, 144.97, 148.86, 151.18, 169.80. Anal. ($C_{19}H_{22}O_2$) calcd: C, 80.82; H, 7.85. Found: C, 80.57; H, 7.80.

(3*Z*)-5,6,7,8-Tetrahydro-3-pentylidene-3*H*-cyclohepta[*c*]furan-1(4*H*)-one (**7e**): Oil; IR (neat) 2924, 2855, 1751, 1667, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.31–1.48 (m, 4H), 1.60–1.72 (m, 4H), 1.80–1.86 (m, 2H), 2.34–2.40 (m, 2H), 2.46–2.51 (m, 4H), 5.25 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.59, 25.00, 26.09, 26.22, 26.82, 26.92, 31.04, 31.56, 111.42, 129.70, 149.26, 153.24, 170.93. Anal. ($C_{14}H_{20}O_2$) calcd: C, 76.33; H, 9.15. Found: C, 76.09; H, 9.17.

(3*Z*)-4,5,6,7,8,9-Hexahydro-3-pentylidenecycloocta[*c*]furan-1(3*H*)-one (**7f**): Oil; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.33–1.38 (m, 2H), 1.40–1.47 (m, 2H), 1.48–1.53 (m, 4H), 1.68–1.76 (m, 4H), 2.35–2.41 (m, 2H), 2.48–2.51 (m, 2H), 2.56–2.59 (m, 2H), 5.22 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.46, 22.58, 23.46, 25.70, 25.83, 25.98, 27.89, 28.10, 31.55, 111.06, 128.08, 149.12, 151.90, 170.89. Anal. ($C_{15}H_{22}O_2$) calcd: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.40.

(3*Z*)-4,5,6,7,8,9,10,11,12,13-Decahydro-3-pentylidene cyclododeca[*c*]furan-1(3*H*)-one (**7g**): Oil; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.24–1.48 (m, 16H), 1.64–1.75 (m, 4H), 2.32–2.40 (m, 4H), 2.44–2.48 (m, 2H), 5.22 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 21.35, 22.05, 22.17, 22.51, 22.62, 24.42, 24.75, 24.95, 25.67, 25.75, 25.98, 27.70, 31.59, 112.04, 128.44, 149.45, 151.74, 170.98. Anal. ($C_{19}H_{30}O_2$) calcd: C, 78.57; H, 10.41. Found: C, 78.48; H, 10.35.

(1*Z*)-4,5-Dihydro-1-pentylidenenaphtho[2,1-*c*]furan-3(1*H*)-one (**7h**): Oil; ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.36–1.45 (m, 2H), 1.49–1.56 (m, 2H), 2.48–2.53 (m, 2H), 2.58 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 5.79 (t, J = 7.8 Hz, 1H), 7.29–7.38 (m, 3H), 7.56–7.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.08, 18.41, 22.65, 26.56, 28.67, 31.55, 115.72, 125.46, 126.67, 127.21, 127.96, 129.12, 130.50, 138.74, 146.68, 146.91, 169.01. Anal. ($C_{17}H_{18}O_2$) calcd: C, 80.28; H, 7.13. Found: C, 80.02; H, 7.08.

(5*Z*)-4-Methyl-5-pentylidene-3-phenylfuran-2(5*H*)-one (**7i**): Oil; ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.35–1.44 (m, 2H), 1.46–1.53 (m, 2H), 2.24 (s, 3H),

2.42–2.48 (m, 2H), 5.41 (t, J = 7.8 Hz, 1H), 7.35–7.39 (m, 1H), 7.43–7.46 (m, 2H), 7.52–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.13, 14.07, 22.64, 26.21, 31.52, 113.44, 126.66, 128.73, 128.75, 129.22, 130.19, 146.86, 150.09, 169.39. Anal. ($C_{16}H_{18}O_2$) calcd: C, 79.31; H, 7.49. Found: C, 79.15; H, 7.40.

4 Conclusion

In summary, it has been shown that various cyclic and acyclic β-bromo-α,β-unsaturated ketones, which are readily prepared from ketones, undergo carbonylation and intramolecular cyclization under carbon monoxide pressure in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ along with Et_3N to give the corresponding (*Z*)-alkylidenefuranones in good yields. The present reaction is a straightforward methodology for the synthesis of valuable heterocycles from readily available starting ketones. Further study of synthetic applications to *N*-heterocycles using β-bromo-α,β-unsaturated ketones is in progress.

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