

Synthesis of 3-Vinyl- β -lactams via Palladium-Catalyzed Carbonylative Heteroannulation of Allylic Compounds with Imines

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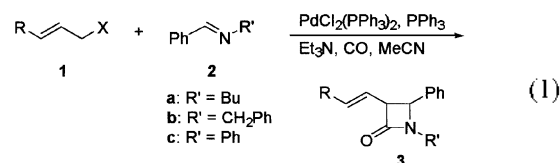
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Received February 21, 2000

Transition metal-catalyzed heteroannulation process has been widely used for the formation of many heterocyclic compounds which play an important role as a basic skeleton for the design of many pharmacologically active compounds.¹ In connection with this report, it is well-known that β -lactams also exert a broad spectrum of physiological activities and the formation of β -lactam skeleton is the annulation of ketene precursors such as acid chlorides and activated carboxylic acids with imines via a [2+2] cycloaddition process.² Thus, many synthetic methods including transition metal-catalyzed versions have been reported for the formation of the structural core of β -lactams.³ Among them, Torii *et al.* reported a palladium-catalyzed approach for the synthesis of β -lactams via carbonylative [2+2] cycloaddition of allyl diethyl phosphates with imines.⁴⁻⁶ However, the ketene precursor seems to be limited to the phosphates, other allylic substrates such as bromide, acetate, phenyl ether, carbonate, and sulfone being not successful for the β -lactam. As part of our series of studies on the synthesis of N-heterocyclic compounds catalyzed by transition metals, we found recently that benzyl and allyl halides reacted with imines under carbon monoxide pressure in the presence of a palladium catalyst to give β -lactams via a carbonylative [2+2] cycloaddition pathway.^{7,8} We here report a facile synthesis of 3-vinyl- β -lactams from readily available allylic compounds and imines through the intrinsic palladium-catalyzed carbonylative [2+2] cycloaddition protocol.

We examined the carbonylative heteroannulation between allylic compounds (**1**) and imines (**2**) under analogous catalytic conditions that have been used in our previous β -lactam formation (eq. 1).⁷ Several representative results are summarized in Table 1. Treatment of cinnamyl chloride (**1**, R=Ph; X=Cl) with *N*-butylbenzaldimine (**2a**) and carbon monoxide in the presence of PdCl₂(PPh₃)₂ (2 mol%) in anhydrous acetonitrile at 100 °C afforded 1-butyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetone in 74% isolated yield as *trans* and *cis* isomeric mixture. When benzene was used as solvent in place of acetonitrile under the same catalytic system, the β -lactam was also formed in similar yield (72%). For the purpose of the synthetic application of other cinnamyl compounds upon this heteroannulation, the reaction of cinnamyl bromide (**1**, R=Ph; X=Br) and acetate (**1**, R=Ph; X=OAc) with **2a** was examined under the same catalytic system. As shown in Table 1, these cinnamyl compounds were also effective in the formation of the β -lactam, giving yields as good as that of cinnamyl chloride. In all cases, the pendant olefinic stereochemistry of β -lactam was retained as the initial *trans* of cinnamyl compounds and the

stereochemistry of β -lactam framework favored the formation of *trans* isomer as has been observed in our previous β -lactam synthesis.⁷



On the other hand, the β -lactam yield was considerably affected by the structural nature of the primary amine counterpart of the imines. In the reactions of cinnamyl chloride with imines such as *N*-butylbenzaldimine (**2a**), *N*-benzylbenzaldimine (**2b**), and *N*-phenylbenzaldimine (**2c**), the yield of β -lactam formation decreased with the increase of steric bulkiness on the primary amine counterpart of the imines. How-

Table 1. Palladium-catalyzed synthesis of 3-vinyl- β -lactams^a

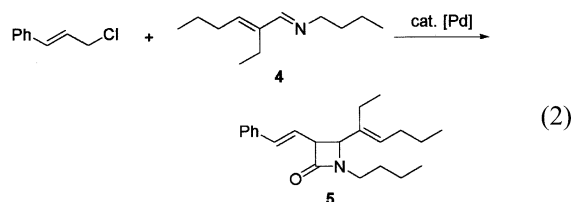
Allylic compounds	Imines	3-Vinyl- β -lactams	Yield (%) ^b	<i>Trans/cis</i> ^c
	2a		74	4/1
	2a		79	4/1
	2a		73	2.3/1
	2b		77	4/1
	2c		44	3/1
	2a		39	>99/<1
	2a		78	>99/<1
	2b		88	>99/<1
	2a		48	3/1 ^d
	2c		59	3/1 ^d
	2b		0	—

^aAll reactions were carried out with allylic compound (3 mmol), imine (2 mmol), PdCl₂(PPh₃)₂ (0.04 mmol), PPh₃ (0.16 mmol), and triethylamine (5 mmol) in acetonitrile under carbon monoxide (27 atm) at 100 °C for 24 h. ^bIsolated yield based on imine. ^cExcept as noted, all isomeric ratios were calculated on an isolated state. ^dDetermined by ¹H NMR (300 MHz) spectroscopy.

ever, the stereochemical outcome of the β -lactam framework showed no considerable influence according to the steric bulkiness. In addition, the stereochemistry of β -lactam framework was decisively affected by the kind of allylic compounds. Treatment of allyl chloride and bromide with imines (**2a** and **2b**) under the same reaction conditions afforded almost exclusively *trans* stereoisomer in high yields. Even if *cis* isomer is present, its amount is a trace on both GLC and ^1H NMR. As shown in Table 1, in contrast to cinnamyl halides, allyl bromide was more effective than allyl chloride for the formation of β -lactam.

The heteroannulation reaction of crotyl chloride with imines also gave the corresponding β -lactams as an isomeric mixture as has been observed in the reaction of cinnamyl halides with imines. Since it was not possible to separate these stereoisomers by the usual chromatography technology, the total yield and the product distribution were analyzed from the intensity of the clearly separated protons in the ^1H NMR spectrum (see Experimental Section). However, when prenyl chloride is used as cyclization counterpart, the heteroannulation toward the formation of β -lactam fails to occur and the starting imine was almost recovered on GLC.

Similar treatment of cinnamyl chloride with α,β -unsaturated imine **4** under the above reaction system afforded 3,4-divinyl- β -lactam **5** in 45% isolated yield as a stereoisomeric mixture with the retention of the pendant olefinic stereochemistry, also favoring the formation of *trans* isomer (eq. 2)



In summary, we have demonstrated that 3-vinyl- β -lactams can be easily synthesized by reaction of allylic compounds with imines under carbon monoxide in the presence of a palladium catalyst. The present heteroannulation is a novel synthetic approach for the one-pot three-component reaction leading to 3-vinyl- β -lactams.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded on Varian Unity Plus 300 (300 MHz for ^1H NMR; 75.5 MHz for ^{13}C NMR), Bruker Avance Digital 400 (400 MHz for ^1H NMR; 100 MHz for ^{13}C NMR), and Varian Unity Inova (500 MHz for ^1H NMR; 125 MHz for ^{13}C NMR) spectrometers using TMS as an internal standard. Chemical shifts are reported in δ units downfield from TMS. Infrared spectra were recorded on a Galaxy Series FT-IR 7000M spectrophotometer. Electron impact mass spectra were obtained on a Shimadzu QP-1000 spectrometer. Melting points were determined on a Thomas Scientific capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via column chromatography (silica gel 60 HF₂₅₄, Merck). Imines were synthesized by condensation of the corresponding primary amines with benz-

aldehyde. $\text{PdCl}_2(\text{PPh}_3)_2$ was prepared by the reported method.⁹

General procedure for palladium-catalyzed synthesis of 3-vinyl- β -lactams. A mixture of allylic compound (3 mmol), imine (2 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.028 g, 0.04 mmol), PPh_3 (0.042 g, 0.16 mmol), and triethylamine (0.506 g, 5 mmol) in anhydrous acetonitrile (10 mL) was placed in a pressure vessel. After the system was flushed and then pressurized with CO (27 atm), the reaction mixture was stirred at 100 °C for 24 h. The reddish brown reaction mixture was filtered through a short silica gel column (CHCl_3 -ethyl acetate), poured into brine and extracted two times with CHCl_3 . The combined organic layer was dried over anhydrous Na_2SO_4 . Removal of the solvent under reduced pressure left an oil which was separated by column chromatography using ethyl acetate-hexane mixture as an eluent to give the corresponding 3-vinyl- β -lactams. The products prepared by the above procedure were fully characterized as shown below.

***trans*-1-Butyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

The spectroscopic data for this compound are noted in ref. 7.

***cis*-1-Butyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

The spectroscopic data for this compound are noted in ref. 7.

***trans*-1-Benzyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

white solid; mp 84-86 °C (from ether); ^1H NMR (500 MHz, CDCl_3) δ 3.76-3.80 (m, 2H), 4.25 (d, $J = 2.0$ Hz, 1H), 4.85 (d, $J = 15.0$ Hz, 1H), 6.24 (dd, $J = 16.0$ and 8.0 Hz, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 7.13-7.35 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 44.2, 60.8, 63.5, 121.8, 126.1, 126.2, 127.4, 127.5, 128.1, 128.2, 128.3, 128.5, 128.7, 133.8, 135.2, 136.0, 136.7, 167.7 (C=O); MS m/z (relative intensity) 339 (M^+ , 0.9), 206 (100), 115 (20), 91 (42).

***cis*-1-Benzyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

white solid; mp 86-88 °C (from CHCl_3 /hexane); ^1H NMR (500 MHz, CDCl_3) δ 3.92 (d, $J = 14.5$ Hz, 1H), 4.24-4.27 (m, 1H), 4.70 (d, $J = 5.5$ Hz, 1H), 4.92 (d, $J = 14.5$ Hz, 1H), 5.62 (dd, $J = 15.5$ and 8.0 Hz, 1H), 6.61 (d, $J = 15.5$ Hz, 1H), 7.06-7.37 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 44.4, 58.4, 58.6, 126.2, 127.3, 127.4, 127.6, 128.2 (x2), 128.4, 128.5, 128.6, 128.7, 134.4, 134.9, 135.3, 136.5, 168.1 (C=O); MS m/z (relative intensity) 339 (M^+ , 13), 206 (73), 115 (40), 91 (100).

***trans*-1,4-Diphenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

white solid; mp 162-164 °C (from CHCl_3 /hexane); IR (KBr) 1742 (C=O) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.90 (dd, $J = 8.4$ and 2.4 Hz, 1H), 4.88 (d, $J = 2.4$ Hz, 1H), 6.39 (dd, $J = 15.9$ and 8.4 Hz, 1H), 6.67 (d, $J = 15.9$ Hz, 1H), 7.23-7.40 (m, 15H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 61.1, 63.7, 117.1, 121.7, 124.0, 125.9, 126.5, 128.0, 128.6 (x2), 129.1, 129.2, 134.8, 136.2, 137.3, 137.5, 165.5 (C=O); MS m/z (relative intensity) 325 (M^+ , 1.2), 206 (100), 191 (37), 180 (27), 128 (50), 115 (40), 91 (79), 77 (44). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{NO}$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.63; H, 6.31; N, 4.41.

***cis*-1,4-Diphenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:**

white solid; mp 179-180 °C (from CHCl_3 /hexane); IR (KBr) 1736 (C=O) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.45 (dd, $J = 8.1$ and 5.7 Hz, 1H), 5.34 (d, $J = 5.7$ Hz, 1H), 5.61 (dd, $J = 15.9$ and 8.1 Hz, 1H), 6.67 (d, $J = 15.9$ Hz, 1H), 7.04-7.38 (m, 15H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 57.9, 59.1, 117.2, 120.2, 124.0, 126.3, 127.0, 127.7, 128.4 (x2), 128.8, 129.1, 134.8, 135.2, 136.5, 137.5, 165.6 (C=O); MS m/z (relative intensity) 325 (M^+ ,

4), 206 (100), 191 (38), 180 (40), 144 (41), 128 (54), 115 (52), 91 (77), 77 (59). Anal. Calcd for $C_{21}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.57; H, 6.23; N, 4.37.

trans-1-Butyl-4-phenyl-3-vinyl-2-azetanone: pale yellow oil; IR (neat) 1746 (C=O) cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.5$ Hz, 3H), 1.27-1.37 (m, 2H), 1.42-1.51 (m, 2H), 2.84 (dt, $J = 14.1$ and 6.6 Hz, 1H), 3.50 (dt, $J = 14.1$ and 7.2 Hz, 1H), 3.60 (br d, $J = 7.5$ Hz, 1H), 4.36 (d, $J = 1.8$ Hz, 1H), 5.24 (dd, $J = 10.2$ and 1.2 Hz, 1H), 5.30 (dd, $J = 17.1$ and 1.2 Hz, 1H), 5.98 (ddd, $J = 17.1$, 10.2, and 7.5 Hz, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 19.8, 29.3, 40.0, 61.0, 63.6, 118.7, 126.0, 128.2, 128.7, 131.0, 137.3, 167.7 (C=O); MS m/z (relative intensity) 229 (M^+ , 0.2), 186 (1), 162 (2), 130 (100), 115 (25), 104 (5), 91 (17), 77 (8). Anal. Calcd for $C_{13}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.79; H, 7.95; N, 6.09.

trans-1-Benzyl-4-phenyl-3-vinyl-2-azetanone: pale yellow oil; 1H NMR (500 MHz, $CDCl_3$) 3.63 (dd, $J = 8.0$ and 1.0 Hz, 1H), 3.75 (d, $J = 15.0$ Hz, 1H), 4.19 (d, $J = 2.5$ Hz, 1H), 4.82 (d, $J = 15.0$ Hz, 1H), 5.18 (dd, $J = 10.0$ and 1.0 Hz, 1H), 5.25 (dd, $J = 17.0$ and 1.0 Hz, 1H), 5.89 (ddd, $J = 17.0$, 10.0 and 8.0 Hz, 1H), 7.11 (d, $J = 6.5$ Hz, 2H), 7.21-7.34 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.3, 60.5, 63.9, 119.0, 126.4, 127.6, 128.2, 128.5, 128.7, 128.9, 130.9, 135.4, 137.0, 167.7 (C=O). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.36; H, 6.32; N, 5.28.

trans- and cis-1-Butyl-4-phenyl-3-[(E)-1-propenyl]-2-azetanone: pale yellow oil as an isomeric mixture, representative spectroscopic data are as follows; IR (neat) 1755 (C=O) cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.2$ Hz, 3H), 1.25-1.37 (m, 2H), 1.41-1.51 (m, 2H), 1.56 (d, $J = 6.6$ Hz, 3/4H, =CH- CH_3 , *cis* isomer), 1.72 (d, $J = 6.3$ Hz, 9/4H, =CH- CH_3 , *trans* isomer), 2.78-2.87 (m, 1H), 3.44-3.54 (m, 7/4H), 3.87 (d, $J = 9.0$ Hz, 1/4H, -CHPh, *cis* isomer), 4.28-4.30 (m, 1H), 5.56-5.77 (m, 2H), 7.28-7.42 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.8 (C=O), 168.9 (C=O); MS m/z (relative intensity) 243 (M^+ , 1.6). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.93; H, 9.16; N, 5.76.

trans- and cis-1,4-Diphenyl-3-[(E)-1-propenyl]-2-azetanone: white solid as an isomeric mixture, representative spectroscopic data are as follows; IR (neat) 1755 (C=O) cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 1.57 (dd, $J = 6.9$ and 1.2 Hz, - CH_3 , 3/4H, *cis* isomer), 1.70 (d, $J = 6.0$ Hz, - CH_3 , 9/4H, *trans* isomer), 3.61 (dd, $J = 6.8$ and 2.1 Hz, =CH- CH_2 , 3/4H, *trans* isomer), 3.97 (br d, $J = 8.1$ Hz, =CH- CH_2 , 1/4H, *cis* isomer), 4.72-4.73 (m, 1H), 5.57-5.79 (m, 2H), 6.95 (t, $J = 7.5$ Hz, 2/4H), 7.15 (t, $J = 7.5$ Hz, 6/4H), 7.25-7.35 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7 (C=O), 165.8 (C=O). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.01; H, 6.52; N, 5.31.

trans- and cis-1-Butyl-4-[(E)-1-ethyl-1-pentenyl]-3-[(E)-2-phenyl-1-ethenyl]-2-azetanone: pale yellow oil as an isomeric mixture, representative spectroscopic data are as follows; 1H NMR (400 MHz, $CDCl_3$) δ 3.59 (br d, $J = 8.0$ Hz, 3/5H, PhCH=CH- CH_2 , *trans* isomer), 3.73 (br d, $J = 8.0$ Hz, 2/5H, PhCH=CH- CH_2 , *cis* isomer), 3.82 (d, $J = 1.6$ Hz, 3/5H, -CHC(CH_2CH_3)=CH-, *trans* isomer), 4.40 (d, $J = 2.0$ Hz, 2/5H, -CHC(CH_2CH_3)=CH-, *cis* isomer), 5.44 (t, $J = 7.2$ Hz, 3/5H, -C=CH- CH_2 -, *trans* isomer), 5.51 (t, $J = 7.2$ Hz, 2/5H, -C=CH-

CH_2 -, *cis* isomer), 6.26 (dd, $J = 16.0$ and 8.0 Hz, 3/5H, PhCH=CH-, *trans* isomer), 6.27 (dd, $J = 16.0$ and 8.0 Hz, 2/5H, PhCH=CH-, *cis* isomer), 6.60 (d, $J = 16.0$ Hz, 3/5H, PhCH=CH-, *trans* isomer), 6.61 (d, $J = 16.0$ Hz, 2/5H, PhCH=CH-, *cis* isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (C=O), 168.2 (C=O); MS m/z (relative intensity) 326 (M^+ , 4), 325 (M^+ , 8). Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.36; H, 9.38; N, 4.27.

Acknowledgment. This work was supported by the Korea Research Foundation (1999-015-DI0064) and grant of Post-Doctoral Fellow (C.S.C.) Program from Kyungpook National University (1999).

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