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Palladium(0)-catalyzed tandem cyclization of *N*-(2′,4′-dienyl)alkynamides to α-alkylidene-γ-lactams

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Abstract

α-Alkylidene-γ-lactams were synthesized from *N*-(2′,4′-dienyl)alkynamides via Pd(0)-catalyzed reactions in moderate to good yields.

Keywords: α-alkylidene-γ-lactams; palladium(0); π-allyl palladium complex.

The γ-lactam skeleton is commonly found in molecules of medicinal importance.[1] In particular, α-alkylidene-γ-lactams show cytotoxicity, antitumor and antiinflamation activities[2] but lower toxicity when compared with the corresponding α-alkylidene-γ-lactones.[3] Their potential clinical utility has stimulated much interest in construction of this kind of molecule.[4]

In our studies of Pd(II)-catalyzed reactions of electron-deficient alkynes, we have developed a series of stereoselective cyclization methods to build α-alkylidene-γ-lactones[5] and γ-lactam analogues.[6] In these reactions, a Pd(II) catalyst was used because of the possible cleavage of the allylic carbon–oxygen bond in the starting allylic alkynoates in the presence of a Pd(0) catalyst.[7] On the contrary, an allylic carbon–nitrogen bond is generally stable to Pd(0) species. Thus, it is possible to use a Pd(0) catalyst to construct γ-lactams. Here, we wish to report our recent results in the synthesis of α-alkylidene-γ-lactams via Pd(0) catalyzed reactions.

At first, the reaction of PhI and the precursor **1** was carried out under typical Pd(0) catalyzed reaction conditions (10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 1.5 equiv. of Et_3N in MeCN, 70°C for 2 h). The double-bond isomerized products (**2a, 2b**) were obtained in low yield due to the easy polymerization of the products. If Ag_2CO_3 was used,[8] a mixture of **2a** and **2a′** (the normal product without isomerization of the double bond) was obtained in a total yield of 42%. Thus, the simple cyclization terminated by β-H elimination is not a good method to synthesize γ-lactams.

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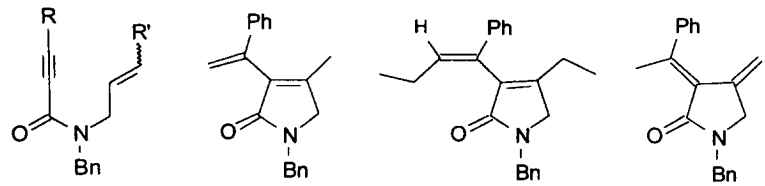
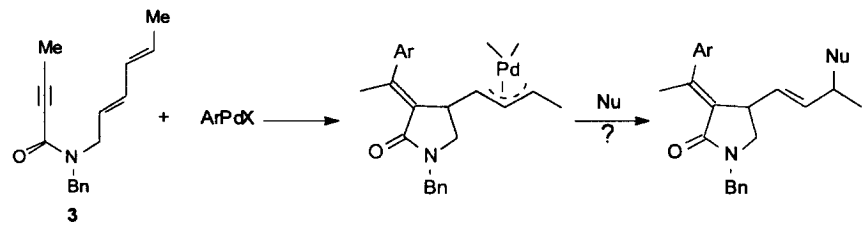


Based on the reaction of conjugated dienes with aryl and alkenyl halides in the presence of nucleophiles,[9] we tried the Pd(0) catalyzed cyclization of enyne precursor **3**, expecting that the finally formed π-allyl palladium complex could be quenched by the attack of a nucleophile to regenerate the Pd(0) species.



Treatment of the acyclic compound **3** with different aryl iodides and nitrogen nucleophiles in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 in MeCN afforded the corresponding cyclization products in reasonable yields in most cases (Table 1).[10] A by-product produced by the Diels–Alder reaction of the starting compound **3** was also isolated in 5–8% yield. The nucleophiles regioselectively attacked the site remote from the lactam ring and the double bond formed from the π-allyl palladium complex has the *E* configuration as detemined by NOESY spectra.

When an aryl iodide with an electron-withdrawing group was reacted with **3**, the Diels–Alder adduct **5** was obtained as the major product with a low yield of **4**. Various aliphatic amines including primary and secondary ones proved to be good nucleophiles giving good yields of the corresponding α-alkylidene-γ-lactams. On the contrary, aromatic amines are poor nucleophiles in this reaction and afford only by-product **5**. Carbon nucleophiles, such as dimethyl malonate, can also give the corresponding α-alkylidene-γ-lactam in 55% yield using $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$, BSA/KOAc system and THF as the solvent.[11]

The following mechanism is proposed: oxidative addition of the aryl iodide to palladium(0) generates ArPdI which then undergoes tandem insertion into the triple and the double bonds of compound **3**, successively, to give intermediate **A**, which is in equilibrium with the π-allyl palladium(II) intermediate **B** and leads to the product after nucleophilic attack.

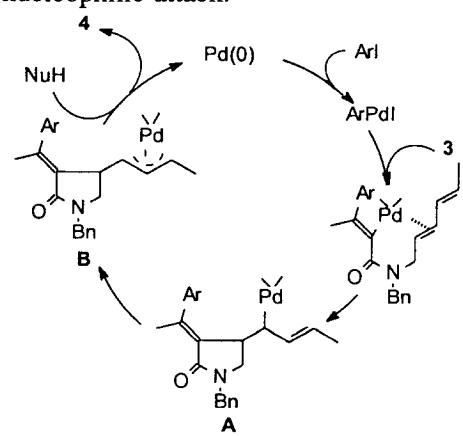
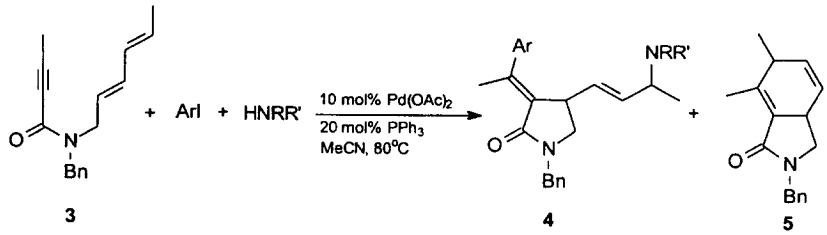


Table 1
Palladium(0) catalyzed cyclization of **3**[a]



entry	amine	Ar	product	4 yield%[b]
1	Piperidine	Ph	**4a**	71[c]
2	Piperidine	*p*-MeO-C_6H_4-	**4b**	67[c]
3	Piperidine	*p*-Me-C_6H_4-	**4c**	68[c]
4	Piperidine	*p*-NO_2-C_6H_4-	**4d**	27[d]
5	Morpholine	Ph	**4e**	66[c]
6	Pyrrolidine	Ph	**4f**	71[c]
7	Benzylamine	Ph	**4g**	67[c]
8	Isobutylamine	Ph	**4f**	70[c]
9	Butylamine	Ph	**4g**	68[c]
10	Aniline	Ph	**5**	78[e]

a. Reaction codition: **3** (0.5mmol), amine (0.6 mmol), ArI (0.6 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), MeCN (2 ml), 80°C, 2 hrs.

b. Isolated yield.

c. Together with 5-8% yield of by-product **5**.

d. Together with 51% yield of **5**.

e. Only **5** was obtained.

In summary, we have developed a tandem palladium catalyzed cyclization to synthesize the α-alkylidene-γ-lactams in reasonable yields. The simple operation, ready availability of the starting materials and a high selectivity in preparing α-alkylidene-γ-lactams analogues are noteworthy.

Acknowledgements

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10. All the products were characterized by spectral data. Typical ^{1}H NMR data of compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, J=6.7 Hz, 3H), 1.37 (m, 2H), 1.50 (m, 4H), 2.24 (m, 4H), 2.61 (d, J=1.0 Hz, 3H), 2.65 (m, 1H), 2.85 (dd, J_1=9.3 Hz, J_2=1.3 Hz, 1H), 3.43 (m, 2H), 4.40 (d, J=14.7 Hz, 1H), 4.68 (d, J=14.7 Hz, 1H), 4.96 (ddd, J_1=15.3 Hz, J_2=8.0 Hz, J_3=0.6 Hz, 1H), 5.20 (dd, J_1=15.2 Hz, J_2=6.9 Hz, 1H), 7.17–7.35 (m, 10H); MS: 415 (M+1, 3.25), 399 (100.00), 91 (89.87), 124 (66.50), 112 (44.37), 400 (30.88), 329 (27.58); IR: 2931, 1675, 1440, 703; HRMS: calcd: 414.2671, found: 414.2651. The stereochemistry of the double bonds on α and β substituents of **4a** are both *E* configurations determined by NOESY spectra.
11. When dimethyl sodiomalonate was taken as the nucleophile, only 18% yield of the corresponding α-alkylidene-γ-lactam was obtained.