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Synthesis of Unsaturated Seven-Membered Ring Lactams through Palladium-Catalyzed Amination and Intramolecular Cyclocarbonylation Reactions of Amines and Baylis−Hillman Acetates

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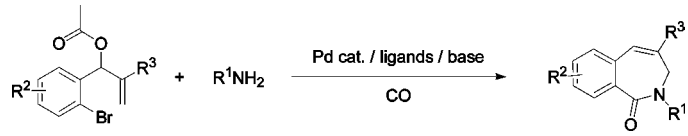
ABSTRACT



A versatile synthesis of unsaturated seven-membered ring lactams has been developed. The sequence involves hydroamination of Baylis−Hillman acetate with amines, followed by intramolecular cyclocarbonylation reactions of the resulting allylamines. This process can tolerate a wide array of functional groups, and affords lactams in excellent yields.

Medium-sized unsaturated lactams are important components of natural products that possess many and varied biological properties, including antitumor, antibiotic, antithelmintic[1,2] and insecticidal activity.[3] They also find wide use in organic synthesis[4] and as a basis of peptidomimetic scaffolds that accurately define and stabilize the biologically active conformations of peptides and proteins.[5] As such, a good deal of effort has focused on developing general synthetic approaches to simple monocyclic lactams based on ring closure, ring expansion, cycloaddition, and fragmentation reactions.[1] Success has been achieved by means of transition metal catalysis.[6] Among these, palladium-catalyzed carbonylation reactions represent a convenient and efficient one-step method to prepare a wide variety of the medium-sized lactams.[7]

The Baylis−Hillman reaction is a useful carbon−carbon bond-forming reaction for organic synthesis.[8] Baylis−Hillman

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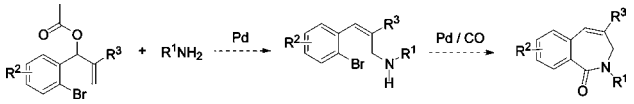
adducts are prepared by the reaction of activated alkenes such as ethyl acrylate, acrylonitrile, and methyl vinyl ketone with aldehydes or imines in the presence of nucleophilic catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO), quinuclidine, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and phosphine.[9] In addition to the intrinsic usefulness of the Baylis−Hillman adducts, they and their acetates are valuable precursors for the preparation of a variety of trisubstituted alkenes with various functional groups such as esters, ketones, and nitriles by reaction with a variety of nucleophiles.[10,11]

We have been investigating alternative protocols for the synthesis of nitrogen-containing heterocycles, based on transition-metal-mediated carbonylation reactions.[12] In this paper, we report an interesting method for the synthesis of seven-membered unsaturated ring lactams as well as substituted benzazepine derivatives, by the palladium-catalyzed one-pot amination and intramolecular cyclocarbonylation reactions of amines and Baylis−Hillman acetates (Scheme 1).

Scheme 1. Strategic Approach to the Synthesis of Substituted Benzazepine Derivatives



First, various Baylis−Hillman acetates were prepared from different 2-halobenzaldehydes according to the literature[8] (Scheme 2).

Then the ethyl 2-(acetoxy(2- bromophenyl)methyl)acrylate and benzyl amine were chosen as the model substrates to perform the amination and intramolecular cyclocarbonylation reaction under different reaction conditions. The results are shown in Table 1.

Scheme 2. Synthesis of Baylis−Hillman Acetates

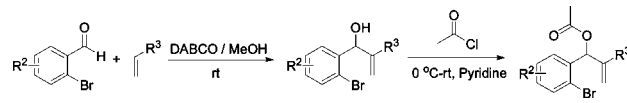
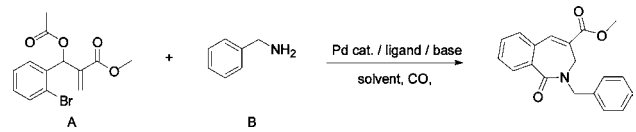


Table 1. Optimization of the Palladium-Catalyzed Amination and Carbonylation Reaction of Baylis−Hillman Acetate and Benzylamine[a]



A B

entry	catalyst	ligand	A/B	base	CO	time	isolated yield
1	$Pd(OAc)_2$	dppb	1:1.2	DBU	400 psi	20 h	16%
2	$Pd(OAc)_2$	dppb		K_2CO_3	400 psi	20 h	62%
3	$Pd(OAc)_2$	PPh_3		K_2CO_3	400 psi	20 h	35%
4	$Pd(OAc)_2$	BIPHEP		K_2CO_3	400 psi	20 h	52%
5	$Pd(OAc)_2$	dppb		K_2CO_3	1 atm	20 h	55%
6	$Pd(OAc)_2$	dppb	1:3	K_2CO_3	100 psi	30 h	75%

[a] Reaction conditions: **A** (1 mmol), **B** (1.2 or 3 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_2 (0.20 mmol), dppb or BIPHEP (0.10 mmol), base (2 mmol), toluene (5 mL), 110 °C.

In our first trial, with $Pd(OAc)_2$/dppb as the catalyst system, DBU as base, toluene as the solvent, at 400 psi of CO for 20 h, the reaction gave a 16% yield of the desired product. To find the best conditions for this new hydroamination and intramolecular cyclocarbonylation reaction of Baylis−Hillman acetate and amines, we tried different ligands and bases and varied the ratio between the two substrates. The results showed that dppb was more efficient than other bidentate ligands and PPh_3 (Table 1, entries 2−4). The inorganic base K_2CO_3 is better than DBU (Table 1, entries 1, 2). The reaction could be carried out under 1 atm of CO affording the product in 55% yield (Table 1, entry 5). We were pleased to observe that, with 3 equiv of benzylamine and 100 psi of CO, the reaction provided the highest yield (75%) of the seven-membered ring lactam after 30 h (Table 1, entry 6).

Having determined the optimized conditions, we carried out the palladium-catalyzed amination and intramolecular cyclocarbonylation reaction with a series of amines. The results are listed in Figure 1. Most of the amines employed for the reaction showed good reactivities and provided the target seven-membered ring lactams in good to excellent yields. Both aromatic and aliphatic amines were active for the reactions. Aliphatic amines usually afforded lower yields than aromatic amines with 4-$MePhCH_2NH_2$ giving the highest product yield (98%).

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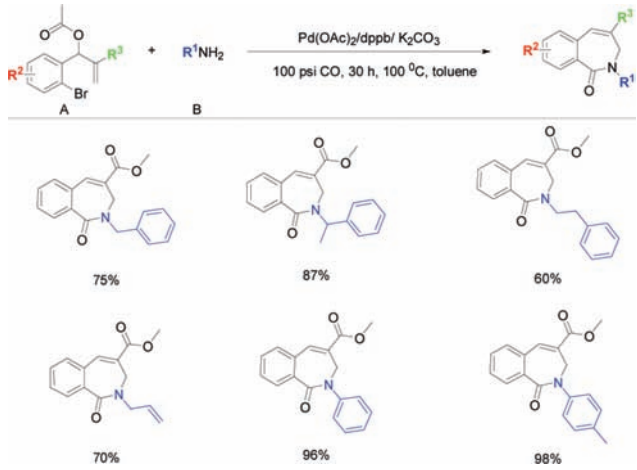

Figure 1. Substrates scope of the palladium-catalyzed amination and intramolecular cyclocarbonylation reactions of different amines. Reaction conditions: A (1 mmol), B (3 mmol), K_2CO_3 (2 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb(0.1 mmol), toluene (5 mL).

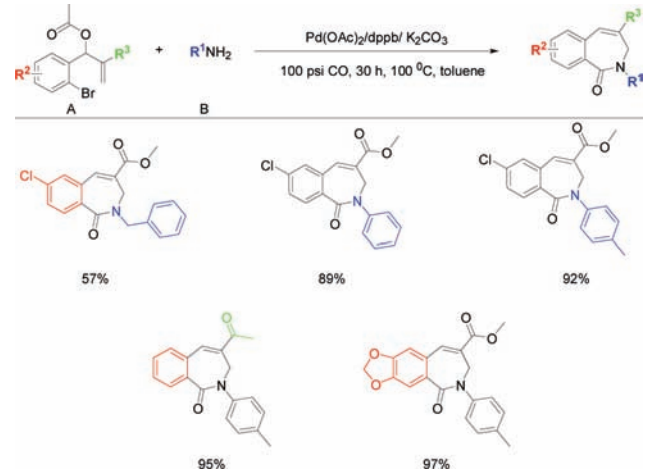

Figure 2. Substrates scope of the palladium-catalyzed amination and intramolecular cyclocarbonylation reactions of different Baylis−Hillman acetates. Reaction conditions: A (1 mmol), B (3 mmol), K_2CO_3 (2 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb(0.1 mmol), toluene (5 mL).

We then determined the efficiency of different Baylis−Hillman acetates for this reaction (Figure 2). From the results we can see that most of the substrates afford benzazepinones in excellent yields. Substituents (R_2, R_3) had a modest effect on the yield when the same amine was applied. The reaction afforded higher product yields (97%) when R_2 is an electron-donating group.

In summary, we have described a convenient and efficient protocol for the synthesis of substituted benzazepine derivatives in fine yields under mild conditions. This protocol is based on the sequential use of amination and intramolecular carbonylation reactions between Baylis−Hillman acetates and various amines with palladium complexes as catalysts. The success of this palladium-catalyzed one-pot reaction opens the possibility of a new synthetic route for the formation of a number of biologically important natural or unnatural products containing the benzazepine ring system.

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Supporting Information Available: Full experiment details, characterization for all compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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