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Palladium-catalyzed reaction of 2-alkynylhalobenzene with 2-alkynylbenzamide: an efficient approach to indeno[1,2-*c*]azepin-3(2*H*)-ones†

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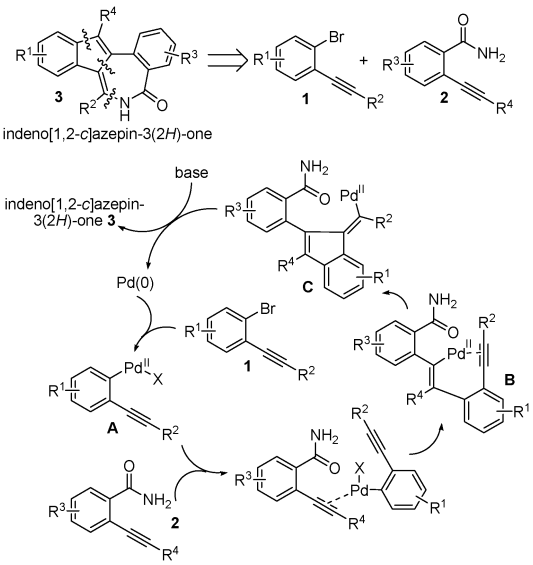
A novel and efficient route for rapid access to indeno[1,2-*c*]-azepin-3(2*H*)-ones is described, which proceeds through a palladium-catalyzed tandem reaction of 2-alkynylhalobenzene with 2-alkynylbenzamide in the presence of PPh_3 or PCy_3. The indeno[1,2-*c*]azepin-3(2*H*)-ones which incorporate both indene and unsaturated seven-membered ring lactam skeletons are obtained in good to excellent yields.

It is well recognized that a medium-sized unsaturated lactam is the core structure of natural products that possess important biological properties, including antibiotic, antitumor, antihelminthic[1,2] and insecticidal activity.[3] These compounds find wide applications in organic synthesis.[4] Moreover, they serve as a basis of the peptidomimetic scaffold, which is utilized to define and stabilize the biologically active conformations of peptides and proteins.[5] So far, methods for the formation of simple monocyclic lactams have been developed, including ring expansion, cycloaddition, ring closure, and fragmentation reactions.[1] Transition metal catalyzed approaches such as palladium-catalyzed carbonylation reactions have been successfully applied for the preparation of medium-sized lactams as well.[6,7] The indene is another kind of privileged fragment, which can be discovered in many drug candidates with remarkable biological activities.[8] Additionally, these compounds have found applications in materials science[9] as well as in olefin polymerization as catalysts.[10]

Currently, a good deal of effort has centered on diversity-oriented synthesis for the generation of small molecules in the field of chemical genetics.[11] The development of efficient and concise pathways for rapid construction of molecular complexity is a major concern of the synthetic organic chemical community. Strategies that allow multiple transformations in a single-pot process with high selectivity and efficiency are especially attractive. Recently, we have been involved in this field for rapid access to natural product-like compounds with privileged scaffolds.[12] Inspired by the core structures of medium-sized unsaturated lactam and indene, we conceived that indeno[1,2-*c*]azepin-3(2*H*)-one (Scheme 1) could be regarded as a privileged scaffold as well, which incorporated both indene and unsaturated seven-membered ring lactam skeletons. We expected that interesting biological activities would be displayed from a focused library of indeno[1,2-*c*]azepin-3(2*H*)-ones. With the above consideration in mind, we started to explore the possibility for efficient assembly of indeno[1,2-*c*]azepin-3(2*H*)-ones.

Intense interest has been directed toward the tandem reaction due to its high efficiency and other attractive advantages.[13,14] Recently, we described a novel method for the generation of structurally complex molecules *via* a palladium-catalyzed tandem reaction of 2-alkynylhalobenzene.[12c,e] Encouraged by this result, we envisioned that indeno[1,2-*c*]azepin-3(2*H*)-one could be constructed starting from 2-alkynylhalobenzene **1** as well (Scheme 1). We reasoned that the intermediate **A** would be formed *via* oxidative addition of Pd(0) to 2-alkynylhalobenzene **1**. This Pd(II) complex would coordinate with the triple bond of 2-alkynylbenzamide **2**, followed by insertion of the triple bond to afford an intermediate **B**. Subsequently an intramolecular C≡C insertion and C–N bond formation occurred to



Scheme 1 Indeno[1,2-*c*]azepin-3(2*H*)-ones generation *via* a Pd-catalyzed reaction of 2-alkynylhalobenzene **1** with 2-alkynylbenzamide **2**.

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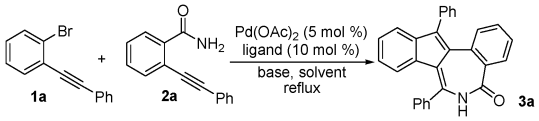
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compound **3**. CCDC 836855. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14480d

Table 1 Initial studies for the palladium-catalyzed reaction of 1-bromo-2-(phenylethynyl)benzene **1a** with 2-(2-phenylethynyl)benzamide **2a**



Entry	Ligand	Base	Solvent	Yield[a] (%)
1	PPh_3	NaO^tBu	1,4-Dioxane	nr
2	PPh_3	$NaOCH_3$	1,4-Dioxane	nr
3	PPh_3	Na_2CO_3	1,4-Dioxane	nr
4	PPh_3	Cs_2CO_3	1,4-Dioxane	94
5	—	Cs_2CO_3	1,4-Dioxane	60
6	PCy_3	Cs_2CO_3	1,4-Dioxane	91
7	Xantphos	Cs_2CO_3	1,4-Dioxane	91
8	DPEphos	Cs_2CO_3	1,4-Dioxane	90
9	DPPP	Cs_2CO_3	1,4-Dioxane	60
10	PPh_3	K_2CO_3	1,4-Dioxane	96
11	PPh_3	K_3PO_4	1,4-Dioxane	82
12	PPh_3	K_2CO_3	DMF	Trace
13	PPh_3	K_2CO_3	DMSO	Trace
14	PPh_3	K_2CO_3	Toluene	51
15[b]	PPh_3	K_2CO_3	1,4-Dioxane	79

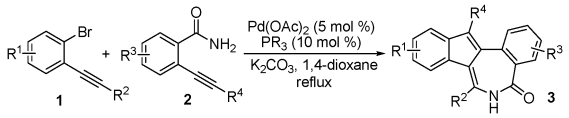
[a] Isolated yield based on 2-(2-phenylethynyl)benzamide **2a**. [b] The reaction occurred at 80 °C.

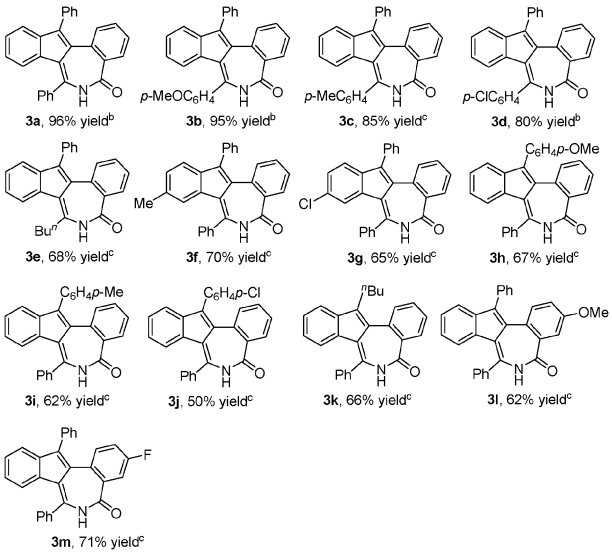
generate the desired indeno[1,2-*c*]azepin-3(2*H*)-one **3**. Herein, we wish to disclose our preliminary results for this transformation.

We selected 1-bromo-2-(phenylethynyl)benzene **1a** and 2-(2-phenylethynyl)benzamide **2a** as the model substrates for reaction development. The preliminary screening results are presented in Table 1. Initially, no reaction occurred when the reaction was catalyzed by $Pd(OAc)_2$ in the presence of PPh_3 and NaO^tBu in 1,4-dioxane under reflux conditions (entry 1). The same results were observed when the base was changed to $NaOCH_3$ or Na_2CO_3 (entries 2 and 3). Interestingly, the desired indeno[1,2-*c*]azepin-3(2*H*)-one **3a** was obtained in good yield when Cs_2CO_3 was employed as a base in the reaction (94% yield, entry 4). In the meantime, the structure of product **3a** was unambiguously illustrated by X-ray diffraction analysis (see the ESI†). A control experiment without the addition of phosphine ligand indicated that the reactivity was diminished (entry 5). Further screening of ligands revealed that PCy_3, Xantphos, and DPEphos were all good choices (entries 6–8). Considering the easy availability, PPh_3 was selected for the further development. An excellent yield was afforded when the reaction was performed in the presence of K_2CO_3 as a base (entry 10). The reaction occurred in other solvents leading to inferior results (entries 12–14). The yield was decreased with prolonged reaction time when the reaction took place at 80 °C (entry 15).

With the optimized conditions in hand [$Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3, 1,4-dioxane, 105 °C], we started to explore the scope of the palladium-catalyzed cascade reaction of 2-alkynylhalobenzene **1** with 2-alkynylbenzamide **2**, and the results are shown in Table 2. We found in some cases better results were afforded when PCy_3 was utilized instead of PPh_3. All the reactions worked well to afford a variety of indeno[1,2-*c*]azepin-3(2*H*)-ones **3** in good to excellent yields. Various substitutions including aryl and alkyl groups attached to the triple bond were all tolerated in the transformations.

Table 2 Synthesis of indeno[1,2-*c*]azepin-3(2*H*)-ones *via* a Pd-catalyzed reaction of 2-alkynylbromobenzene **1** with 2-alkynylbenzamide **2**[a]



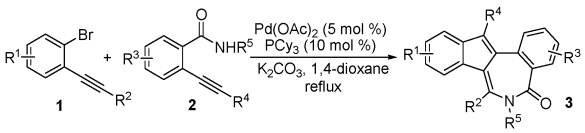


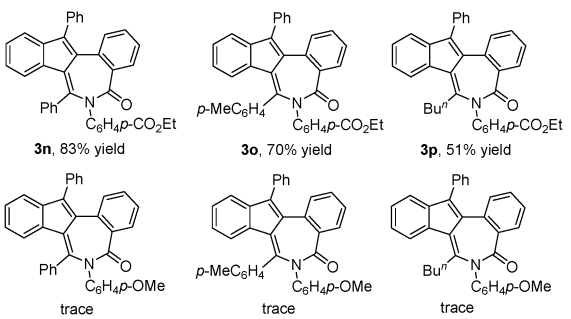
[a] Isolated yield based on 2-alkynylbenzamide **2**. [b] PPh_3 was used as the ligand. [c] PCy_3 was used as the ligand.

Additionally, the substrates with electron-donating or electron-withdrawing groups attached to the aromatic ring were good partners for the generation of indeno[1,2-*c*]azepin-3(2*H*)-ones. In some cases, the yields were not satisfied, which was due to the existence of the un-reacted starting materials. The reaction time could not be prolonged since the products would be hydrolyzed slowly under the basic reaction conditions.

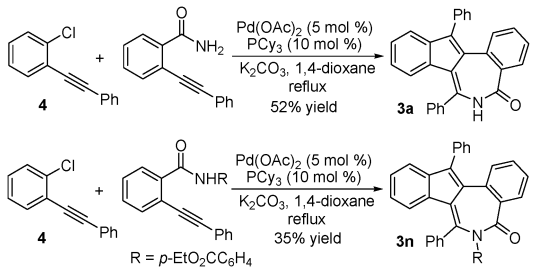
We further investigated the reactions of 2-alkynylbromobenzene **1** and 2-alkynylbenzamide **2** with substitutions in the amide group under the standard conditions shown in Table 2 (Table 3).

Table 3 Palladium-catalyzed reaction of alkynylbromobenzene **1** with 2-alkynylbenzamide **2**[a]





[a] Isolated yield based on 2-alkynylbenzamide **2**.



Scheme 2 Pd-catalyzed reaction of 2-alkynylchlorobenzene **4** with 2-alkynylbenzamide **2**.

It is noteworthy that the yields of this conversion are very sensitive to the substrates. For example, the reaction proceeded smoothly when R^5 was an ester substituted phenyl group. However, no product was formed when the 4-methoxyphenyl group was attached to the amide. We reasoned that it might be due to the acidity of the amide (N–H) in the substrate.

Moreover, the reactions of 1-chloro-2-(2-phenylethynyl)-benzene **4** with 2-alkynylbenzamides were explored (Scheme 2). The corresponding products could be obtained as well under the standard conditions. From these results, we are convinced that the substrate scope can be expanded since aryl chloride is also suitable in this transformation.

In summary, we have presented a novel and efficient route for the generation of indeno[1,2-*c*]azepin-3(2*H*)-ones through a palladium-catalyzed tandem reaction of 2-alkynylhalobenzene with 2-alkynylbenzamide. The indeno[1,2-*c*]azepin-3(2*H*)-ones which incorporates both indene and unsaturated seven-membered ring lactam skeletons are obtained in good to excellent yields. Investigation of 2-alkynylhalobenzenes in other transformations is currently underway.

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