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Synthesis of 4,5-Dihydropyrazoles via Palladium-Catalyzed Cyclization Reactions of β,γ-Unsaturated Hydrazones with Aryl Iodides

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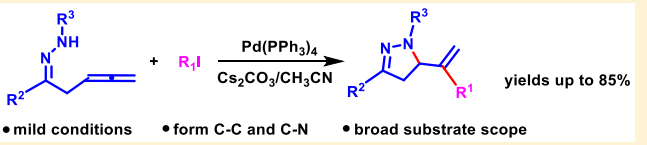
Supporting Information

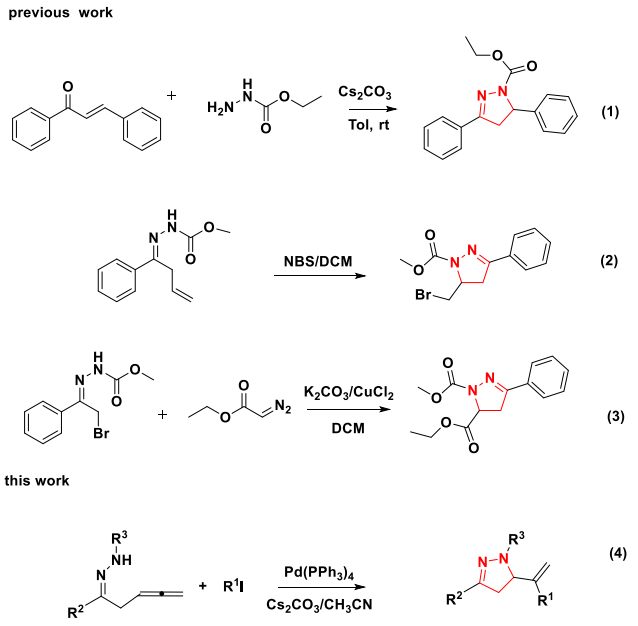
ABSTRACT: A novel two-component cyclization toward the synthesis of polysubstituted 4,5-dihydropyrazoles was carried out: i.e., cyclization of β,γ-unsaturated hydrazones with aryl iodides catalyzed by Pd(0). The reaction forms new carbon−carbon bonds and carbon−nitrogen bonds with moderate to good reactivity.



Five-membered nitrogen heterocycles are an important class of compounds that are widespread in natural products, bioactive molecules, and drugs.[1] Dihydropyrazoles and their derivatives have been found to show a diverse range of biological activities, including anticancer, antiviral, and antidiabetic activities and blood pressure lowering effects.[2] After years of research, scientists have discovered a number of methods to synthesize dihydropyrazoles.

Brière's group adopted enantioselective phase-transfer catalysis to synthesize pyrazolines (Scheme 1, eq 1).[3] Xiao's group explored a new strategy to synthesize 4,5-dihydropyrazoles through halocyclization with β,γ-unsaturated hydrazones and *N*-bromosuccinimide (Scheme 1, eq 2).[4] Afterward, Nicolini's group reported a copper-catalyzed interceptive [4 + 1] annulation of 1,2-diaza-1,3-dienes with diazo esters, leading to substituted 4,5-dihydropyrazoles (Scheme 1, eq 3).[5]

Scheme 1. Selected Synthetic Methods for Dihydropyrazoles



In recent years, metal-catalyzed functional grouping of allenes to synthesize various heterocyclic compounds has become a research hotspot.[6−10] In particular, the study of pyrazoline compounds remains a challenge for researchers. In our study on allene chemistry, we have demonstrated that allenes with nucleophilic functional groups are common building blocks for the synthesis of potentially important heterocyclic compounds, such as imidazolidines.[11] Here we wish to report our most recent observation on the Pd-catalyzed cyclization for the synthesis of polysubstituted dihydropyrazoles from β,γ-unsaturated hydrazones and aryl iodides (Scheme 1, eq 4).

On the basis of the results of previous experiments, we attempted the reaction of β,γ-unsaturated hydrazones and aryl iodides under identical conditions (conditions: **1a** (1.0 equiv), aryl halide (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (1.5 equiv), THF under reflux) (Table 1, entry 1). During screening, 4,5-dihydropyrazole **3aa** was obtained in 58% isolated yield. Compound **3aa** was fully characterized by $^1H/^{13}C$ NMR, MS, and HRMS methods. Subsequently, on the basis of previous research, we tested a number of Pd catalysts. As expected, the yields obtained with other Pd catalysts were reduced by different levels (Table 1, entries 2−4). We also found that the reaction did not proceed in the absence of Pd catalyst (Table 1, entry 5). Afterward, we investigated the effect of various bases on the reaction yield (Table 1, entries 6−11). Among them, Cs_2CO_3 promoted the reaction effect the best (Table 1, entry 8). Then, we tested the effectiveness of

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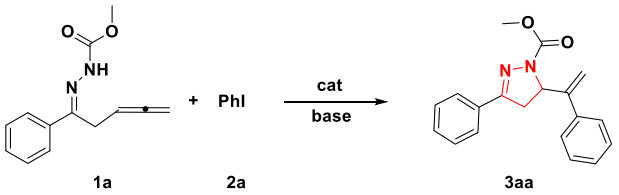
Table 1. Optimization of Reaction Conditions[a]



entry	cat.	base	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	THF	58
2	$Pd(OAc)_2$	K_2CO_3	THF	46
3	$Pd(PPh_3)_2Cl_2$	K_2CO_3	THF	43
4	$Pd(CF_3COO)_2$	K_2CO_3	THF	50
5		K_2CO_3	THF	n.d.[c]
6	$Pd(PPh_3)_4$	Na_2CO_3	THF	31
7	$Pd(PPh_3)_4$	CsF	THF	20
8	$Pd(PPh_3)_4$	Cs_2CO_3	THF	65
9	$Pd(PPh_3)_4$	*t*-BuOLi	THF	21
10	$Pd(PPh_3)_4$	NaOH	THF	trace
11	$Pd(PPh_3)_4$	NaH	THF	32
12	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	53
13	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane	65
14	$Pd(PPh_3)_4$	Cs_2CO_3	DCM	trace
15	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	53
16	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	67
17	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	70[d]
18	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	68[e]

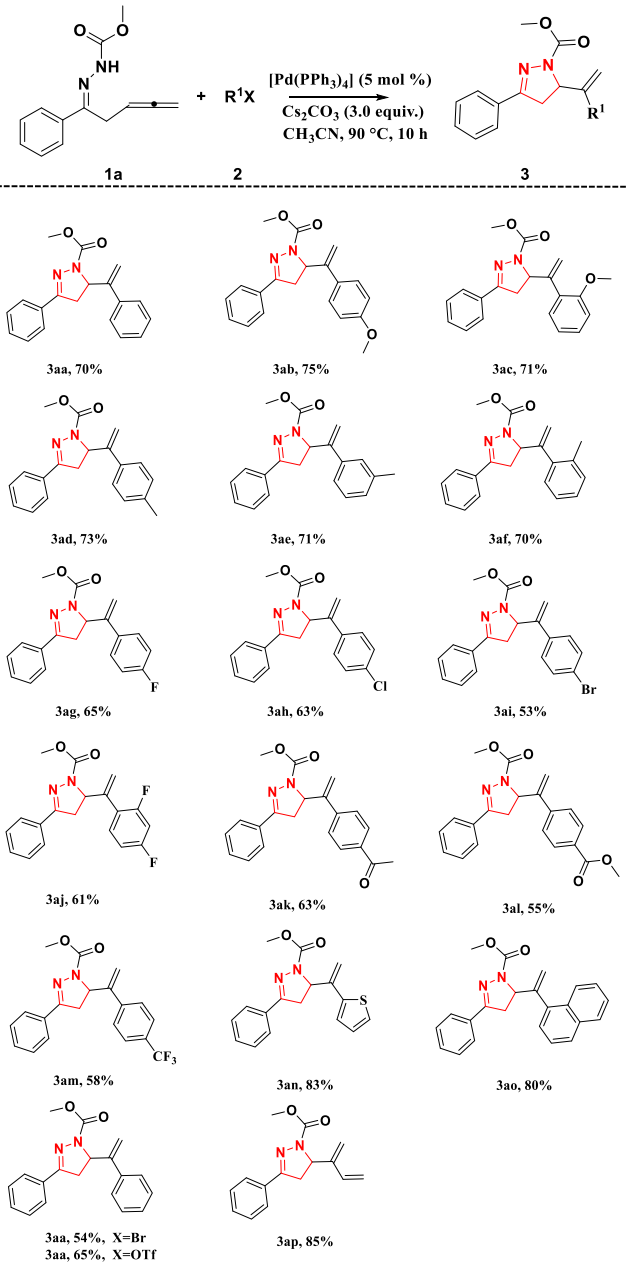
[a]Reaction conditions: under a N_2 atmosphere, **1a** (0.20 mmol, in 3 mL of CH_3CN), PhI (1.2 equiv), base (1.5 equiv), and [Pd^0] (5 mol %) at reflux. [b]Isolated yields. [c]n.d. = not detected. [d]Reaction carried out in a tube with a screw cap in 90 °C. [e]Reaction carried out in a tube with a screw cap in 110 °C.

several solvents on the reaction outcome (Table 1, entries 12−16) and achieved the optimal results with CH_3CN (Table 1, entry 16). Subsequently, we investigated the effect of the reaction temperature on the yield (Table 1, entries 16−18). Finally, the standard reaction conditions used for further investigations were established as **1a** (1 equiv), **2a** (1.2 equiv) with Cs_2CO_3 (1.3 equiv) in CH_3CN at 90 °C with [$Pd(PPh_3)_4$] (5 mol %) as the catalyst.

The results of the coupling cyclization of **1a** with other differently substituted aryl halides **2** under Pd(0) catalysis and the standard conditions are summarized in Scheme 2.

Among the substrates, disubstituted halides gave a much lower reaction yield. As can be seen from Scheme 2, electron-donating (Scheme 2, **3ab−af**) and electron-withdrawing substituents (Scheme 2, **3ag−aj**) on the benzene ring were well tolerated under the cyclization conditions. It was also found that the reaction outcome was better when electron-donating substituents were present on the phenyl ring (Scheme 2, **3ab−af**). Moreover, the reaction effect of the dihalogen substitution was lower than that of the monohalogen substitution: for example, the reaction yield of **3aj** was lower than that of **3ag**. The reaction proceeded smoothly even when a sensitive group was present on the phenyl ring (Scheme 2, **3ak,al**). In addition, when a strongly electron withdrawing group such as CF_3 was present on the benzene ring, the corresponding pyrazoline derivative **3am** was obtained in 58% yield. Finally, we studied the effect of heterocyclic substitution on the cyclization and obtained the corresponding thiophene- and naphthalene-substituted pyrazoline compounds **3an,ao** in 83% and 80% yields, respectively. In addition, we also

Scheme 2. Substrate Scope of Aryl Iodides.[a,b]



[a]Reaction conditions: under a N_2 atmosphere, **1a** (0.20 mmol, in 3 mL of CH_3CN), $Pd(PPh_3)_4$ (5 mol %), **2** (1.2 equiv), and Cs_2CO_3 (1.5 equiv). [b]Isolated yields.

investigated the reaction of phenyl bromide or phenyl triflate with **1a** to obtain the desired compound **3aa** in a moderate yield. Surprisingly, **1a** reacted with vinyl iodide to produce the corresponding compound **3ap**; the yield increased to 85%. From the above results, we conclude that aryl iodides are good ligands, which could generate various pyrazoline derivatives with potential biological activity.

Subsequently, we investigated the cyclization of different substituted *β,γ*-unsaturated hydrazones (**1**) and iodobenzenes (**2a**). Irrespective of the presence of electron-withdrawing (Scheme 3, **3ba−da**) or electron-donating substituents (Scheme 3, **3ga**), the reactions afforded the corresponding pyrazoline derivatives. Even substrates bearing strongly electron withdrawing groups such as CF_3 (Scheme 3, **3ea**)

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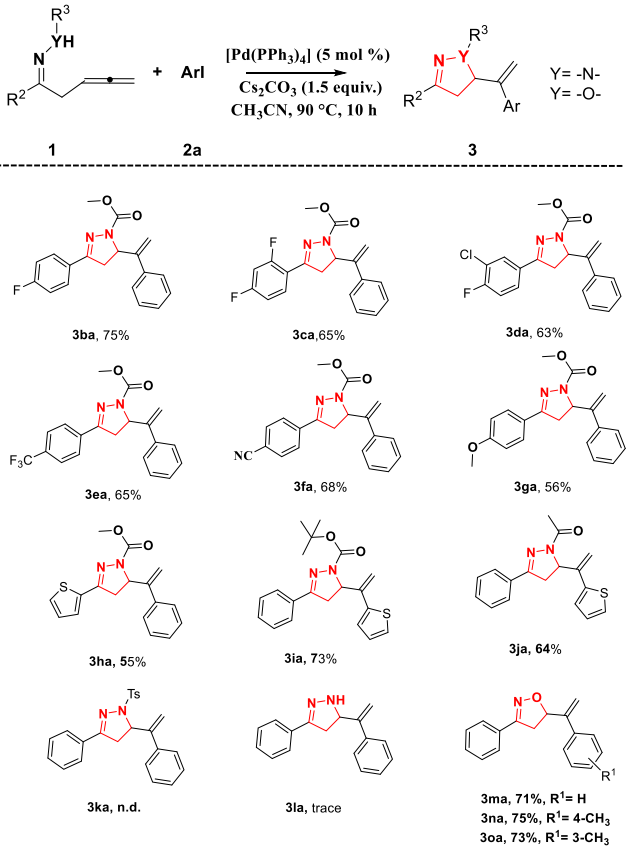
Scheme 3. Substrate Scope of β,γ-Unsaturated Hydrazones[a,b]



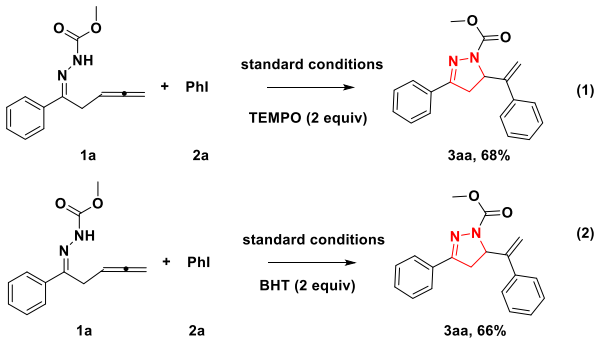
[a]Reaction conditions: under a N_2 atmosphere, **1** (0.20 mmol, in 3 mL of CH_3CN), $Pd(PPh_3)_4$ (5 mol %), **2a** (1.2 equiv), and Cs_2CO_3 (1.5 equiv). [b]Isolated yields.

and CN (Scheme 3, **3fa**) gave the target compounds in 65% and 68% yields. It is worth mentioning that thiophene-substituted β,γ-unsaturated hydrazone can also form pyrazoline derivative (Scheme 3, **3ha**) in 55% yield, thereby expanding the application of the method. In addition, we changed the terminal substituents of the β,γ-unsaturated hydrazones to investigate the effect of different substituents on the reaction outcome.

This procedure was also applicable to the reaction of β,γ-unsaturated hydrazones with different substituted protective groups and aryl iodides under the standard conditions: boc (**3ia**, 73%) and acetyl (**3ja**, 64%) analogues were isolated in moderate yields. When the terminal ester group was replaced with a sulfonyl group, the reaction did not proceed smoothly. (Scheme 3, **3ka**). Subsequently, the effect of removing the terminal substituents on the reaction outcome was investigated (Scheme 3, **3la**). In this case, the reaction did not proceed smoothly, revealing the importance of terminal protective group substitution. Finally, replacement of unsaturated hydrazones with unsaturated oximes led to a smooth reaction (Scheme 3, **3ma**–**oa**). This provides a new synthesis route to 4,5-dihydroisoxazole derivatives.

On the basis of the above experimental results, we attempted to elucidate the mechanism of the reaction. According to previous research,[9,11] we attempted to add radical scavengers (TEMPO, BHT) to study their effect on the reaction (Scheme 4, eqs 1 and eq 2). The addition of these scavengers did not hinder the cyclization, and it was revealed that the reaction did not proceed via a radical mechanism.

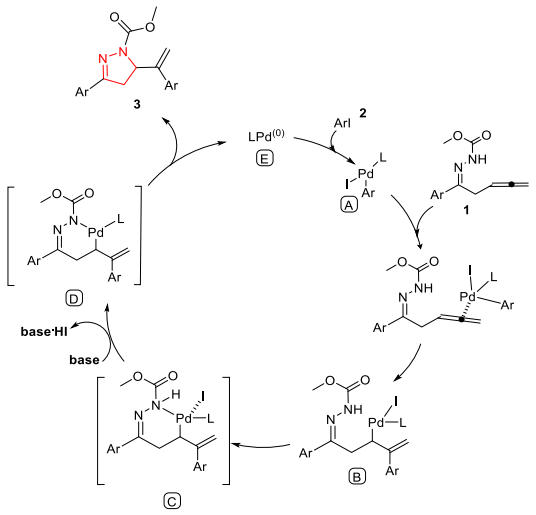
Scheme 4. Mechanistic Studies[a,b]



[a]Reaction conditions: under a N_2 atmosphere, **1** (0.20 mmol, in 3 mL of CH_3CN), $Pd(PPh_3)_4$ (5 mol %), **2a** (1.2 equiv), and Cs_2CO_3 (1.5 equiv). [b]Isolated yields.

On the basis of previous research,[6−11] we propose a possible reaction mechanism in Scheme 5. Initially, Pd(0) reacts with

Scheme 5. Proposed Mechanism



the aryl iodide to give oxidative addition product **A**. Then, the allene double bond is coordinated with the electrophilic complex **A** and subsequent carbopalladation affords the intermediate **B**. Afterward, **B** initiated by intramolecular attack of the lone pair electrons by the imine nitrogen affords the intermediate **C**. Subsequently, amine complex **C** reacts with base to generate the intermediate **D**. The last, resulting complex **D** undergoes reductive elimination to afford the target pyrazoline **3**, while releasing the Pd(0) catalyst for the next cycle.

In summary, we have developed an efficient method for the synthesis of polysubstituted 4,5-dihydropyrazole and 4,5-dihydroisoxazole derivatives. The experimental results showed that a variety of substituents were well tolerated in this method. This study provides a novel synthesis route to nitrogen-containing heterocycles and potentially bioactive compounds. Further research aimed at expanding the applications of this method is underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.9b00656.

Experimental procedures, full spectroscopic data for all new compounds, and of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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