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A Regioselective Approach to Trisubstituted Pyrazoles via Palladium-Catalyzed Oxidative Sonogashira-Carbonylation of Arylhydrazines

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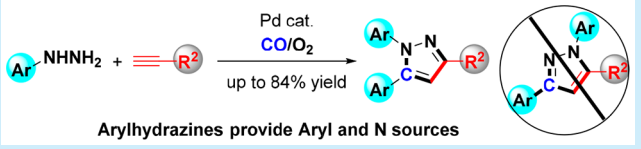
Supporting Information

ABSTRACT: A palladium-catalyzed oxidative carbonylation of arylhydrazines and alkynes with balloon pressure CO/O_2 to afford trisubstituted pyrazoles in a one-pot manner has been developed. The formation of trisubstituted pyrazoles involves a sequential C−N bond cleavage, carbonylation, Sonogashira coupling, Michael addition, and intramolecular condensation cyclization tandem process. An unprecedented oxidative Sonogashira-carbonylation reaction of arylhydrazine plays a key role for such a facile approach to pyrazoles.



Pyrazole is an important motif for large varieties of natural products and biomolecules, which exhibit remarkable biological and therapeutic activities.[1] For example, PNU-32945 (**I**) is used as a nonnucleoside reverse transcriptase inhibitor for treatment of HIV.[2] Polysubstituted pyrazoles are the core structures of a broad range of commercial available drugs such as Rimonabant (**II**),[3] CDPPB (**III**),[1b] Zoniporide (**IV**),[4] Celecoxib (**V**),[5] and PDE5 inhibitor (**VI**) (Figure 1).[6] Consequently, searching for efficient synthetic methodology for pyrazole derivatives has attracted much attention.[7]

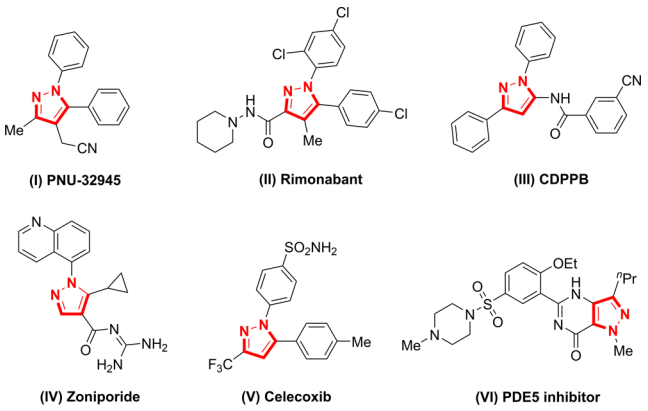


Figure 1. Examples of pyrazole-containing bioactive compounds.

Traditional synthesis of multisubstituted pyrazoles usually adopts addition condensation of hydrazines with carbonyl derivatives,[8] or cycloadditions of diazo compounds with alkenes or alkynes.[9] Moreover, hydrazones have also been employed as starting materials in the synthesis of pyrazoles.[10] Among the reported methods, the addition condensation reaction of hydrazine with ynones is featured as one of most efficient strategies to construct pyrazoles.[11] Recently, palladium-catalyzed multicomponent cascade reactions of hyrdrazine to afford pyrazoles through an ynone intermediate, which was formed *in situ* via Sonogashira coupling reaction of alkynes with acyl chlorides[12] or aryl iodides in the presence of CO,[13] have also been developed. Theoretically, two regioisomers can be produced via 1,2-addition of the terminal nitrogen and 1,4-addition of the terminal or internal nitrogen of hydrazine, respectively (Scheme 1). Although excellent regioselectivity could be obtained for methylhydrazine due to the stronger nucleophilicity of the internal nitrogen of methylhydrazine,[12d] the regioselectivity of arylhydrazines is still a challenge and unpredictable which might be attributed to the similar nucleophilicity of both nitrogen atoms of arylhydrazines (Scheme 1).[14] It is highly desirable to develop efficient reaction systems for the synthesis of aryl substituted pyrazoles from arylhydrazines with high efficiency and regioselectivity under mild reaction conditions.

Since Loh and co-workers' pioneering work in 2011,[15] arylhydrazines aroused much attention in palladium-catalyzed crossing-coupling reactions as environmentally friendly arylation reagents under aerobic oxidative reaction conditions because N_2 and H_2O were the only byproducts.[16] On the other hand, palladium-catalyzed carbonylation has evolved into a useful and straightforward synthetic strategy for introducing one carbon unit to construct various carbonyl-containing compounds.[17] We envisioned that arylhydrazines could be applied as an arylation reagent under oxidative carbonylation reaction conditions[18] to provide ynone, which could be trapped by another molecular arylhyrazine to furnish pyrazoles (Scheme 1). Herein, we reported a novel method for the synthesis of pyrazoles with excellent regioselectivity by a palladium-catalyzed tandem reaction based on an unprecedented oxidative Sonogashira-carbonylation of arylhydrazines.

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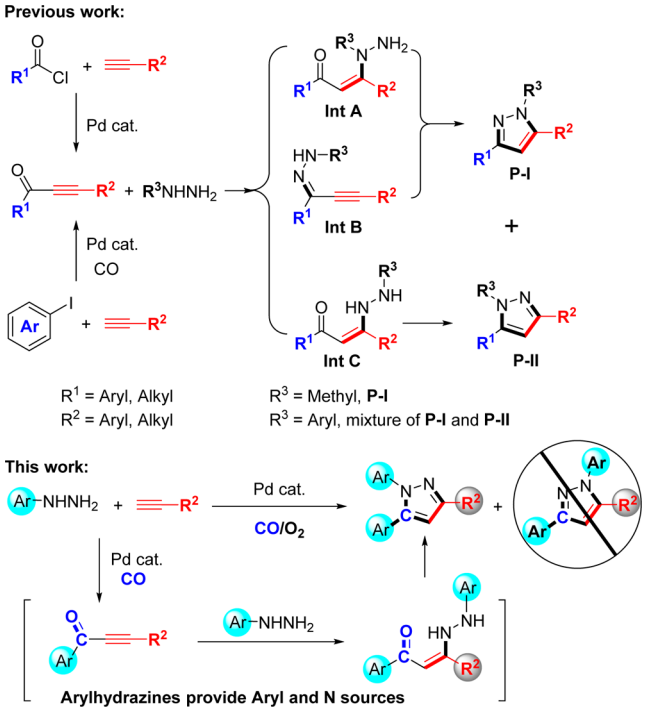
Scheme 1. Synthetic Strategies for Pyrazoles

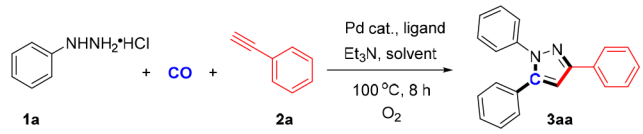


Initially, the Pd-catalyzed oxidative cascade carbonylation of phenylhydrazine hydrochloride (**1a**) and phenylacetylene (**2a**) with a balloon of CO/O_2 (3:1) was investigated (Table 1; see the Supporting Information for details). Fortunately, the desired product 1,3,5-triphenyl-1*H*-pyrazole (**3aa**) was obtained in 59% yield in the presence of $Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %) in DMF (Table 1, entry 1). Further screening of the catalyst showed that other catalysts such as $Pd(dba)_2$, $PdCl_2$, $Pd(TFA)_2$, and $Pd(acac)_2$ produced the corresponding pyrazole (**3aa**) in lower yields (Table 1, entries 2−5).

Ligand screening revealed that PPh_3 was the best ligand in this transformation (Table 1, entries 6−10). The solvent has a remarkable effect on the reaction efficiency, and DMF was identified as the best choice of solvent (Table 1, entries 11−14). The base played a crucial role in this transformation, as a higher yield up to 72% could be attained when 4.0 equiv of Et_3N were used (Table 1, entries 15−20). Gratifyingly, the presence of 4 Å molecular sieve was helpful to improve the reaction efficiency and 1,3,5-triphenyl-1*H*-pyrazole (**3aa**) could be obtained in 78% isolated yield (Table 1, entry 20).

Under the optimized reaction conditions, the scope of arylhydrazines **1** was investigated with alkyne **2a** as the model substrate (Scheme 2). It appears that the position of the substituents on the phenyl ring has a very limited effect on the reaction efficiency. The *o*-Me, *m*-Me, *p*-Me, *p*-Et, and *p*-^{t}Bu substituted arylhydrazines all reacted smoothly and afforded the pyrazole products (**3ba−fa**) in high yields (72%−84%). Disubstituted substrates such as 3,4-dimethyl, 2,4-dimethyl, and 3,5-dimethyl phenylhydrazines could also successfully undergo the CO-insert cascade reaction with phenyl acetylene to produce the corresponding products (**3ga**, **3ha**, and **3ia**) in 74%, 74%, and 73% yields, respectively. In addition, the strong electron-donating group 4-OMe− is also tolerated. Moderate electron-withdrawing substituent F− turned out to be compatible under the standard reaction condition and gave the corresponding pyrazole **3ka** in moderate yield. However,

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	DMF	59
2	$Pd(dba)_2$	PPh_3	DMF	47
3	$PdCl_2$	PPh_3	DMF	49
4	$Pd(TFA)_2$	PPh_3	DMF	50
5	$Pd(acac)_2$	PPh_3	DMF	32
6	$Pd(OAc)_2$	Bpy	DMF	4
7	$Pd(OAc)_2$	*o*-tol_3P	DMF	3
8	$Pd(OAc)_2$	Ph_2PCy	DMF	43
9	$Pd(OAc)_2$	DPPPy	DMF	52
10	$Pd(OAc)_2$	DPPE	DMF	trace
11	$Pd(OAc)_2$	PPh_3	MeCN	ND
12	$Pd(OAc)_2$	PPh_3	DMSO	30
13	$Pd(OAc)_2$	PPh_3	EtOH	4
14	$Pd(OAc)_2$	PPh_3	THF	trace
15[c]	$Pd(OAc)_2$	PPh_3	DMF	3
16[d]	$Pd(OAc)_2$	PPh_3	DMF	40
17[e]	$Pd(OAc)_2$	PPh_3	DMF	62
18[e,f]	$Pd(OAc)_2$	PPh_3	DMF	48
19[e,g]	$Pd(OAc)_2$	PPh_3	DMF	72 (69)
20[e,g,h]	**$Pd(OAc)_2$**	**PPh_3**	**DMF**	**81 (78)**

[a]Reaction condition: phenylhydrazine hydrochloride **1a** (0.6 mmol), phenylacetylene **2a** (0.2 mmol), Et_3N (2.0 equiv) in the presence of Pd cat. (5 mol %), and ligand (20 mol %) in solvent (2.0 mL) at 100 °C for 8 h, with a balloon of CO/O_2 (3:1). [b]GC yield with naphthalene as the internal standard. Isolated yield is in parentheses. [c]No Et_3N. [d]1.0 equiv of Et_3N was used. [e]4.0 equiv of Et_3N was used. [f]2.0 equiv of **1a** were used. [g]4.0 equiv of **1a** were used. [h]50 mg of 4 Å molecular sieve were used. Bpy = 2,2′-Dipyridyl, DPPPy = Diphenyl-2-pyridylphosphine, DPPE = 1,2-Bis(diphenylphosphino)ethane, THF = Tetrahydrofuran, DMF = *N*,*N*-Dimethylformamide, DMSO = Dimethyl sulfoxide.

strong electron-withdrawing groups such as 4-cyano and 4-nitro have a significant detrimental effect on the reaction efficiency and prohibited the reaction completely (data not shown). It should be noted that aliphatic hydrazines are also not valid substrates for this transformation.

Next, the substrate scope regarding the alkyne partner was further examined and the results are summarized in Scheme 3. Generally, phenyl acetylenes with substituents such as *p*-Me, *m*-Me, and *p*-^{t}Bu afforded the corresponding products (**3ab−ad**) in good yields. In addition, phenyl acetylenes bearing a methoxy group could afford the target products (**3ae−af**) in 50%−71% yields. The fluoro- and chloro-substituted phenyl acetylene could also be used as valid substrates to produce **3ai** and **3aj** in 63% and 61% yields. In addition, 4-bromophenyl acetylene was also compatible with this reaction conditions to afford the target product (**3ak**) albeit in low yield.[19] The structures of these pyrazoles were unambiguously assigned by NMR and X-ray crystallography (see the Supporting Information for details). Moreover, aliphatic alkynes could also be tolerated to furnish pyrazoles (**3am**, **3an**, and **3ao**) in moderate yields. However, phenyl acetylenes containing a strong electron-withdrawing group such as a 4-cyano group (**3al**) is not tolerated.

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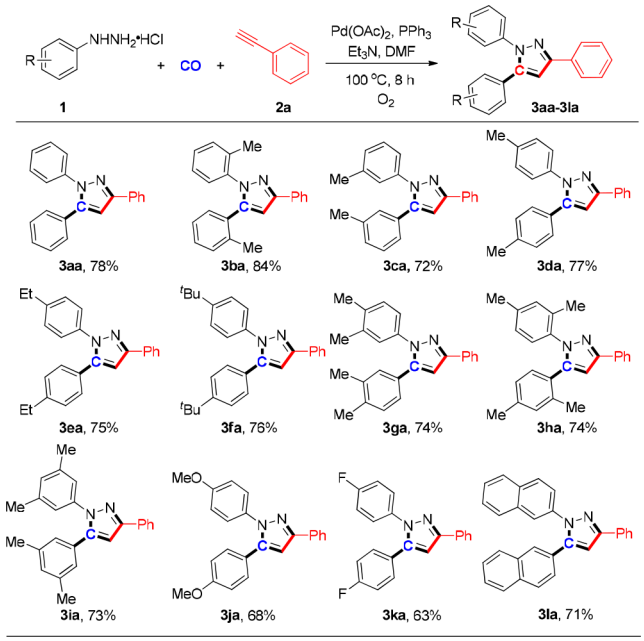
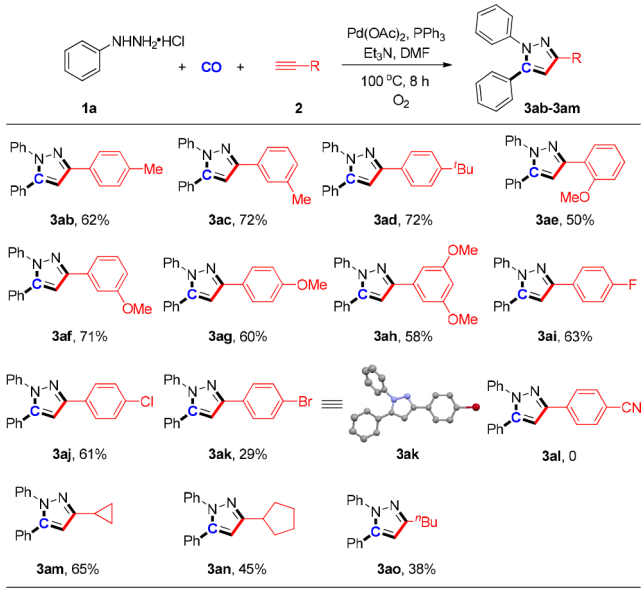
Scheme 2. Substrate Scope of Arylhydrazines[a]



[a]Reaction conditions: **1** (0.8 mmol), **2a** (0.2 mmol), 5 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 4.0 equiv of Et_3N, and 4 Å molecular sieve (50 mg) in 2.0 mL of DMF with a balloon of CO/O_2 (3:1) at 100 °C for 8 h.

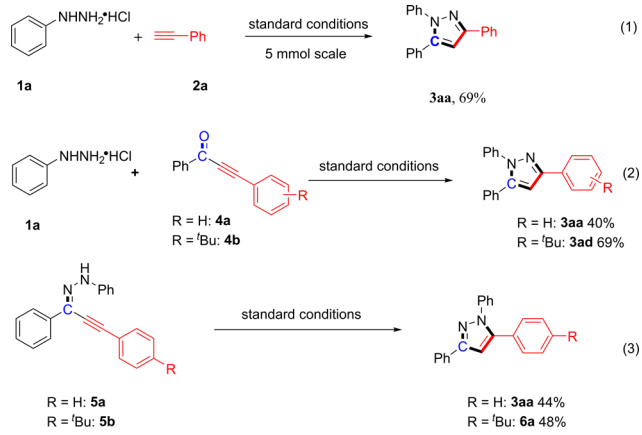
Scheme 3. Substrate Scope of Terminal Alkynes[a]



[a]Reaction conditions: **1** (0.8 mmol), **2a** (0.2 mmol), 5 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 4.0 equiv of Et_3N, and 4 Å molecular sieve (50 mg) in DMF (2.0 mL) with a balloon of CO/O_2 (3:1) at 100 °C for 8 h.

To highlight the utility of the synthetic method for pyrazoles, we successfully scaled the reaction up to 5 mmol and obtained product **3aa** in 69% yield under standard conditions (Scheme 4, eq 1). In order to gain insight into the reaction mechanism, several control experiments were conducted. Under the standard reaction conditions, the pyrazole products **3aa** and **3ad** could be obtained in 40% and 69% yields, respectively,

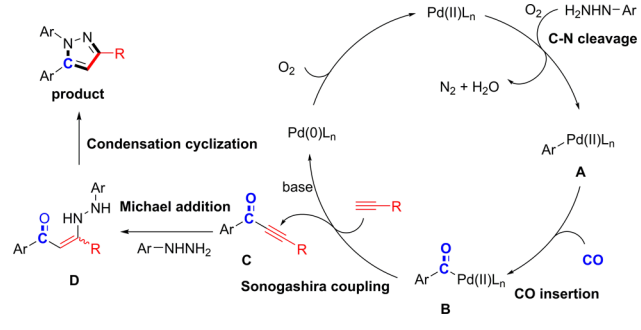
Scheme 4. Control Experiments



when phenylhydrazine reacted with ynone substrates (Scheme 4, eq 2). Therefore, we proposed that ynone should be a key intermediate in this transformation. α,β-Alkynic hydrazones **5a** and **5b** were synthesized and treated with the standard reaction conditions. As expected, pyrazoles **3aa** and **6a** were obtained in moderate yields. This experimental result unambiguously excluded the possibility that the tandem process proceeded with hydrazone as the intermediate (Scheme 4, eq 3).

On the basis of the above experimental results, a plausible reaction mechanism is proposed in Scheme 5. Arylpalladium

Scheme 5. Proposed Reaction Mechanism



species **A** is formed in situ via an oxidative C–N cleavage of arylhydrazine with the Pd(II) catalyst under atmospheric O_2. Subsequently, CO insertion of complex **A** results in acylpalladium **B**. Then, the acyl palladium **B** reacts with the terminal alkyne to afford ynone **C** and Pd(0). The active Pd(II) species is regenerated by oxidation of Pd(0) with O_2, and the catalytic cycle is closed.[20] On the other hand, the ynone **C** undergoes a Michael addition reaction with another molecule arylhydrazine via the terminal amino group to yield enamine intermediate **D**. Finally, intramolecular condensation cyclization of intermediate **D** provides the target pyrazole product.[21]

In conclusion, we have developed a highly efficient multicomponent reaction system for the synthesis of trisubstituted pyrazoles with the unprecedented palladium-catalyzed aerobic oxidative Sonogashira-carbonylation of arylhydrazines with terminal alkynes and CO as the key step. The reaction is believed to proceed through a five-step tandem reaction including C–N cleavage, CO insertion, Sonogashira coupling, Michael addition, and cyclization. Arylhydrazines played two roles in this transformation. Importantly, excellent regioselectivity was observed, and only one regioisomer was

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formed during this tandem process. It is foreseeable that this reaction will find broad application in drug discovery and other related research fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01447.

Experimental procedures, compound characterization data, copies of NMR spectra (PDF)

Crystallographic data for compound **3ak** (CIF)

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Notes

The authors declare no competing financial interest.

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(19) The CCDC number of compound **3ak** is 1548912. For more details, see the Supporting Information.

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