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Two-Component Approach Toward Fully-Substituted N-Fused Pyrrole Ring

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Abstract

An efficient two-component palladium-catalyzed arylation/cyclization cascade approach toward a variety of N-fused pyrroloheterocycles has been developed. This transformation proceeds via the palladium-catalyzed coupling of aryl halides with propargylic esters or ethers followed by the 5-*endo-dig* cyclization leading to highly functionalized pyrroloheterocycles in good to excellent yield.

Nitrogen-containing heteroaromatic molecules and their analogs are pharmaceutically important scaffolds, broadly present in naturally occurring and synthetic biologically active molecules.¹ For example, molecules containing indolizine and other closely related cores exhibit a wide array of biological activities, including cytotoxicity,² multi-drug resistance (MDR) reversal in some cancer cell lines,³ and immunomodulation.⁴

In this regard, transformations that utilize readily available substrates to provide access to densely substituted pyrroloheterocycles are in high demand.⁵ Previously, our group reported silver-catalyzed cycloisomerization of propargyl heterocycles as a route to 1, 3-disubstituted N-fused heterocycles (Scheme 1, eq 1).⁶ An alternative protocol is based on the the gold-catalyzed migratory cycloisomerization of propargyl ethers into various types of 1, 2-disubstituted N-fused heterocycles (eq 2).⁷ Although these methods are general with respect to the heterocyclic core, these approaches are limited to the synthesis of 1, 3- or 1, 2-disubstituted indolizines, while either the C-2 or C-3 position remain unfunctionalized. This problem was recently mitigated by employing stoichiometric amounts of iodine,^{5f,g,h} followed by cross-coupling steps. Herein, we report a Pd-catalyzed two-component arylation/cyclization cascade approach toward 1, 2, 3-trisubstituted N-fused heterocycles in good to excellent yields (eq 3).⁸

We hypothesized that Ar-Pd-X species would undergo carbopalladation of the propargylic moiety of **1** with subsequent 5-*endo-dig* cyclization to produce **2** (eq 3).

To test this idea, the easily accessible propargyl-containing pyridine **19** was first subjected to the palladium-catalyzed arylation/cyclization reaction. Employing iodobenzene as the

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Supporting Information Available: Experimental details and characterization data for all new compounds is available free of charge via the Internet at <http://pubs.acs.org>.

electrophilic component led to formation of the desired indolizine **2a** in 49 % yield (Table 1, entry 1). Attempts to substitute DMF with other solvents were not particularly successful (entries 2–4). Utilizing different lithium and ammonium salts led to a significant improvement in the reaction yields (entries 5–8). Switching the base from NEt₃ to K₂CO₃ was also beneficial (entry 9).

Furthermore, using triphenylphosphine as an additive led to the formation of **2a** in 78 % yield (entry 10). Employment of bromo-benzene under these conditions proved to be less efficient producing indolizine **2a** in 29 % yield only (entry 11).

Next, under the optimized conditions, the scope of this cascade cyclization was examined (Table 2). Thus, acetyloxy and pivalyloxy-propargylic esters possessing alkyl (entries 1–7), aryl (entries 8, 9), or alkenyl (entry 10) substituents at the triple bond underwent smooth conversion to give the corresponding heterocycles **2a–j** in good to excellent yields. To provide a handle for further functionalization, pivalates were chosen over acetates due to their greater potential to participate in Suzuki-Miyaura¹⁰ and Kumada^{5e} coupling reactions.

The generality of this process was expanded by utilization of a variety of functionalized iodobenzenes which uneventfully cyclized into the corresponding indolizines **2k–p** (entries 11–16). Notably, this reaction proceeded equally efficiently with other heterocyclic cores; quinoline and isoquinoline propargylic esters were successfully utilized in this transformation providing access to tricyclic cores **2q–t** in a highly efficient manner (entries 17–20).

It was also found that propargylic phenylethers **3** could be employed in this transformation (Scheme 2). Interestingly, bromobenzenes performed equally well in this process (**4a–c**). Similarly, the cascade cyclization of propargylic silylether **3** gave the corresponding indolizine **4e** in 73 % yield.

Presumably, this palladium-catalyzed arylation/-cyclization reaction proceeds through a coordination of the triple bond of an alkyne **1** with ArPdX, triggering the *5-endo-dig* cyclization by the nucleophilic attack of the pyridyl nitrogen, leading to the formation of zwitterionic adduct **5**. The latter, upon deprotonation/tautomerization and subsequent reductive elimination¹¹ would give product **2**.

In summary, we have developed a practical and efficient two-component coupling method toward fully-substituted fused pyrroloheterocycles, including indolizines, pyrroloquinolines, and pyrroloisoquinolines. This method is complementary to the previously developed approaches^{6,7,12} toward mono- and disubstituted N-fused pyrroloheterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Approaches Toward Indolizines with Different Substitution Pattern

Scheme 2. Arylation/Cyclization Cascade Reactions of Propargylic Ethers **3**^a Reaction was performed under optimized conditions reported in Table 2.

Scheme 3.
Proposed Mechanism

Table 1

Optimization of Cascade Approach

entry	X	Pd	base	solvent	additive	yield, % ^b
1	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMF	-	49
2	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMA	-	46
3	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	NMP	-	47
4	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	MeCN	-	34 ^c
5	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMF	LiCl	54
6	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMF	TBAC	57
7	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMF	TBAB	60
8	I	PdCl ₂ (PPh ₃) ₂	NEt ₃	DMF	TBAI	62
9	I	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	DMF	TBAI	69
10	I	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	DMF	TBAI ^d	72
11	Br	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	DMF	TBAI ^d	26

^aReactions were run in the presence of 5 mol % of catalyst in appropriate solvent (0.33 M) at 120 °C for 4 hours.

^bGC/MS yields.

^cReaction was performed at 90 °C.

^dReaction was run with additional 40 mol % of PPh₃.

Table 2

Arylation/Cyclization Cascade Reactions of Propargylic Esters **1**^a

entry	2	yield, % ^b
1		72
2		76
3		94
4		77
5		94
6		50

entry	2	yield, % ^b
7	 2g	94
8	 2h	69
9	 2i	68
10	 2j	96
11	 2k	87
12	 2l	53

entry	2	yield, % ^{a,b}
13	 2m	70
14	 2n	90
15	 2o	93
16	 2p	88
17	 2q	71
18	 2r	74

entry	2	yield, % ^b
19	 2s	78
20	 2t	88

^a All reactions were performed with on 0.5 mmol scale in DMF (0.33 M) at 120 °C.

^b Yield of the isolated product after flash chromatography on silica gel.