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General and Direct Synthesis of 3-Aminoindolizines and Their Analogues via Pd/Cu-Catalyzed Sequential Cross-Coupling/Cycloisomerization Reactions

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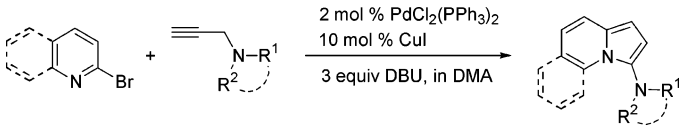
ABSTRACT



An efficient and one-step synthesis of 3-aminoindolizines or benz[*e*]indolizines from the reactions of propargyl amines or amides with heteroaryl bromides was developed. This methodology is realized by a tandem reaction using Pd/Cu catalysts, which could catalyze coupling and cycloisomerization reactions in the same vessel.

Indolizines, which exhibit intriguing molecular structures featured by an N-bridgehead bicyclic ring system fused with both a π-excessive pyrrole and a π-deficient pyridine, have received much attention in recent years.[1] Many of the synthetic and natural indolizines have displayed important biological activities which can find a variety of applications in pharmaceutical use.[2] For example, they have been employed as antibacterial, antiviral, antiinflammatory,[3a,b] and cardiovascular agents,[3c] as testosterone 3α-reductase inhibitors,[3d] as 5-HT4 receptor antagonists,[3e] and as CNS depression agents.[3f] As a consequence, there is a growing interest in the synthesis of indolizine derivatives. The synthetic approaches for indolizines[4−12] mainly include: reactions of 2-alkylpyridine with acid anhydrides (Scholtz reaction)[5] or α-halo ketones (Tschitschibabin reaction);[6] 1,3-dipolar cycloadditions of pyridinium and related heteroaromatic ylides

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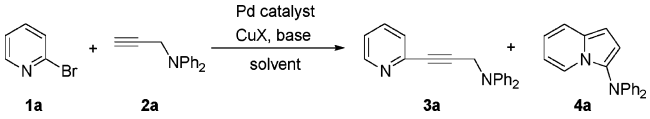
with electron-deficient alkynes or alkenes;[7] 1,5-dipolar cyclizations of *N*-allylpyridinium salts;[8] reactions of 2-halopyridinium salts with β-dicarbonyl compounds;[9] iron-catalyzed carbocyclization of N-substituted pyrrolotrienes;[10] and cyclization of the silicon-capped (*Z*)-2-pyridine vinylacetylene with basic alcohol solutions.[11] However, these strategies have some limitations, more or less, such as being restricted to specific substituted substrates or involvement of multistage synthesis. Recently, Gevorgyan et al. reported an efficient synthesis of 3-indolizines[12] via CuX-mediated cycloisomerization of alkynyl pyridines. In this reaction, a high catalyst loading (0.5−1 equiv) and high reaction temperature (130−150 °C) were required, and only 3-alkyl-substituted indolizines were constructed according to the report.[12] Nevertheless, a general synthetic method for functionalized indolizines such as 3-aminoindolizines has not been established.[13] In our ongoing efforts to investigate the coordination behavior of (2-pyridyl)alkynes with early transition metals, we have developed a zirconium-mediated cyclodimerization of these heteroaryl-substituted alkynes.[14] Within this program, pyridyl alkynes tethered with an amino group were needed as substrates.[14b] When we applied Sonogashira coupling[15] of the corresponding heteroaryl bromides with propargylic amines to form the requisite *N*-(2-alkynyl)amines, we noted that, in some cases, a small amount of byproduct with strong fluorescence was always formed during the reaction. The byproduct was identified as 3-aminoindolizines. For example, the reaction of 2-bromopyridine **1a** with *N*,*N*-diphenyl(prop-2-ynyl)amine **2a** in Et_2NH using 1 mol % of $PdCl_2(PPh_3)_2$ and 2 mol % of CuI as catalysts afforded the (2-pyridyl)alkyne **3a** in 89% yield along with 2% of indolizine **4a** (see Table 1, entry 1). Inspired by the results outlined above, we became interested in developing a direct route to indolizines from readily available precursors of heteroaryl bromides and propargyl amines via a domino process because a domino or cascade reaction would greatly enhance the efficiency of the synthesis and minimize the amount of the required reagents.[16] Herein, we report a one-step synthetic route to 3-substituted indolizines, in which a Pd/Cu catalyst was utilized as a single-pot catalyst to catalyze independent reactions in the same reaction vessel, and there is no need to isolate the intermediate of pyridyl alkynes. The yields of this process range from 41% to 96%, and the procedure readily accommodates considerable functionalities.

Table 1. Optimization Studies for the Pd/Cu-Catalyzed Coupling/Cycloisomerization Reactions



1a 2a 3a 4a

entry	Pd cat.[a]	CuX	base	solvent	temp/time	yield (%) of **3a**[b]	yield (%) of **4a**[b]
1	1%	2% CuI	–	Et_2NH	50 °C, 12 h	89[c]	2[c]
2	2%	30% CuCl	Et_2NH[d]	DMA	50 °C, 16 h	31	8
3	2%	10% CuI	1.5 K_2CO_3	DMA	50 °C, 12 h	88	4
4	2%	10% CuCl	4.0 DBU	DMA	50 °C, 12 h	3	89
5	2%	10% CuCl	2.0 DBU	DMA	50 °C, 12 h	2	61
6	1%	4% CuCl	4.0 DBU	DMA	50 °C, 12 h	7	76
7	2%	10% CuI	4.0 DBU	DMA	50 °C, 12 h	7	92
8	2%	10% CuI	4.0 DBU	THF	50 °C, 12 h	70	18
9	2%	10% CuI	3.0 DBU	DMA	80 °C, 2 h	<1	96
10	2%	10% CuI	3.0 DBU	toluene	80 °C, 20 h	7	85
11	2%	10% CuI	3.0 piperidine	DMA	80 °C, 20 h	76	9
12	2%	10% CuI	3.0 Cs_2CO_3	DMA	80 °C, 9 h	<1	75
13	2%	10% CuI	3.0 DBU	DMA	80 °C, 2 h	<1	96
14	2%	10% CuI	NEt_3[e]	DMA	80 °C, 18 h	86	7
15	2%[f]	10% CuI	3.0 DBU	DMA	80 °C, 2 h	5	91
16	1%	10% CuI	3.0 DBU	DMA	80 °C, 4 h	<1	96

[a] Unless otherwise noted, all the Pd catalysts were $PdCl_2(PPh_3)_2$. [b]Unless otherwise noted, all the yields were GC yields. [c]Isolated yields. [d]Et_2NH was used as cosolvent, and the ratio of Et_2NH/DMA was 4:1. [e]Et_3N was used as cosolvent, and the ratio of Et_3N/DMA was 1:7. [f]$Pd(PPh_3)_4$ was used as a catalyst.

The above-mentioned reaction of 2-bromopyridine **1a** and propargyl amine **2a** was chosen for optimization of the coupling/cycloisomerization process. The representative results are shown in Table 1. We first examined the reaction using 2 mol % of $PdCl_2(PPh_3)_2$ and 30 mol % of CuCl in Et_2NH−DMA; however, the yield of the coupling product **3a** was decreased to 31%, and the desired indolizine **4a** was formed in 8% yield after stirring at 50 °C for 16 h (Table 1, entry 2). Switching the base to a carbonate base such as K_2CO_3 only increased the yield of **3a** to 88% (Table 1, entry 3). After many efforts, we were delighted to find that cyclization proceeded smoothly and provided a 89% GC yield of the indolizine **4a** in DMA at 50 °C for 12 h with 4 equiv of DBU as a base (Table 1, entry 4). The structure of **4a** was unambiguously confirmed by X-ray crystallographic analysis, which clearly showed N-bridgehead heterocycles.[17] Decreasing the amount of DBU to 2 equiv resulted in a lower yield of **4a** (61%, Table 1, entry 5). When the reaction was carried out in THF (Table 1, entry 8), the coupling product of **3a** was formed in 70% yield, whereas only 18% of **4a** was produced. Interestingly, the reaction time was dramati-

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(13) A one-pot procedure for the synthesis of 3-(dialkylamino)indolizines has been reported by the Pd-catalyzed reaction of 2-bromopyridine, propargyl alcohol, and secondary amine; however, the reaction usually afforded low yields of the products (<49%). See: (a) Ohsawa, A.; Abe, Y.; Igeta, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3273. For the use of 3-aminoindolizines in the treatment of cancer, see: (b) Koya, K.; Sun, L.; Ono, M.; Ying, W.; Li, H. PCT Int. Appl. WO 03022846, 2003.

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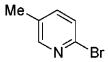
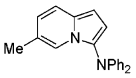
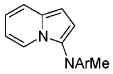
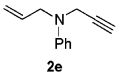
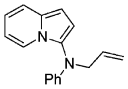
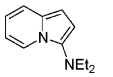
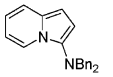
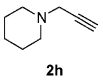
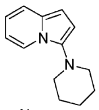
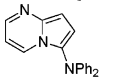
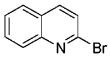
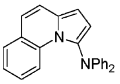
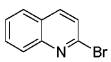
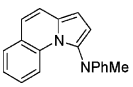
(17) See Supporting Information.

cally reduced to 2 h by increasing the reaction temperature to 80 °C. In this case, only a trace amount of **3a** was observed (Table 1, entry 9). The use of mixed solvents of NEt_3−DMA only resulted in the formation of **3a** as a major product after 18 h at 80 °C (Table 1, entry 14). $Pd(PPh_3)_4$ also served as a suitable palladium source for this reaction to give **4a** in 91% yield (Table 1, entry 15).

On the basis of the above optimization results, we chose the following reaction conditions: 2 mol % of $PdCl_2(PPh_3)_2$, 10 mol % of CuI, and 3 equiv of DBU in DMA stirred at 80 °C for an appropriate time. The present method could be applied successfully to a variety of heteroaryl bromides and propargyl amines bearing various types of functionalities. The results are summarized in Table 2. In most cases, the

Table 2. One-Step Synthesis of 3-Aminoindolizines from the Reaction of Heteroaryl Bromides With Propargyl Amines

entry	ArBr	propargyl amines	temp. / time	product		yield(%)[a]
1		 **2a**	80 °C, 9 h		**4b**	83
						
2		**2b**	80 °C, 9 h	Ar= C_6H_5	**4c**	88
3		**2c**	80 °C, 12 h	Ar= *p*-$OMeC_6H_4$	**4d**	76
4		**2d**	80 °C, 6 h	R= *p*-ClC_6H_4	**4e**	74
5		 **2e**	80 °C, 12 h		**4f**	82
6		 **2f**	130 °C,20 h		**4g**	48
7		 **2g**	130 °C, 16 h		**4h**	66
8		 **2h**	130 °C, 20 h		**4i**	46
9		**2a**	80 °C, 2 h		**4j**	47
10		**2a**	80 °C, 2 h		**4k**	92
11		**2b**	80 °C, 2 h		**4l**	93

[a] Isolated yields. All the reactions were carried out using 2 mol % of $PdCl_2(PPh_3)_2$, 10 mol % of CuI, and 3 equiv of DBU in DMA.

intermediates of the coupling product **3** were completely consumed, and the corresponding 3-aminoindolizines were formed in 46−93% yields. 5-Methylpyridyl-substituted substrate afforded the corresponding indolizine **4b** in 83% yield (Table 2, entry 1). Alkyne **2a**, with a phenyl and a methyl group on the nitrogen, underwent coupling/cyclization smoothly and afforded **4c** in 88% yield (Table 2, entry 2). Substitution on the aromatic ring with a methoxy or chloride group afforded the corresponding indolizines **4d** and **4e** in 76% and 74% yields, respectively (Table 2, entries 3 and 4). The reaction also proceeded well with alkyne **2e** bearing an allylic group, which was well tolerated during the Pd/Cu-catalyzed process, affording **4f** in 82% yield (Table 2, entry 5). Introducing dialkyl or dibenzyl groups on the nitrogen of the amine resulted in a low yield reaction at 80 °C; however, the results improved considerably at 130 °C to give 3-(dialkylamino)indolizine **4g** and **4h** in 48 and 66% yields, respectively (Table 2, entries 6 and 7). The use of (1-prop-2-ynyl)piperidine **2h** afforded 3-(1-piperidyl)indolizine **4i** in 46% yield at 130 °C (Table 2, entry 8). When 2-bromopyrimidine was subjected to the reaction, the corresponding product **4j** was obtained in 47% yield (Table 2, entry 9). Employing 2-bromoquinoline also proceeded well to give benz[*e*]indolizine **4k** and **4l** in 92% and 93% yields, respectively (Table 2, entries 10 and 11). These results indicated that the nature of the substituent on nitrogen had a strong influence on the cyclization reactions. The reaction worked well with aryl/methyl, aryl/allyl, or diaryl-substituted propargyl amines, giving generally good yields of the corresponding products. Conversely, the dialkyl substitutions on nitrogen gave lower chemical yields and a higher reaction temperature of 130 °C was needed. This might be because the initial propargyl−allenyl isomerization required for cycloisomerization in the coupling intermediate of alkynyl pyridines[12a] became more difficult.

Propargyl amides possess acidic propargylic hydrogens that allow facile base-induced isomerization to an allenic intermediate,[18] thus it was expected to be also a good substrate for indolizine formation. We next investigated Pd/Cu-catalyzed reactions of 2-bromopyridine with various propargyl amides (Table 3, entries 1−4). As we expected, all the reactions proceeded very well to afford the corresponding indolizines in 63−83% yields within 1.5−6 h at 80 °C. A heterocyclic group could be easily introduced to the product by employing an α-thienyl-substituted *N*-propargylamide **2k** (Table 3, entry 3). The reaction with a cyclic amide such as (1-prop-2-ynyl)azepan-2-one **2l** afforded **5d** in 79% yield (Table 3, entry 4). The *N*-Boc-protected propargylic amides **2m**−**o** cyclized smoothly to generate the corresponding compounds **5e**−**g** in 72−80% yields (Table 3, entries 5−7). The reaction has also been accomplished starting from an alkyne tethered with a heterocycle group such as the carbazolyl group, furnishing **5h** in 59% yield (Table 3, entry 8).

Di- or triarylamines are important in the fields of both chemistry and material science. They have been used as oxidative catalysts in electronic chemistry,[19a] hole-transport materials in OLEDs,[19b] organic electrooptic materials,[19c] and organic ferromagnets,[19d] etc.[19] The above methodology provided a new class of indolizine-incorporated di- or triarylamines which may find potential utilities in these areas.

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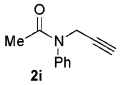
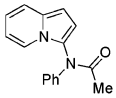
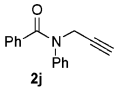
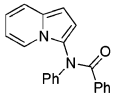
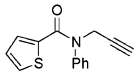
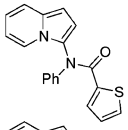
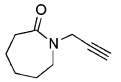
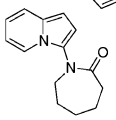
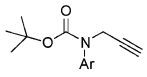
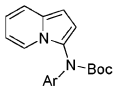
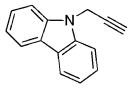
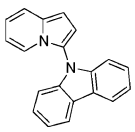
Table 3. One-Step Synthesis of 3-Indolizines from 2-Bromopyridines with Various Alkynes

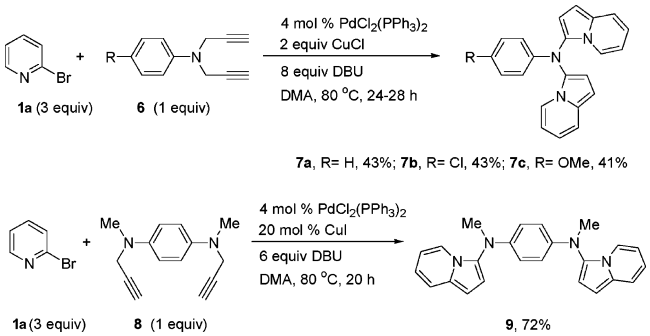
entry	ArBr	alkyne	temp. / time	product		yield(%)[a]
1		 **2i**	80°C, 1.5 h		**5a**	63
2		 **2j**	80°C, 3 h		**5b**	83
3		 **2k**	80°C, 6 h		**5c**	71
4		 **2l**	80°C, 3 h		**5d**	79
						
5		**2m**	80 °C, 6 h	Ar= C_6H_5	**5e**	72
6		**2n**	80 °C, 8 h	Ar=*p*-$MeOC_6H_4$	**5f**	80
7		**2o**	80 °C, 4 h	Ar=*p*-ClC_6H_4	**5g**	79
8		 **2p**	80 °C, 3 h		**5h**	59

[a] Isolated yields. All the reactions were carried out using 2 mol % of $PdCl_2(PPh_3)_2$, 10 mol % of CuI, and 3 equiv of DBU in DMA.

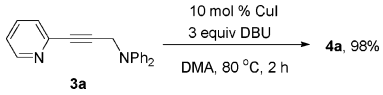
Interestingly, a triarylamine with two indolizine units could be constructed by this one-step procedure. For example, the reaction of *N*,*N*-dipropargyl arylamine **6** with excess amounts of 2-bromopyridine (3 equiv) employing 4 mol % of $PdCl_2(PPh_3)_2$, 2 equiv of CuCl, and 8 equiv of DBU gave the triarylamines **7a**−**c** in 41−43% yields (Scheme 1). Additionally, clean formation of a phenyl-bridged diaryl amine **9** was achieved in 72% yield by using 1,4-diaminobenzene **8** as substrate (Scheme 1).

To elucidate the reaction mechanism, we investigated the indolizine formation from the coupling product of *N*-(2-alkynyl)amine **3a** (Scheme 2). The cycloisomerization occurred efficiently with a CuI/DBU/DMA system without using a palladium catalyst. However, under literature conditions[12a] for the synthesis of 3-alkylindolizines (50 mol % of CuCl in Et_3N/DMA = 1:7, 130 °C for 7 h), only 16% of **4a** was formed, along with several undefined products. These results indicated that only CuI is effective for the second step of cycloisomerization, and the use of DBU as a base is superior to other bases. DBU may facilitate a propargyl−allenyl isomerization to an allenic intermediate or serve as a good ligand to stabilize the copper intermediates.

Scheme 1



Scheme 2



In summary, we have developed a Pd/Cu-catalyzed coupling/cycloisomerization of propargyl amines or amides with various haloheteroaromatic substrates under mild reaction conditions, which provided an efficient and one-step route to 3-aminoindolizines or benz[*e*]indolizines with a wide range of substituents. These compounds are potentially useful in pharmaceutical and material science. This work also represents a valuable complement relative to existing procedures for the synthesis of 3-indolizines. Further studies to extend the scope of synthetic utility for this Pd/Cu-catalyzed cascade reaction are in progress in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds and CIF file giving crystallographic data of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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