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Synthesis of Functionalized Indolizines via Copper-Catalyzed Annulation of 2-Alkylazaarenes with α,β-Unsaturated Carboxylic Acids

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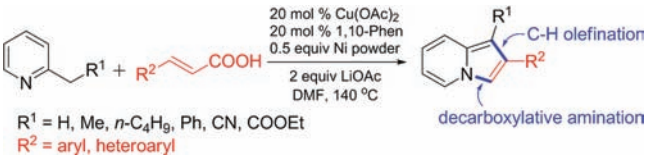
ABSTRACT



A novel copper-catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids has been accomplished. This reaction featuring C−H olefination and decarboxylative amination processes provides a concise access to C-2 arylated indolizines from simple and readily available starting materials.

Indolizines represent a significant class of nitrogen-fused heterocylces, which are ubiquitous in many natural products and biologically active compounds.[1] Many synthetic and naturally occurring indolizine derivatives have found wide applications in pharmaceuticals,[2] such as in anti-inflammatory agents,[2a,b] H3 receptor antagonists,[2c] anti-HIV agents,[2d] and usage as molecular probes.[2e] Consequently, the development of efficient especially convergent methods for rapid construction of indolizines has stimulated considerable interest. The majority of the methods for indolizine synthesis include 1,3-dipolar cycloaddition of pyridinium *N*-methylides with electron-deficient alkynes or alkenes[3] and transition-metal-catalyzed intramolecular cycloisomerizations of pyridines with specific C-2 functionalization.[4] Recent published reports involved a copper-catalyzed [3 + 2] cyclization of pyridines with alkenyldiazoacetates[5] and a muticomponent approach for the synthesis of indolizine derivatives.[6] However, these methods often suffer from limitations, such as substrate availability and involvement of multistage synthesis. Thus general and convenient methods for the synthesis of indolizines from simple and readily available precursors are still of great value.

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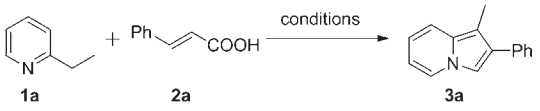
During the past few years, transition-metal-catalyzed direct benzylic C−H functionalization of 2-alkylazaarenes has attracted much attention.[7] These reactions were supposed to be initiated by the formation of metal enamide species through the electrophilic metalation of 2-alkylazaarenes. In the course of our ongoing efforts devoted toward studying transition-metal-catalyzed C−H functionalization,[8] we discovered that, by virtue of copper as an inexpensive catalyst, indolizine derivatives were able to be accessed directly by annulation of 2-alkylazaarenes and cinnamic acids featuring C−H olefination and decarboxylative amination processes. This methodology addresses many current limitations for the synthesis of indolizines, furnishing a diverse collection of valuable C-2 arylated indolizines using readily and commercially available reagents.[9]

Our initial attempt started with the reaction of 2-ethylpyridine and cinnamic acid at 140 °C under a N_2 atmosphere. Screening of the copper catalysts (Table 1, entries 1−6) revealed that $Cu(OAc)_2$ was optimal to give the annulation product **3a** in 45% yield (Table 1, entry 6). In contrast to other copper-catalyzed C−H activation processes,[10] the reaction failed to work under oxidative reaction conditions (Table 1, entry 7 and Supporting Information). Surprisingly, the product was isolated in 39% yield when copper bronze was employed as the catalyst (Table 1, entry 8), and the reaction failed again when the atmosphere was switched from N_2 to O_2 (Table 1, entry 9). It was found that employing 2 equiv LiOAc as an additive elevated the yield to 51% (Table 1, entry 10), while other additives such as NaOAc, KOAc, and LiCl were less effective (Table 1, entries 11−13). To improve the yield, we exploited active metal powders in the $Cu(OAc)_2$ system to generate in situ Cu(0) species (Table 1, entries 14−17). Gratifyingly, adding 0.5 equiv of nickel powder increased the yield of the product to 62% (Table 1, entry 17). No reaction was observed in the absence of copper catalyst (Table 1, entry 18), and the ligand (1,10-phenanthroline) was required to obtain a higher yield (Table 1, entry 19 and Supporting Information). It was found that, by extending the reaction time to 36 h, the yield of the product reached the highest yield (66%) (Table 1, entry 20). A 3 equiv amount of 2-ethylpyridine substrate was required to get the best yield, and the yield decreased to 31% when 1 equiv of 2-ethylpyridine as the substrate and 2 equiv of pyridine as the base were employed (Table 1, entry 22). When the reaction was conducted at a lower temperature, it proceeded with a lower yield, and a higher reaction temperature did not help increase the yield (Table 1, entry 23 and Supporting Information). Further attempts to substitute DMF with other solvents failed to yield better results (see Supporting Information).

Table 1. Reaction Optimization[a]



entry	catalyst	additive	time (h)	yield (%)[b]
1	CuI	–	24	trace
2	CuCl	–	24	11
3	$Cu(OTf)_2$	–	24	28
4	$CuCl_2$	–	24	23
5	$CuBr_2$	–	24	0
6	$Cu(OAc)_2$	–	24	45
7[c]	$Cu(OAc)_2$	–	24	0
8	copper bronze	–	24	39
9[c]	copper bronze	–	24	0
10	$Cu(OAc)_2$	LiOAc	24	51
11	$Cu(OAc)_2$	NaOAc	24	29
12	$Cu(OAc)_2$	KOAc	24	trace
13	$Cu(OAc)_2$	LiCl	24	46
14	$Cu(OAc)_2$	Fe powder + LiOAc	24	38
15	$Cu(OAc)_2$	Al powder + LiOAc	24	44
16	$Cu(OAc)_2$	Zn powder + LiOAc	24	49
17	$Cu(OAc)_2$	Ni powder + LiOAc	24	62
18	–	Ni powder + LiOAc	24	0
19[d]	$Cu(OAc)_2$	Ni powder + LiOAc	24	35
20	$Cu(OAc)_2$	Ni powder + LiOAc	36	66
21	$Cu(OAc)_2$	Ni powder + LiOAc	48	65
22[e]	$Cu(OAc)_2$	Ni powder + LiOAc	36	31
23[f]	$Cu(OAc)_2$	Ni powder + LiOAc	36	58

[a] Reaction conditions: 2-ethylpyridine (1.5 mmol), cinnamic acid (0.5 mmol), catalyst (0.1 mmol), 1,10-phenanthroline (0.1 mmol), additive (0.25 mmol for reductive metal powder and 1 mmol for the other), DMF (*N*,*N*-dimethylformamide, 1 mL), 140 °C, N_2. [b] Isolated yield. [c] Under O_2. [d] In the absence of 1,10-phenanthroline. [e] 0.5 mmol of 2-ethylpyridine and 1.0 mmol of pyridine were employed in the reaction. [f] The reaction was performed at 160 °C.

With the optimal reaction conditions in hand, we next examined the scope of substituted 2-alkylazaarenes in this annulation process as shown in Scheme 1. Various pyridines with C-2 functional groups such as CH_2CN, CH_2COOEt, CH_2Ph, and n-C_5H_{11} were compatible with the reaction conditions, resulting in the formation of the desired products in moderate yields (**3b**−**3e**). When 2-picoline participated in this reaction, the corresponding product **3f** was isolated in 45% yield. 2,6-Lutidine and 2,3-lutidine were transferred via this reaction to give the expected indolizines with methyl substituents on C-5 and C-8 positions respectively (**3g** and **3h**). It is noteworthy that

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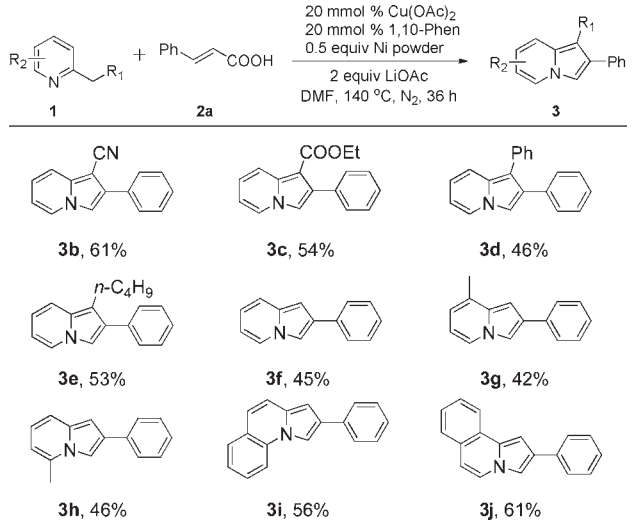
(9) Direct C-2 arylation of indolizines is difficult to realize because the C−H arylation of indolizines occurs on the most electron-rich C-3 position; see: (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. For the synthesis of C-2 arylated indolizines through palladium-catalyzed approaches, see: (b) Chernyak, D.; Skontos, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 3242. (c) Chernyak, D.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 5558.

(10) For a recent review on copper-catalyzed C−H functionalizatioin under oxidative reaction conditions, see: Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062.

Scheme 1. Scope of the Synthesis of Indolizines: Substituents on 2-Alkylazaarenes[a]



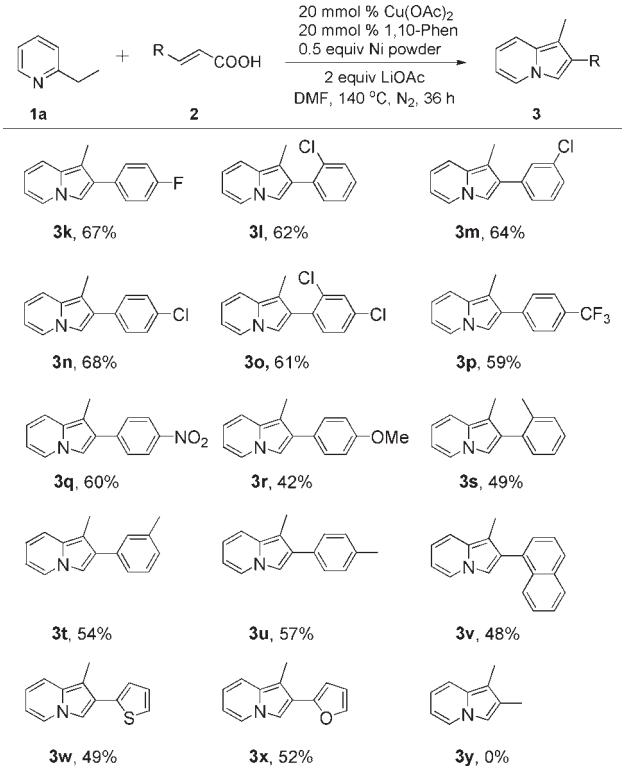
[a] Reaction conditions: 2-alkylazaarene (1.5 mmol), cinnamic acid (0.5 mmol), $Cu(OAc)_2$ (0.1 mmol), 1,10-phenanthroline (0.1 mmol), nickel powder (0.25 mmol), LiOAc (1 mmol), DMF (1 mL), 140 °C, N_2, 36 h. Isolated yield.

2-methyl quinoline and 1-methyl isoquinoline also reacted with cinnamic acid to afford the annulation products **3i** and **3j** in moderate yields.

We next examined the scope of substituted α,β-unsaturated carboxylic acids in this annulation process as shown in Scheme 2. It was found that a variety of substituted cinnamic acids can be converted to the desired products in modest yields, showing good functional group tolerance of both electron-withdrawing substituents (F, Cl, CF_3, and NO_2) and electron-donating substituents (OMe and Me). The ability to incorporate halogen substituents (F and Cl, **3k**−**3o**) and a nitro group (**3q**) into the product makes this process possess potential for further synthetic transformations. As for substitution patterns, *ortho*-substituted cinnamic acid delivered a relatively lower yield compared with its *meta*- or *para*-analogues probably due to the steric hindrance (**3s**, **3t**, and **3u**). Moreover, we were delighted to find that naphthyl- and heteroaryl-substituted α,β-unsaturated carboxylic acids were tolerated in this process, providing the corresponding indolizine derivatives (**3v**−**3x**). But alkyl-substituted α,β-unsaturated carboxylic acid such as crotonic acid failed in the reaction to give the desired product **3y**.

Although the mechanistic details are not clear at present, some experiments have been done to verify the catalytic pathways (see Supporting Information). GC analyses of the gases captured during the reaction confirmed the release of CO_2 and H_2, indicating this process involves decarboxylation and the dehydrogenative coupling does

Scheme 2. Scope of the Synthesis of Indolizines: Substituents on α,β-Unsaturated Carboxylic Acids[a]



[a] Reaction conditions: 2-ethylpyridine (1.5 mmol), substituted α,β-unsaturated carboxylic acid (0.5 mmol), $Cu(OAc)_2$ (0.1 mmol), 1,10-phenanthroline (0.1 mmol), nickel powder (0.25 mmol), LiOAc (1 mmol), DMF (1 mL), 140 °C, N_2, 36 h. Isolated yield.

not need oxidants. In addition, powder XRD analyses of the precipitates after the reaction revealed that a typical Cu(0) diffraction pattern was presented, illustrating that Cu(0) species may be involved in this reaction. Further research is required to elucidate the detailed mechaism.

In summary, we have developed a novel and convenient copper-catalyzed direct synthesis of indolizines from readily available 2-alkylazaarenes and α,β-unsaturated carboxylic acid. This new reaction can tolerate a broad variety of substituents, leading to C-2 arylated indolizines.

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Supporting Information Available. Experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.