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Synthesis of Aza-Fused Polycyclic Quinolines through Copper-Catalyzed Cascade Reactions

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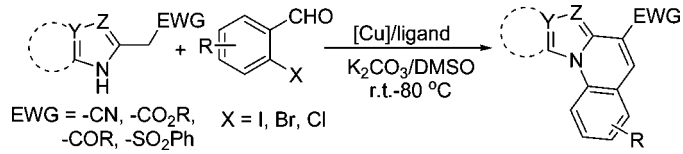
ABSTRACT



A new and efficient method for the synthesis of aza-fused polycyclic quinolines (e.g., benzimidazo[1,2-*a*]quinolines) is described. This protocol includes an intermolecular condensation followed by a copper-catalyzed intramolecular C−N coupling reaction. The method is applied to a wide range of 2-iodo, 2-bromo, and 2-chloro aryl aldehyde substrates to yield the aza-fused polycyclic quinolines in good yields.

Subsituted quinolines represent a class of important compounds that display a broad spectrum of biological functions.[1,2] They are also versatile as dyestuffs and photographic sensitizers.[3] However, the biological investigations on benzimidazo[1,2-*a*]quinolines, imidazo[1,2-*a*]quinolines, or other aza-fused polycyclic quinolines are rare, which might be due to the lack of general methods for the synthesis of these compounds.[4] Traditional synthetic methods for aza-fused quinolines included thermal or acid-catalyzed cyclization,[5] photochemical dehydrocyclization,[4,6] superelectrophilic cylications,[7] and other approaches.[8,9] However, most of these methods suffer from low yields and/or poor precursor scopes.

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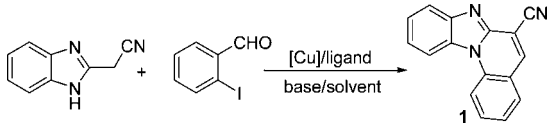
Recently, coupling reactions catalyzed by transition metals, such as Pd and Pt, have been successfully applied to the preparation of this important class of heterocyclic compounds.[10]

Copper-catalyzed Ullmann-type coupling reactions[11] have been extensively explored and widely used in the synthesis of diversified aromatic compounds, such as indole, benzoimidazole, etc.[12] In this paper, we would like to report a simple and efficient synthesis of benzimidazol[1,2-*a*] or other aza-fused polycyclic quinolines through a copper-catalyzed cascade reaction under mild conditions.

The study was initiated by investigating the potential reaction of 2-iodobenzene aldehyde with 2-(1*H*-benzo[*d*]imidazole-2-yl)acetonitrile to form benzimidazolol[1,2-*a*]quinoline **1** (Table 1). Although no desired product was detected in the absence of copper salts, we were pleased to find that the benzimidazolol[1,2-*a*]quinoline product **1** was obtained with 17% yield under the catalysis of 10 mol % CuI at room temperature using K_2CO_3 as the necessary base (Table 1, entry 1), indicating that copper catalyst was essential for this cascade reaction. Further investigation revealed that the well-known supporting ligands such as quinolin-8-ol, picolinic acid, or L-proline could significantly improve the reaction effeciency (Table 1, entries 2−4). When 20 mol % of L-proline was utilized, about 90% of the desired product was isolated after the reaction was performed at room temperature for 8 h. The following condition screening suggested that most of the common inorganic bases such as K_2CO_3, Cs_2CO_3, or K_3PO_4 were highly efficient for this cascade reaction (Table 1, entries 4−7). Investigation on the reaction medium revealed that DMSO was the optimal solvent for this new reaction. When other solvents (DMF or dioxane) were utilized, obviously lower yields were obtained (Table 1, entries 8 and 9). It was also noteworthy that nonpolar solvent such as toluene was highly detrimental to this reaction (Table 1, entry 10). The optimal conditions of 10 mol % CuI, 20 mol % L-proline, and 200 mol % inexpensive K_2CO_3 in DMSO at room temperature were used for further investigation.

Table 1. Synthesis of Benzimidazolol[1,2,*a*]quinoline through Copper-Catalyzed Cascade Reaction[a]



entry	ligand[b]	base	solvent	yield (%)[c]
1		K_2CO_3	DMSO	17
2	A	K_2CO_3	DMSO	60
3	B	K_2CO_3	DMSO	62
4	C	K_2CO_3	DMSO	91
5	C	K_3PO_4	DMSO	87
6	C	NaOH	DMSO	62
7	C	Cs_2CO_3	DMSO	92
8	C	K_2CO_3	DMF	76
9	C	K_2CO_3	Dioxne	55
10	C	K_2CO_3	Toluene	n.d.[d]

[a] Reaction conditions: benzimidazole substrate (1.0 mmol), 2-iodobenzene aldehyde (1.0 mmol), CuI (0.1 mmol), ligand (0.2 mmol), base (2.0 mmol), solvent (1.0 mL), rt. [b] Ligand A, quinolin-8-ol; B, picolinic acid; C: L-proline. [c] Isolated yields. [d] No desired product.

Under the optimized conditions, the scope of this new protocol was further explored by using the combinations of 2-(1*H*-benzo[*d*]imidazole-2-yl) acetonitrile with a variety of 2-iodo aryl aldehydes. As shown in Table 2, almost all of the tested combinations successfully produced the desired benzimidazolol[1,2-*a*]quinolines with good or excellent isolated yields. The results also suggested that the electronic density of the corresponding 2-iodo aryl aldehydes might have some influences on the copper-catalyzed cascade processess. Electron-deficient substrates were more favorite than that with electron-rich groups to deliver the corresponding products at room temperature (Table 2, entries 1−7). However, significantly improved results could be achieved for electron-rich 2-iodobenzaldehydes by slightly increasing the reaction temperature to 50 °C (Table 2, entries 1−3). For instance, only a 52% desired product was isolated wthen 5-hydroxy-2-iodobenzaldehyde reacted with 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile at room temperature, but the yield was obviously improved to 75% when the reaction was performed at 50 °C (Table 2, entry3). The reaction was also well tolerated with a variety of functionized groups such as ester, nitro, nitrile, alkyl, hydroxyl, halides, and trifluoromethyl goups.

It was noteworthy that less reactive 2-bromobenzaldehydes could successfully react with the 2-(1*H*-benzo[*d*]imidazole-2-yl) acetonitriles to produce the desired benzimidazolol[1,2-*a*]quinolines with good yields when the temperature was elevated to 80 °C for 4−6 h (Table 2, entries 8−13). In addition, the protocol also worked well for the heteroaromatic bromide substrates (Table 2, entries 13−15). Aryl chlorides are highly challenging substrates for most Ullmann-type coupling reactions.[11] We also wished to investigate if our new protocol worked well for *o*-chlorobenzaldehyde substrates. Although only a trace

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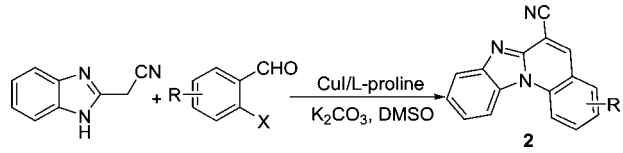
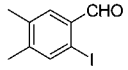
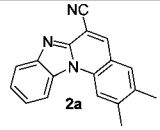
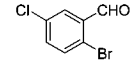
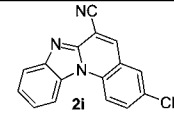
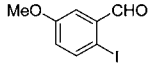
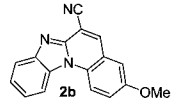
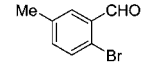
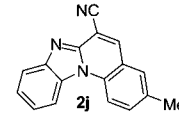
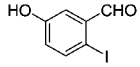
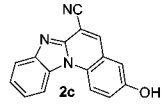
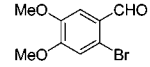
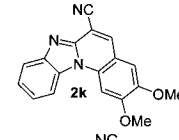
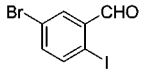
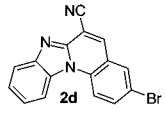
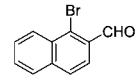
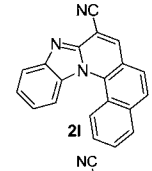
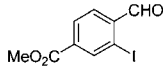
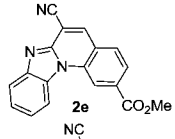
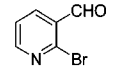
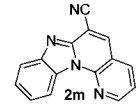
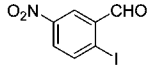
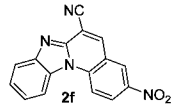
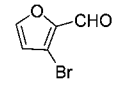
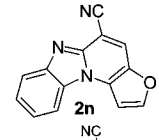
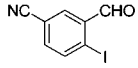
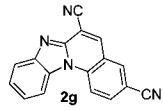
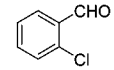
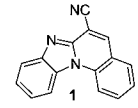
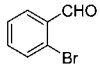
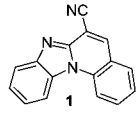
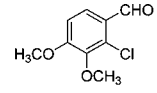
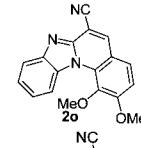
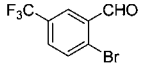
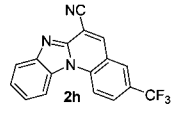
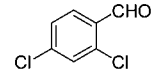
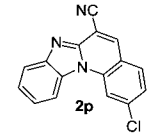
Table 2. Investigation on the Scope of *o*-Halogenated Aryl Aldehydes for the Formation of Benzimidazolol[1,2-*a*]quinolines[a]



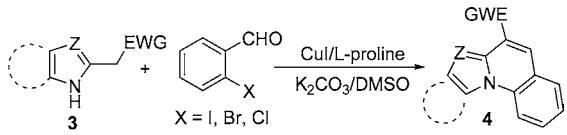
entry	aryl halides	product	yield(%) [b]	entry	aryl halides	product	yield(%) [b]
1		 2a	70(85 [c])	10		 2i	91
2		 2b	66 (89 [c])	11		 2j	45
3		 2c	52 (75 [c])	12		 2k	43
4		 2d	82	13		 2l	80
5		 2e	85	14		 2m	93
6		 2f	85	15		 2n	65
7		 2g	90	16		 1	62
8		 1	87	17		 2o	47
9		 2h	81	18		 2p	50

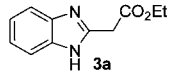
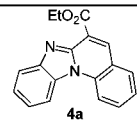
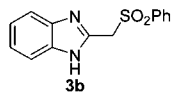
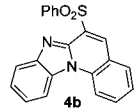
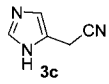
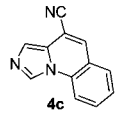
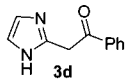
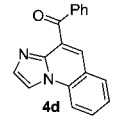
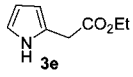
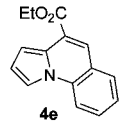
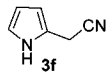
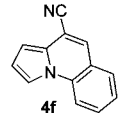
[a] Reaction conditions: for aryl iodides, rt, 6−8 h; for aryl bromides, 80 °C, 4−6 h; for aryl chlorides, 110 °C, 6−8 h. [b] Isolated yields. [c] Performed at 50 °C.

amount of the desired product was detected when 2-chlorobenzaldehyde reacted with 2-(1*H*-benzo[*d*]imidazole-2-yl) acetonitrile at room temperature, the yield was significantly improved to 62% when the reacting temperature was elevated to 110 °C for 6 h (Table 2, entry 16). The reactions were also performed well for two other 2-chlorobenzene aldehyde substrates (Table 2, entries 17 and 18).

The scope of the heterocyclic substrates were also explored, and the results are summarized in Table 3. Almost all of the benzimidazoles or imidazoles bearing electron-withdrawing groups were able to react with the corresponding 2-halogenerated aryl aldehydes to offer the desired products with good or moderate yields (Table 3, entries 1−10). Other heterocyclic moieties such as substituted pyrroles were obviously less active and only about

Table 3. Investigation on the Scope of the Heterocyclic Substrates[a]



entry	heterocyclic substrates	X	products	yield (%)[b]
1		I		72
2		Br		60[c]
3		Cl		30[d]
4		I		65
5		Br		62[c]
6		I		53
7		Br		35[c]
8		I		75
9		Br		62[c]
10		Cl		23[d]
11		I		25[e,f]
12		I		30[e,f]

[a] Reaction conditions: K_2CO_3, DMSO, rt, 8 h. [b] Isolated yields. [c] 80 °C. [d] 110 °C. [e] 50 °C. [f] Cs_2CO_3 as base.

25−30% yields were obtained under the similar conditions (Table 3, entries 1−10). No obvious improvement was obtained when the reaction was performed at 80 °C for 24 h. This might be due to the fact that the CH_2 groups in pyrrolic substrates were less nucleophilically active than those in the benzimidazole or imidazole substrates. Our results also revealed that many electron-withdrawing groups such as -CO_2Et, -SO_2Ph, CN, or -COAr groups were sufficiently activating groups for substituted benzimidazoles and imidazoles in the copper-catalyzed cascade reaction.

In summary, a simple and efficient method for the synthesis of benzimidazo[1,2-*a*]quinolines and other aza-fused polycyclic quinolines through a copper-catalyzed cascade reaction was described. The protocol worked well for almost all of the 2-iodo, 2-bromo, and 2-chloro aryl aldehydes and diplayed great functional group compatibility. Our study provided a general way for the synthesis of benzimidazo[1,2-*a*]quinolines or other aza-fused quinolines from easily accessible starting materials and should find great applications in the future.

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Supporting Information Available: Experiment procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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