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Novel Strategy for Synthesis of Substituted Benzimidazo[1,2-*a*]quinolines

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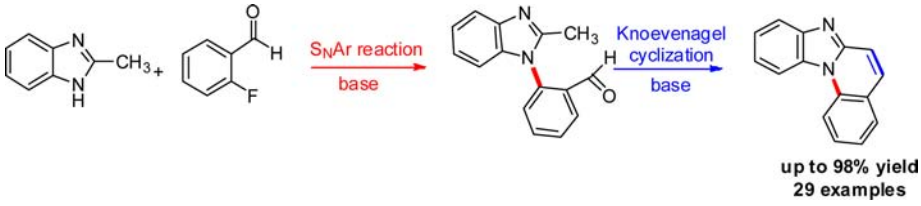
ABSTRACT



An efficient method for the synthesis of benzimidazo[1,2-*a*]quinolines under transition-metal-free conditions has been developed through a cascade reaction involving sequential aromatic nucleophilic substitution and intramolecular Knoevenagel condensation reactions. This method is applicable for the synthesis of a wide range of benzimidazo[1,2-*a*]quinoline derivatives from readily available 2-fluoroarylaldehyde and benzimidazole substrates.

Fused benzimidazoles represent a class of important compounds that display a broad spectrum of biological functions.[1] Among fused benzimidazoles, some benzimidazo[1,2-*a*]quinolines have been recently reported to show powerful activity of DNA-intercalation as well as the inhibition of topoisomerase II activity.[2] To discover biologically more active compounds, the structure−activity relationships of substituted benzimidazo[1,2-*a*]quinolines having a variety of substituents at a varied position of the heterocycle are required. However, such a study has not been intensively examined, which might be due to the lack of facile and general methods for the synthesis of substituted benzimidazo[1,2-*a*]quinoline derivatives.

Substituted benzimidazo[1,2-*a*]quinolines are most commonly synthesized by inconvenient multistep methods,[2−8] and these literature methods do not meet the demands in the study of structure−activity relationships.

In recent efforts to develop more facile methods for the synthesis of substituted benzimidazo[1,2-*a*]quinolines, a cascade reaction involving sequential intermolecular Knoevenagel condensation and Cu-catalyzed intramolecular C−N coupling has been developed (Scheme 1).[9] However, a direct-activating group such as NC− should be incorporated into the α-position to the reacting methylene to induce the intermolecular Knoevenagel condensation effectively.

In our study directed on the development for novel synthetic methods of fused aza-heterocycles, we have reported a conceptually new cascade reaction for the synthesis of pyrazolo[1,5-*a*]quinolines.[10] This cascade reaction involves sequential intermolecular aromatic nucleophilic substitution (S_NAr) and intramolecular Knoevenagel condensation. Remarkable features of the S_NAr/Knoevenagel

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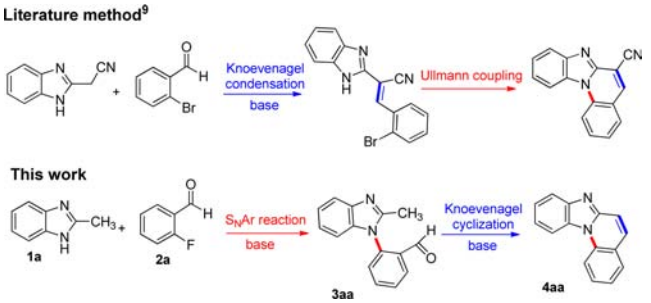
cyclization cascade reaction are that a direct-activating group such as NC− is not necessary for the Knoevenagel condensation and transition-metal-free conditions are available for the S_NAr reaction. In continuous research to develop facile and general methods for the synthesis of fused aza-heterocycles, we applied the S_NAr/Knoevenagel cyclization cascade reaction to the synthesis of benzimidazo-[1,2-*a*]quinolines and the related heterocycles. In this paper we describe the simple and efficient synthesis of benzimidazo-[1,2-*a*]quinolines using our cascade reaction.

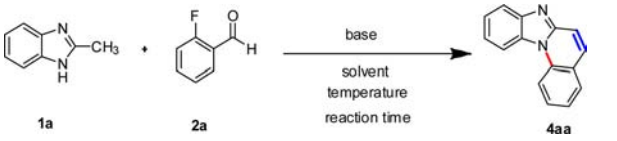
Scheme 1. Strategies for Synthesis of Benzimidazo-[1,2-*a*]quinolines through Cascade Reactions



First, we examined the S_NAr/Knoevenagel cyclization cascade reaction utilizing **1a** and **2a** as model substrates to optimize the reaction conditions (Table 1). When the reaction was conducted in DMF in the presence of K_2CO_3 for 16 h at 120 °C, the optimized conditions for synthesis of the pyrazolo[1,5-*a*]quinolines as reported in a previous paper,[10] the desired benzimidazo[1,2-*a*]quinoline **4aa** was obtained as expected in a 56% yield (entry 1). This reaction seemed to proceed rather slowly as only a small amount of product was obtained upon terminating the reaction within 1 h (entry 2). The reaction rate slightly accelerated upon using K_3PO_4 instead of K_2CO_3 (entry 2 vs 3). We were pleased to find that the reaction rate significantly accelerated upon using Cs_2CO_3[11] as a base instead of K_2CO_3 and comparable high yields (83−86%) were obtained when reactions were conducted for 16 and 1 h, respectively (entries 4 and 5). Further condition screening suggested that most of the common organic bases were highly detrimental to this reaction (entries 6 and 7). The choice of solvent is also critical for this cascade reaction. When the reaction was carried out in the presence of Cs_2CO_3 at reflux, upon switching the solvents from DMF to dioxane or toluene, trace amounts of desired product **4aa** were detected (entries 9 and 10). On the other hand, DMSO was found to also be an efficient solvent to give **4aa** in a comparative yield (entry 8). The cascade reaction was highly affected by the reaction temperature; the yield significantly decreased when the reaction was conducted above or below 120 °C (entry 5 vs entries 11−13). Based on these results, at this stage, the optimal conditions for the cascade reaction were determined to be as conducted with 300 mol % of Cs_2CO_3 in DMF at 120 °C.

When the reaction was carried out at 0.5 h for the conditions of entry 2, **3aa** was isolated in a 19% yield along with trace amounts of **4aa** (entry 14 and Scheme 1). The obtained **3aa** was resubmitted to the same conditions of entry 4 to give **4aa** in a 68% yield. These experiments show that the proposed cascade reaction works well. To the best of our knowledge, the present cascade reaction is the first example in which the methyl group of the 2-methyl-1*H*-benzimidazoles participates in the Knoevenagel cyclization upon arylation at the nitrogen of the 2-methyl-1*H*-benzimidazoles through the S_NAr substitution.

Table 1. Optimization of the S_NAr/Knoevenagel Cyclization Cascade Reaction[a]



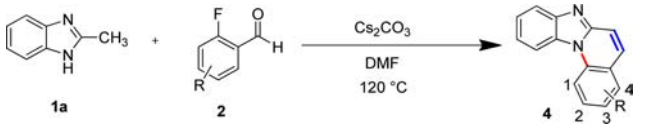
entry	base	solvent	temp (°C)	time (h)	yield[b] (%)
1	K_2CO_3	DMF	120	16	56
2	K_2CO_3	DMF	120	1	12
3	K_3PO_4	DMF	120	1	38
4	Cs_2CO_3	DMF	120	16	83
5	Cs_2CO_3	DMF	120	1	86
6	Et_3N	DMF	120	1	nr[c]
7	DBU	DMF	120	1	trace
8	Cs_2CO_3	DMSO	120	1	70
9	Cs_2CO_3	dioxane	reflux	1	trace
10	Cs_2CO_3	toluene	reflux	1	trace
11	Cs_2CO_3	DMF	140	1	78
12	Cs_2CO_3	DMF	100	2	73
13	Cs_2CO_3	DMF	80	4	41
14	K_2CO_3	DMF	120	0.5	trace[d]

[a] All reactions were carried out in the presence of **1a** (1.0 mmol), 2-fluorobenzaldehyde **2a** (1.2 mmol), and base (3.0 mmol) in the indicated solvent (5 mL). [b] Isolated yield. [c] No reaction. [d] The intermediate **3aa** was isolated in a 19% yield.

Next, we explored the scope with respect to 2-fluorobenzaldehydes (Table 2). This survey revealed that a range of 2-fluorobenzaldehydes bearing an electron-donating group such as CH_3− and CH_3O− are good substrates for the cascade reaction under the optimized conditions (Cs_2CO_3, DMF, 120 °C) to give benzimidazo[1,2-*a*]quinolines **4ah**−**4am** in good to excellent yields (entries 8−13). However, 2-fluorobenzaldehydes bearing an electron-withdrawing group such as F−, Br−, CF_3−, and NC− are found to be surprisingly poor substrates, and desired products **4ab**−**4ae** and **4ag** were obtained with low yields under the conditions (entries 2−5, 7). These low yields resulted from the formation of significant amounts of unidentified byproducts. Upon switching the solvent and base to DMSO and K_2CO_3, respectively, these low yields significantly improved to moderate yields (entries 2−5).

(11) Recently, Cs_2CO_3 was reported to be a better base than K_2CO_3 in an S_NAr reaction of unactivated 2-fluorobenzenes with 1*H*-benzimidazoles: Diness, F.; Fairlie, P. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 8012.

Table 2. Scope of 2-Fluorobenzaldehydes[a]



1a 2 4

	aldehyde		product			
entry	**2**	R	**4**	R	time (h)	yield (%)[b]
1	**2a**	H	**4aa**	H	1	86
2	**2b**	3-F	**4ab**	1-F	24	38 (61)[c]
3	**2c**	5-F	**4ac**	3-F	2	41 (61)[c]
4	**2d**	5-CF_3	**4ad**	3-CF_3	1	29 (65)[d]
5	**2e**	5-Br	**4ae**	3-Br	3	40 (59)[d]
6	**2f**	4-Br	**4af**	2-Br	1	82
7	**2g**	5-CN	**4ag**	3-CN	3	41[c]
8	**2h**	5-CH_3	**4ah**	3-CH_3	3	85
9	**2i**	6-CH_3O	**4ai**	4-CH_3O	2	88
10	**2j**	5-CH_3O	**4aj**	3-CH_3O	4	74
11	**2k**	4-CH_3O	**4ak**	2-CH_3O	1	87
12	**2l**	3-CH_3O	**4al**	1-CH_3O	2	98
13	**2m**	4,5-$(CH_3O)_2$	**4am**	2,3-$(CH_3O)_2$	3	72

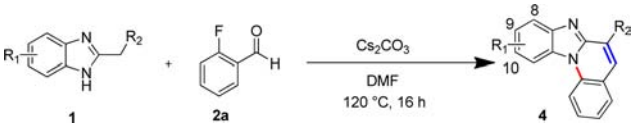
[a] All reactions were carried out in the presence of **1a** (1.0 mmol), aromatic aldehydes **2** (1.2 mmol), and Cs_2CO_3 (3.0 mmol) in DMF (5 mL) at 120 °C for the indicated time unless otherwise stated. [b] Isolated yield. [c] DMSO was used instead of DMF. [d] K_2CO_3 and DMSO were used instead of Cs_2CO_3 and DMF.

To extend the scope of the 2-methyl-1*H*-benzimidazole substrates for our cascade reaction, we next examined the reaction of 2-fluorobenzaldehyde **2a** with a variety of 2-methyl-1*H*-benzimidazole derivatives **1a**–**1k** under the optimized conditions (Cs_2CO_3, DMF, 120 °C). As shown in Table 3, almost all of the tested combinations successfully produced the desired benzimidazo[1,2-*a*]quinolines **4aa**–**4ka** with moderate to good isolated yields. Although 2,5-dimethyl-1*H*-benzimidazole (**1b**) reacted with **2a** to give an inseparable regioisomeric mixture of **4ba** in a modest yield (entry 2), the reaction with unsymmetrical 2-methyl-1*H*-benzimidazoles having a substituent at the 4-position, such as **1e**, **1f**, and **1g**, selectively produced **4ea**, **4fa**, and **4ga** in good yields (entries 5–7). The structure of **4ga** was confirmed by X-ray crystallographic analysis (see Supporting Information). Selective formation of **4da**, **4ea**, and **4fa** may have arisen when the S_NAr reaction regioselectively occurred at the nitrogen opposite to the substituent to avoid the steric hindrance. It is noteworthy that 2-methyl-1*H*-benzimidazole derivatives **1h**, **1i**, **1j**, and **1k** having an electron-donating group, such as CH_3–, CH_3O–, CH_3S–, and the 4-molpholinyl moiety, at the 2-methyl group, reacted with **2a** to give **4ha**, **4ia**, **4ja**, and **4ka** in good yields (entries 8–11). Since these compounds have not been synthesized by methods in the literature,[9] our method is complementary to the classical methods to synthesize a variety of substituted benzimidazo[1,2-*a*]quinolines.

In an effort to apply the present cascade reaction to the synthesis of heterocycles related to benzimidazo[1,2-*a*]quinolines, the feasibility of the cascade reactions with heteroaromatic aldehydes **5a, 5b** and **7a, 7b** was examined (Scheme 2). Although the reaction of **1a** with 3-fluoroisonicotinealdehyde (**5b**) gave the corresponding adduct **6ab**, 3-fluoronicotinaldehyde (**5a**) was found to be a better substrate, giving **6aa** in a modest yield. Pyrazolo-fused analogues **8aa** and **8ab** were also synthesized from chloropyrazoles **7a** and **7b** in low yields (Scheme 2).[12]

Finally, the cascade reactions of **2a** with 2-methyl-1*H*-imidazopyridine (**9a**) and 8-methyl-7*H*-purine (**9b**) were

Table 3. Scope of 1*H*-Benzimidazoles[a]

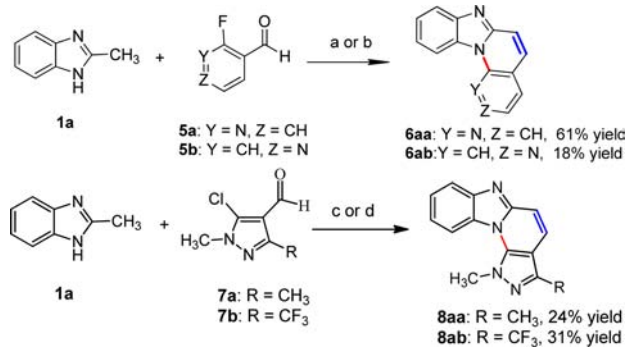


1 2a 4

	1*H*-benzimidazole			product			
entry	**1**	R_1	R_2	**4**	R_1	R_2	yield (%)[b]
1	**1a**	H	H	**4aa**	H	H	83
2	**1b**	5-CH_3	H	**4ba**	9- and 10-CH_3	H	49[c]
3	**1c**	5,6-$(CH_3)_2$	H	**4ca**	9,10-$(CH_3)_2$	H	69
4	**1d**	5,6-$(Cl)_2$	H	**4da**	9,10-$(Cl)_2$	H	62
5	**1e**	4-CH_3	H	**4ea**	8-CH_3	H	67
6	**1f**	4-CH_3O	H	**4fa**	8-CH_3O	H	71
7	**1g**	4-Br	H	**4ga**	8-Br	H	65
8	**1h**	H	CH_3O	**4ha**	H	CH_3O	58
9	**1i**	H	CH_3S	**4ia**	H	CH_3S	80
10	**1j**	H	CH_3	**4ja**	H	CH_3	66
11	**1k**	H	4-molpholinyl	**4ka**	H	4-molpholinyl	39

[a] All reactions were carried out in the presence of 1*H*-benzimidazole **1a**–**1k** (1.0 mmol), 2-fluorobenzaldehyde (**2a**) (1.2 mmol), and Cs_2CO_3 (3.0 mmol) in DMF (5 mL) at 120 °C for 16 h. [b] Isolated yield. [c] For a 1:1 mixture of regioisomers.

Scheme 2. Cascade Reaction of **1a** with Heteroaromatic Aldehydes **5** and **7** in the Presence of Cs_2CO_3[a]

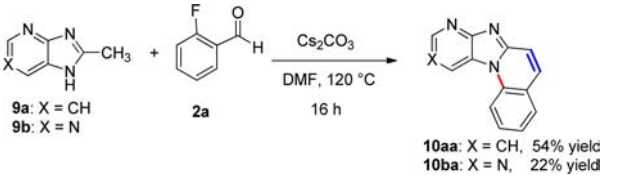


[a] Conditions: (a) Cs_2CO_3, DMF, 120 °C, 20 h for **6aa**; (b) Cs_2CO_3, DMSO, 120 °C, 6 h for **6ab**; (c) Cs_2CO_3, DMA, 150 °C, 8 h for **8aa**; (d) Cs_2CO_3, DMF, 120 °C, 20 h for **8ab**.

examined to verify the effects of their heteroaromatic moiety fused to the imidazole on the yield and their regioselective outcome (Scheme 3). This survey revealed that, among the possible regioisomeric adducts, regioisomers **10aa** and **10ba** are predominantly produced from **9a** and **9b** in 54% and 22% yields, respectively. The structure of **10aa** was determined by direct comparison with the authentic sample prepared by the method previously reported.[13] The structure of the new heterocycle **10ba** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1). The reaction between 2-methyl-1*H*-imidazole and **2a** under the optimized conditions produced a complex mixture of unidentified compounds.[14] The results suggest to us that phenyl moieties of **1a**−**1k** make a contribution to the successful process of our cascade reaction.

In summary, a concise and general method for the synthesis of benzimidazo[1,2-*a*]quinolines and related heterocycles has been developed. The method is based upon a novel cascade reaction through an aromatic nucleophilic substitution of 2-methyl-1*H*-benzimidazoles with 2-fluorobenzaldehydes, followed by the Knoevenagel cyclization of the resulting adducts. Our method potentially provides a variety of substituted benzimidazo[1,2-*a*]quinolines without using any transition metal catalysts upon fine-tuning a combination of two readily available substrates.

Scheme 3. Cascade Reaction of **2a** with 2-Methyl-1*H*-imidazopyridine (**9a**) and 8-Methyl-7*H*-purine (**9b**)



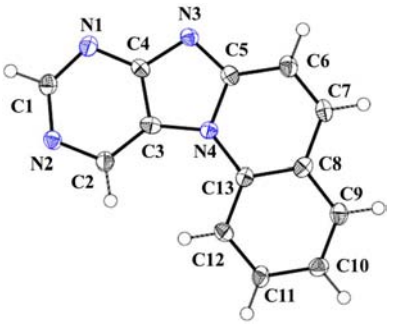


Figure 1. ORTEP drawing of **10ba**.

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Supporting Information Available. Experimental procedures, full spectroscopic data, $^1H/^{13}C$ NMR spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) When the reaction with the chloro-analogue of **5a** was carried out under the same conditions, the yield of **6aa** significantly decreased. The details are described in the Supporting Information.

(13) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260.

(14) The reaction of substituted methyl-1*H*-imidazoles with **2a** was examined. The details of the results are described in the Supporting Information.