Synthesis of Novel Substituted Benzimidazo[1,2-*a*]quinoxalin-6(5*H*)-ones via an Intramolecular Goldberg Reaction

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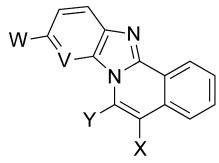
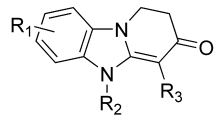
The benzimidazole structural subunit is regarded as a privileged structure in medicinal chemistry and has been extensively employed in drug design.[1,2] Novel fused heterocyclic frameworks often have the most diverse physical, chemical and surprisingly complex biological properties, and almost unlimited combinations of fused heterocyclic structures can be designed. As for the benzimidazoles fused with aza-aromatic ring systems, mostly benzimidazo[2,1-*a*]isoquinolines (I) as anticancer agents[3,4] and pyrido[1,2-*a*]benzimidazole (II) derivatives as anxiolytic,[5,6] antiviral,[7] and antimicrobial[8] agents have been reported.



I



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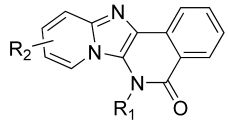

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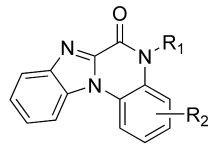
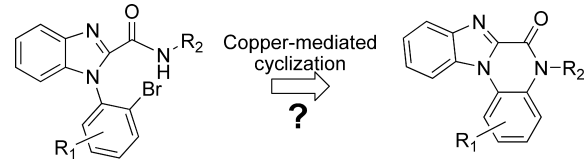


IV

We recently reported a series of 6*H*-pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones(**III**) that showed potent cytotoxicity.[9,10] As part of our ongoing research, we created a series of novel fused benzimidazole containing structures **IV**, which also possesses a structural similarity with **III**. This new series of substituted benzimidazo[1,2-*a*]quinoxalin-6(5*H*)-ones (**IV**) may be used for identification of novel scaffolds with some interesting biological activities.

Our synthetic strategy for the synthesis of the benzimidazo[1,2-*a*]quinoxalin-6(5*H*)-one ring is shown in Scheme 1. We envisioned that the quinoxalinone ring could be synthesized by a Goldberg-type[11] intramolecular amide arylation from 1-(2-bromophenyl)-1*H*-benzo[*d*]imidazole-2-carboxamides. Herein, we report our results on a facile synthesis of nine novel benzimidazo-fused tetracyclic compounds.

Scheme 1. Copper-Mediated Approach to Benzimidazo[1,2-*a*]quinoxalin-6(5*H*)-ones



Initially, the substituted 1-(2-bromophenyl)-1*H*-benzo[*d*]imidazole-2-carboxamides, required as the key precursors for the copper-catalyzed intramolecular cyclization, were synthesized in a three-step sequence as depicted in Scheme 2. Commercially available 1-fluoro-2-nitrobenzene was treated with substituted 2-bromoanilines in DMSO in the presence of KOH at 150 °C to give diphenylamines **2**{*1*−*3*} in good yields, which were used in the next step without purification. The nitro intermediates were then successfully converted to the corresponding amines by reaction with iron in conc. HCl solution under reflux. Notably, debromination was observerd under Pd/C hydrogenation condition in this case. Subsequently, the carboxylate intermediates **3**{*1*−*3*} were synthesized in moderate yields by the condensation of diphenylamines with ethyl triethoxyacetate at 150 °C. However, while the ethyl carboxylate **3**{*1*} was treated with NaOH/H_2O/EtOH or LiOH/H_2O/MeOH, we obtained the decarboxylated compound **6** instead of acid **5**. We thus attempted direct aminolysis by reacting the carboxylates with various primary amines. Following heating under microwave conditions, nine intermediates were obtained in moderate to high yields, with no decarboxylation observed.

To test the feasibility of the proposed cyclization reaction, compound **4**{*1,1*} was first used as the model substrate. Several known copper-catalyzed coupling conditions were tested and are shown in Table 1. However, it was found that under Ullmann reaction conditions, which Ma et al.[12] reported (CuI/L-Proline catalyst, entry 2) or Liu et al.[13] used (bivalent copper salt $Cu(OAc)_2$/DBU-catalyzed conditions, entry 3), only the debenzylated product **8** was obtained. Meanwhile, no reaction was observed in the absence of ligand (entry 1), which indicates that the presence of ligand is essential for the reaction to occur. Further investigation revealed that *N,N*-dimethylglycine as a crucial promoter is essential for this type of Goldberg reaction.[14] When combination of CuI/*N,N*-dimethylglycine, K_2CO_3 as base, was used and the mixture was refluxed in DMF for 12 h (entry 5), cyclized compound **7**{*1,1*} could be isolated in 35% yield. Probing of the temperature and base effects, we observed a sharp decrease in yield under lower reaction temperature (100 °C, entry 4), and K_3PO_4 turned out to be better than K_2CO_3 with 60% yield (entry 6).

Using the optimized conditions, we next investigated the scope of the reaction with five primary amines for R_1 and two 2-bromoanilines for R_2 because of their commercial availability. The 1-(2-bromophenyl)-1*H*-ben-

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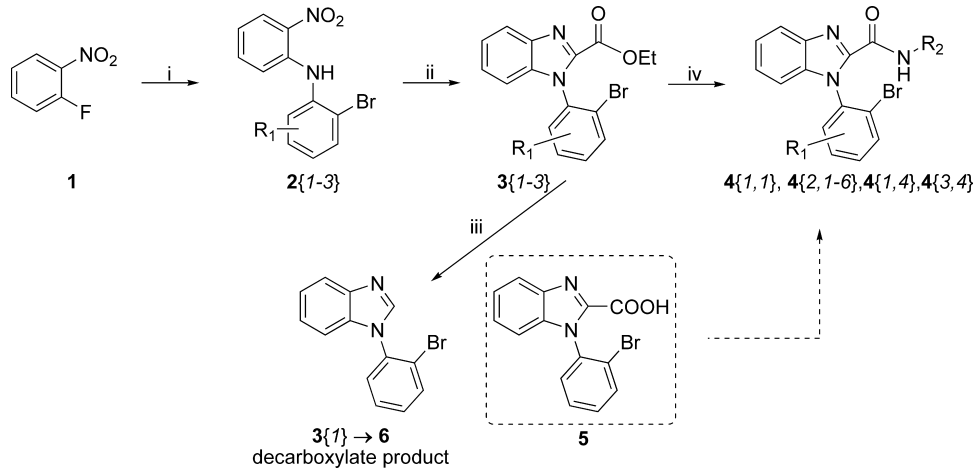
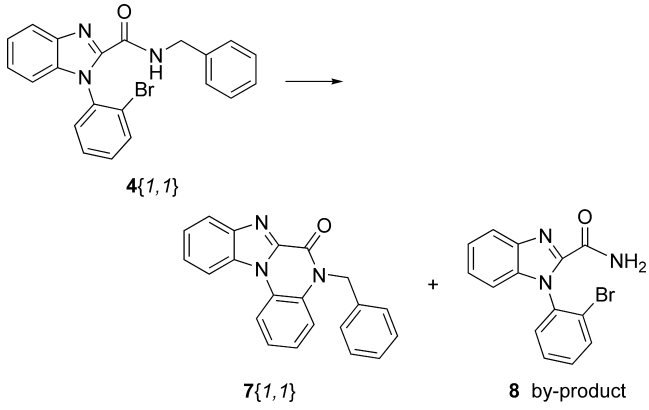
Scheme 2. Synthetic Route of the Key Intermediates[a]



[a] Reagents and conditions: (i) substituted 2-bromoanilines, KOH, DMSO, 150 °C, 5 h (yield 68−90%); (ii) (a) Fe(powder), conc. HCl, reflux, 2 h, (b) ethyl triethoxyacetate, reflux, 10 h (yield 15−47%); (iii) 1 N NaOH aq., EtOH or 1 N LiOH aq., MeOH; (iv) R_2-NH_2, microwave, 130 °C, 1−2 h (yield 25−93%).

Table 1. Optimization of the Reaction Conditions for the Intramolecular Cyclization



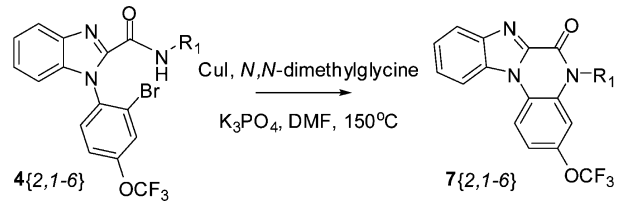
entry	conditions	yield[a] 7{1,1}	yield[a] 8
1	CuI (20 mol %), K_2CO_3 (200 mol %), DMF, 120 °C, 24 h		
2	CuI (15 mol %), L-proline (20 mol %), K_2CO_3 (200 mol %), DMF, 120 °C, 24 h		18
3	$Cu(OAc)_2$ (100 mol %), DBU (200 mol %), DMSO, MW, 150 °C, 1 h		17
4	CuI (20 mol %), *N*,*N*-dimethylglycine (20 mol %), K_2CO_3 (200 mol %), DMF, 100 °C, 12 h	trace	
5	CuI (20 mol %), *N*,*N*-dimethylglycine (20 mol %), K_2CO_3 (200 mol %), DMF, 150 °C, 12 h	35	
6	CuI (20 mol %), *N*,*N*-dimethylglycine (20 mol %), anhydrous K_3PO_4 (200 mol %), DMF, 150 °C, 12 h	60	

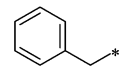
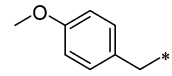
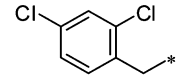
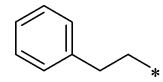
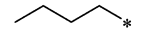
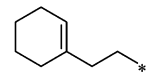
[a] Yield (%) of isolated product after column chromatography.

zo[*d*]imidazole-2-carboxamide derivatives (**4**{*2,1−6*}) were first synthesized as key intermediates. The cyclization reactions were performed on a 12-reaction setup in a parallel synthesizer (Radleys DiscoveryTechnology, Carousel 12 Place Reaction Station). As shown in Tables 2 and 3, only compound **7**{*2,5*} did not give satisfactory results presumably because of the low reactivity of *n*-butyramide. All the other polycyclic products were obtained in moderate to good yields.

In conclusion, the intramolecular Goldberg reaction has been successfully developed to generate novel benzimidazo[1,2-*a*]quinoxalin-6(5*H*)-one derivatives. Conversion

Table 2. Synthesis of 3-(Trifluoromethoxy)benzimidazo[1,2-*a*]-quinoxalin-6(5*H*)-ones with R_1 Variation

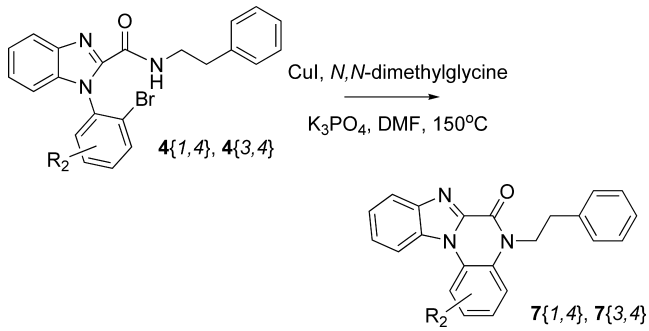


compd	R_1	yield[a]	purity[b]
7{*2,1*}		66	100
7{*2,2*}		71	100
7{*2,3*}		44	100
7{*2,4*}		56	100
7{*2,5*}		trace	-
7{*2,6*}		42	100

[a] Yield (%) of isolated product after column chromatography. [b] The purity (%) was based on the integration area of HPLC peaks detected at 214 nm.

is achieved by treatment of 1-(2-bromophenyl)-1*H*-benzo-[*d*]imidazole-2-carboxamide precursors with CuI/*N*,*N*-

Table 3. Synthesis of 5-(2-Phenylethyl)benzimidazo[1,2-*a*]-quinoxalin-6(5*H*)-ones with R_2 Variation



compd	R_2	yield[a]	purity[b]
7{*1,4*}	H	56	100
7{*3,4*}	5-CF_3	40	100

[a] Yield (%) of isolated product after column chromatography. [b] The purity (%) was based on the integration area of HPLC peaks detected at 214 nm.

dimethylglycine/ K_3PO_4. To the best of our knowledge, this type of scaffold has never been reported. This approach could be easily applied to the synthesis of more privileged structure-based analogues that are of interest in drug discovery. Meanwhile, biological properties of this rarely described class of compounds are currently under investigation in our lab.

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Supporting Information Available. General experimental details and compound characterization data, such as yields, ^{1}H NMR, and MS analysis of all intermediates, products, as well as byproducts and characterization data of final compounds by ^{1}H NMR, ^{13}C NMR, and MS (HREI and LREI). This material is available free of charge via the Internet at http://pubs.acs.org.

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