Facile One-Pot Synthesis of Benzimidazole and Quinoxalin-2(1*H*)-one Scaffolds via Two-Component Coupling Reaction, Deprotection, and Intermolecular Cyclization

Zhong-Zhu Chen, Ying Tang, Lei Zuo, Dian-Yong Tang, Jin Zhang,* Zhi-Gang Xu*

Chongqing Key Laboratory of Environmental Materials and Remediation Technologies, Drug Discovery Center of Innovation, Chongqing University of Arts and Sciences, 319 Honghe Avenue, Yongchuan, Chongqing 402160, P. R. of China
Fax +86(23)61162837; E-mail: xuzhigangyours@yahoo.com; E-mail: hxxzj2282@163.com

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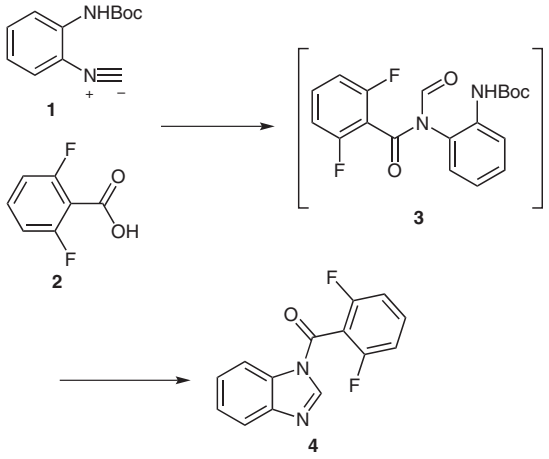
Abstract: Two scaffolds, namely benzimidazole and quinoxalin-2(1*H*)-one, were synthesized by treating 2-(*N*-Boc-amino)phenylisocyanide (Boc: *tert*-butoxycarbonyl) with carboxylic acids and glyoxylic acids, respectively. The target compounds were generated directly after two-component coupling, deprotection, and intermolecular cyclization.

Key words: benzimidazole, quinoxaline-2(1*H*)-one, two-component coupling, one-pot synthesis, intermolecular cyclization

In our previous work, we reported the synthesis of benzimidazoles and quinoxalines using the isonitrile 2-(*N*-Boc-amino)phenyl isocyanide (Boc: *tert*-butoxycarbonyl), in a one-pot Ugi–deprotection–cyclization (UDC) strategy.[1] The use of this isonitrile has significant potential in the synthesis of new scaffolds for biologically active amide or peptide synthesis. Recently, Danishefsky's group reported two-component coupling (2CC) reactions of carboxylic acids and isonitriles under suitable thermolytic conditions.[2] They also proposed a possible mechanism for formation of a formimidate carboxylate mixed anhydride (FCMA) as an intermediate.[3] Many novel amides have been designed, synthesized, and reported based on their research.[4] Here, we report the facile one-pot synthesis of two scaffolds, namely benzimidazole and quinoxalin-2(1*H*)-one, via reactions of *N*-Boc-aminophenyl isocyanide with carboxylic acids and glyoxylic acids, respectively.

The 2CC reactions of acids and isonitriles usually occur at high temperatures, although some have been achieved at 110 °C.[2b] The Boc group in 2-(*N*-Boc-amino)phenylisocyanide is labile at high temperatures in numerous solvents.[1] We therefore designed a synthetic route that uses high temperatures generated by microwave irradiation and suitable solvents for removing the Boc group, as shown in Scheme 1. Treatment of 2-(*N*-Boc-amino)phenylisocyanide (**1**) with carboxylic acid **2** gave the target benzimidazole compound **4** in high yield via the *N*-formylamide intermediate **3**. The results of reaction optimization using various solvents, temperatures, and reaction durations are shown in Table 1.



Scheme 1 Synthetic route of benzimidazole compound **4**

Table 1 Optimization of the Reaction Conditions to Obtain Compound **4**

Entry	Solvent	MW temp (°C)	Time (min)	Yield (%)[a]
1	DMF	150	10	63
2	1,4-dioxane	160	20	56
3	THF	140	10	46
4	MeOH	100	20	18
5	EtOH	140	10	51
6	DCE	140	20	78
7	DCE	150	20	89, 85[b]
8	DCE	160	10	80
9	DMSO	170	10	77
10	acetone	120	20	19
11	EtOAc	120	20	23

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

The data in Table 1 show that dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) gave good yields; even acetone gave a yield of 19%. 1,2-Dichloroethane (DCE) was the best solvent choice, taking purification into con-

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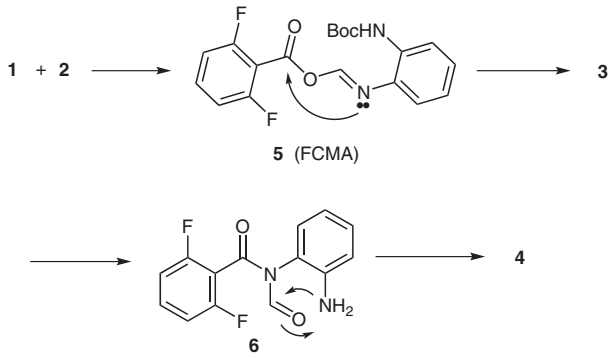
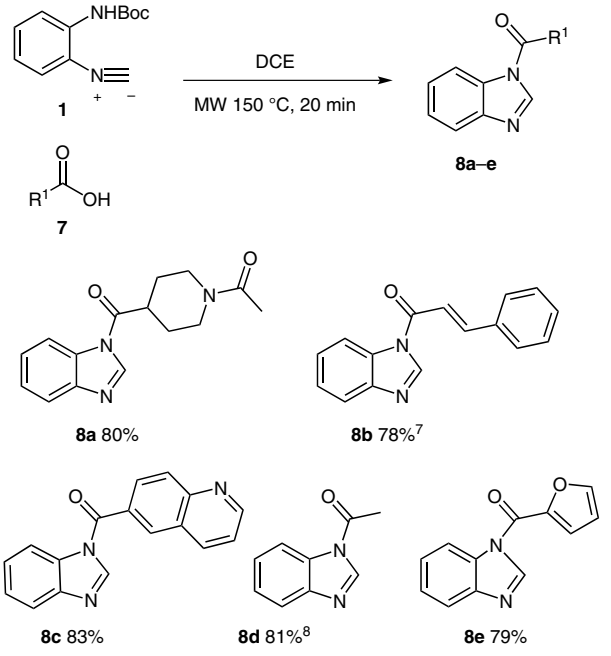
sideration, because it can be easily removed under reduced pressure. Compound **4** was obtained in 85% yield using column chromatography.

Based on experiments[5] and the calculation-supported mechanism proposed by Danishefsky's group,[6] a possible mechanism for the reaction between isonitrile **1** and a carboxylic acid **2** is shown in Scheme 2. FCMA **5** is formed, followed by a 1,3 O→N acyl transfer to give **3**. The following deprotection reaction removes the Boc group to form **6**; the subsequent cyclization gives benzimidazole **4** at high temperature.[7]



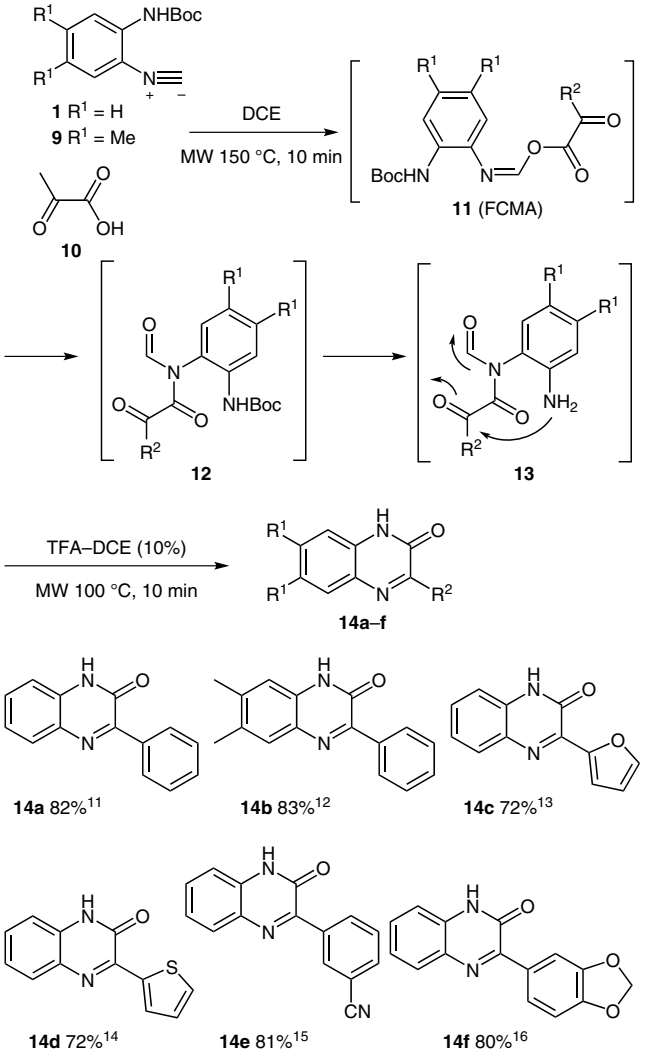
Scheme 2 Proposed mechanism of 2CC reaction between isonitrile and carboxylic acid

A series of benzimidazoles **8** were synthesized using the one-pot conditions, as shown in Scheme 3. The structures of compounds **8b** and **8d** matched those reported in the literature;[7,8] the reactions gave good yields (78–83%), for both alkyl and aromatic carboxylic acids.[9] Various structures of interest in medicinal chemistry can be easily produced by modification of the benzimidazole scaffold by changing the carboxylic acid.



Scheme 3 The detailed structures and yields of benzimidazole compounds **8**

Previous reports have shown that glyoxylic acids are good building blocks for constructing bioactive scaffolds using the UDC strategy.[1b,10] Replacement of the carboxylic acids by glyoxylic acids in the 2CC reaction provides new scaffolds. The reaction of glyoxylic acids **10** with isonitriles is shown in Scheme 4. The microwave irradiation time was shortened to ten minutes, because long reaction times at high temperatures gave low yields. Under these conditions, the intermediate FCMA **11** was obtained, followed by Boc removal from compound **12** to give *N*-formylamide **13**. The addition of trifluoroacetic acid promoted the formation of a Schiff base, leading to ring closure. The unstable amide bond was broken under acidic conditions and formed quinoxalin-2(1*H*)-one **14**[17] in good yields, that is, 72–83%.[15] The use of glyoxylic acids broadens the scope of the 2CC reaction, enabling the creation of diverse platforms of interest in medicinal chemistry.



Scheme 4 The synthetic route, detailed structures, and yields of the

In conclusion, two scaffolds, namely benzimidazole and quinoxalin-2(1*H*)-one, were obtained via a facile one-pot, three-step procedure. The use of carboxylic and glyoxylic acids broadened the scope of the 2CC method and significantly extended the range of biologically active amides or peptides that could be synthesized. The deprotection and intermolecular cyclization steps may have applications in other reactions for designing druglike compounds in medicinal chemistry.

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(9) **General Procedures for Compounds 4 and 8**
A solution of 2-(*N*-Boc-amino)phenylisocyanide (0.50 mmol) and carboxylic acid (0.50 mmol) in DCE (2 mL) was subjected to microwave irradiation at 150 °C for 20 min. After the microwave vial was cooled to r.t., the solvent was removed, and the product was purified by silica gel column chromatography using a gradient of EtOAc–hexane (10–100%) to afford the relative benzimidazole products.
Compound **4**: 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.05–7.96 (m, 1 H), 7.88–7.77 (m, 1 H), 7.67–7.57 (m, 1 H), 7.49–7.46 (m, 2 H), 7.19–7.09 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 158.2, 144.2, 142.1, 134.0, 131.4, 126.3, 125.9, 120.8, 115.5, 112.6, 112.4. HRMS: *m/z* calcd for $C_{14}H_8F_2N_2O$ $[M + H]^+$: 258.0605; found: 258.0603.

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(17) **General Procedure for the Synthesis of Compound 14**
A solution of 2-(*N*-Boc-amino)phenylisocyanide (0.50 mmol) and carboxylic acid (0.50 mmol) in DCE (2 mL) was subjected to microwave irradiation at 150 °C for 10 min. After the microwave vial was cooled to r.t., TFA (0.20 mL) was added to the mixture and treated in microwave again at 100 °C for 10 min. Then, the solvent was removed, and the residue was diluted with EtOAc (15 mL) and washed with sat. Na_2CO_3 (15 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of EtOAc–hexane (10–80%) to afford the relative benzimidazole products.
Compound **14a**: yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (s, 1 H), 8.40–8.21 (m, 2 H), 7.85 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.63–7.44 (m, 4 H), 7.41–7.27 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.0, 154.6, 136.1, 132.5, 130.8, 130.6, 129.7, 129.2, 128.3, 123.8, 115.5. HRMS: *m/z* calcd for $C_{14}H_{10}N_2O$ $[M + H]^+$: 222.0793; found: 222.0796.

