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Synthesis of fused benzimidazole–quinoxalinones via UDC strategy and following the intermolecular nucleophilic substitution reaction

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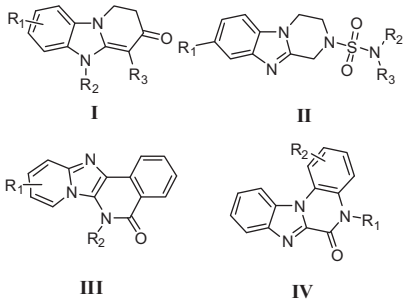
ABSTRACT

A series of fused benzimidazole–quinoxalinones were synthesized utilizing a one-pot UDC (Ugi/de-protection/cyclization) strategy to form a benzimidazole group with subsequent intermolecular nucleophilic substitution reaction to form quinoxalinone functionality. Using combinations of either a tethered ketone acid or aldehyde acid input the Ugi reaction was shown to afford (1) a ring system through lactamization, (2) a benzimidazole through de-protection and cyclization, and (3) a quinoxalinone through the nucleophilic substitution reaction. Scaffolds were produced in good yields and facile operation.

Substituted benzimidazoles and quinoxalinones are important pharmacophores and privileged structures in medicinal chemistry[1] for use as anticancer,[2] anxiolytic,[3] anti-inflammatory,[4] and antimicrobial agents.[5] Benzimidazoles fused with aza-aromatic ring systems have been used as antiviral,[6] antitumor,[7,8] and antihypertensive agents.[9] The scaffolds such as I,[3,6] II,[8] III,[6] and IV[10] have been reported bioactive against GABA-A receptor and RSV (Scheme 1). Recently, the synthesis of new benzimidazole scaffolds has been reported in our group.[11] In the synthesis of pyridoquinoxalinedione, an additional nucleophilic substitution reaction, combined with the Aldol reaction, was introduced to form the new C—N bond.[12] This indicates that the nucleophilic substitution reaction could be used on benzimidazole groups which could be obtained from UDC (Ugi/de-protection/cyclization) strategy to afford a new ring system through C—N bond formation.

Shen's group introduced an intramolecular Goldberg reaction to afford a series of compounds IV (Scheme 1) after a 3-step starting material preparation.[10] The UDC strategy, with its advantage of one-pot operation, could be used to synthesize similar starting material with a 2-step reaction. The difference between these two methods is that the first can form a new quinoxalinone ring from benzimidazole cyclizing the other group. However, in the UDC strategy, the quinoxalinone ring could be formed by closing the benzimidazole group. Herein, we report our result of a facile synthesis of fused benzimidazole–quinoxalinone compounds with only two purification processes.



Scheme 1. Bioactive scaffolds of fused benzimidazoles.

One typical reaction route is shown in Scheme 2. 2-(*N*-Boc-amino)-phenyl-isocyanide **1**, 4-pyridinecarboxylic acid **2**, and valeraldehyde **3** with 2-fluoroaniline **4** could afford the Ugi product **5** after overnight stirring in methanol at room temperature. After de-protection and cyclization in 10% TFA/DCE, benzimidazole compound **6** was obtained with yield as high as 67% in one-pot. With compound **6** in hand, the next nucleophilic substitution reaction was optimized and the results are shown in Table 1.

Organic bases (DIPA, DIPEA, and TEA) and inorganic bases (NaOH, NaH, K_3PO_4, Na_2CO_3, K_2CO_3, and Cs_2CO_3) were all tested. However, organic catalysts did not produce satisfactory results as

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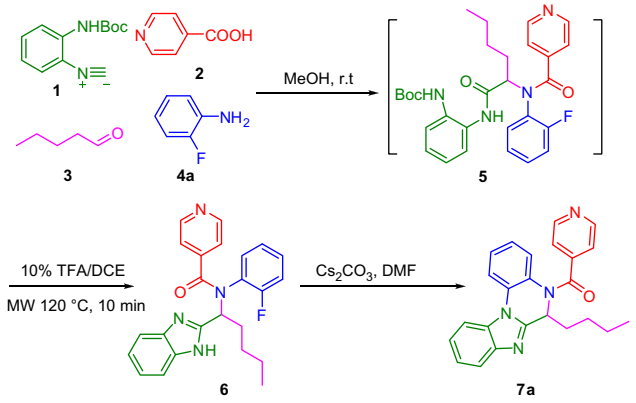


Scheme 2. Synthetic route of benzimidazole–quinoxalinone compound **7a**.

Table 1
Optimization of the reaction conditions to obtain fused benzimidazole–quinoxalinone compound **7a**

Entry	Catalyst	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	DIPA	DMF	MW 140	10	Trace
2	DIPEA	DMF	MW 160	20	6[a]
3	TEA	DMF	MW 140	10	Trace
4	NaOH	DMSO	MW 120	10	15[a]
5	NaOH	DMF	MW 140	10	22[a]
6	NaH	DMF	rt	Overnight	—
7	K_3PO_4	DMF	MW 140	10	11[a]
7	Na_2CO_3	THF	MW 120	10	17[a]
8	K_2CO_3	DMF	MW 140	10	31[a]
9	Cs_2CO_3	DMF	MW 140	10	55[a]
10	Cs_2CO_3	DMF	MW 150	10	94[a], 90[b]

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

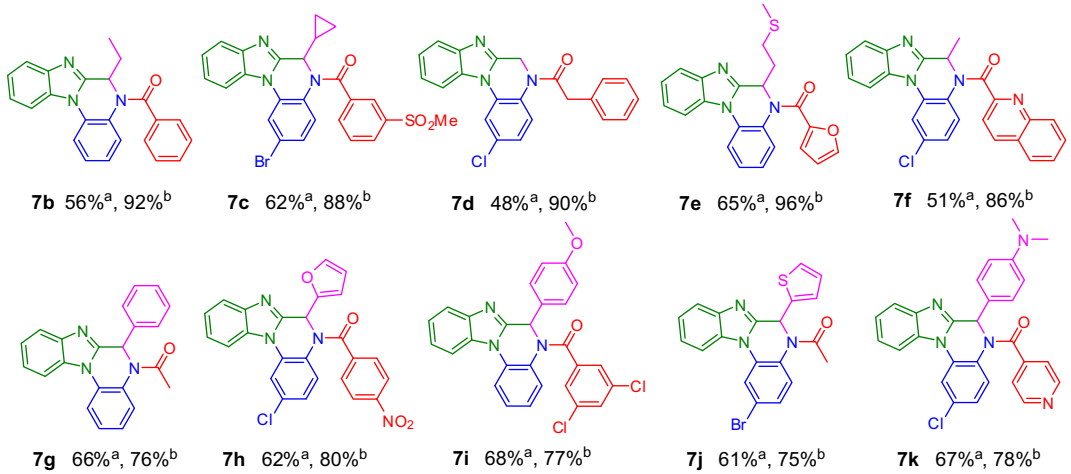
shown in entry 1–3. Strong inorganic base, such as sodium hydride, was also used at room temperature overnight. However, the reaction did not proceed, leaving only starting material. Sodium hydroxide at high temperature brought more side products. This is shown in entry 5 in terms of LC/MS results. Among all bases, Cs_2CO_3 gave excellent yield with 90% after purification under microwave irradiation at 150 °C for 10 min. Using these conditions, a series of benzimidazole–quinoxalinone compounds were designed and synthesized as shown in Scheme 3. The one-pot UDC strategy gave good yield (48–68%) in two steps and the next following nucleophilic substitution gave similar good yields (75–96%). Interestingly, we found the yields of alkyl aldehyde compounds **7a**–**7f** are higher than those of compounds **7g**–**7k** with aromatic aldehyde groups.[13] The possible reason is the aromatic ring would reduce the electron cloud density of the benzimidazole group, so that the attraction affinity of NH was weakened and led to low yield. However, yields are still good enough for compound preparation in high through-put screening in drug discovery.

Similar to this Letter, another series of benzimidazole compounds had also been obtained by using combinations of tethered Ugi inputs typically via tethered ketone acid or aldehyde acid inputs with excellent yields in an operationally friendly manner. The nucleophilic substitution reaction was employed after benzimidazole compounds formed from UDC strategy. The synthetic route is shown in Scheme 4.

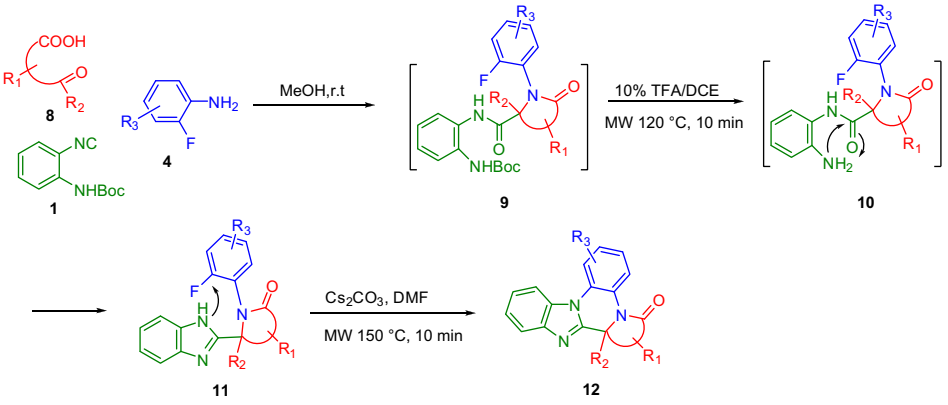
The difference from our previous report[11b] is the replace of normal amines or anilines with substituted 2-fluoroanilines **4**. Following the normal UDC strategy conditions as shown in Scheme 4, one new ring in compound **9** could be formed in the Ugi reaction using tethered ketone acids or aldehyde acids and another benzimidazole ring coming from the isonitrile in the de-protection and cyclization reactions to compound **11**. The nucleophilic substitution reaction was treated in the microwave at 150 °C for 10 min to form the new quinoxalinone ring to compound **12**. So, the nucleophilic substitution reaction connected the other two ring systems and formed a new scaffold of fused benzimidazole–quinoxalinone with high skeletal diversity.

Six different tethered ketone acids or aldehyde acids were introduced in the reaction and the UDC strategy gave good yields ranging from 46% to 62%. However, the next nucleophilic substitution reaction gave different yields for different ketone acids or aldehyde acids as shown in Scheme 4, such as compounds **12a**–**12c** with 90–95% yield and compounds **12d**–**12f** with 62–65% yield.[13] The reason should be the same as aromatic rings reduce electron cloud density in the benzimidazole ring and increase the cyclization difficulty. However, the substituted 2-fluoroanilines and ketone acids or aldehyde acids would provide more opportunities for structure modification and enhanced drug discovery (see Scheme 5).

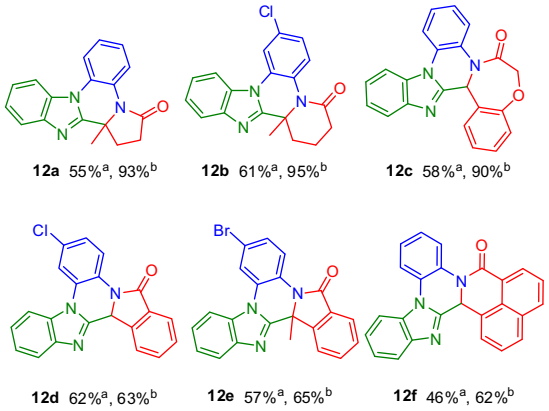
In summary, besides the normal acids and aldehydes, a range of tethered ketone acids or aldehyde acids were all successfully employed in the Ugi reaction, followed by an amino-cyclodehydration to afford benzimidazole with good yields in a general one pot, two-step protocol. The following intermolecular nucleophilic



Scheme 3. The detailed structures and yields of benzimidazole–quinoxalinone compounds **7**. [a]Isolated yield (%) of UDC strategy for two steps. [b]Isolated yield (%) of nucleophilic substitution reaction.



Scheme 4. Synthetic route of benzimidazole–quinoxalinone compounds **12**.



Scheme 5. The detailed structures and yields of compounds **12**. [a]Isolated yield (%) of UDC strategy for two steps. [b]Isolated yield (%) of nucleophilic substitution reaction.

substitution reaction provided the polycyclic heterocycles, benzimidazole–quinoxalinones with high skeletal diversity in good to excellent yields. This novel protocol will facilitate the preparation at a large amount of compounds in high through-put screening in medicinal chemistry.

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13. *General procedures for compounds **7** and **12**:* A solution of aldehyde (0.50 mmol) and substituted 2-fluoroamine (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Then, acid (0.50 mmol) and 2-(*N*-Boc-amino)-phenyl-isocyanide (0.50 mmol) were added separately (for compound **12**, three starting materials (per 0.5 mmol) were added together in MeOH). The mixture was stirred at room temperature overnight. The reaction was monitored by TLC and when there was no 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was removed under nitrogen blowing. The residue was dissolved in 10% TFA/DCE (3 mL) and treated in a microwave at 120 °C for 10 min. After the microwave vial was cooled to room temperature, the solvent was diluted with EtOAc (15 mL) and washed with satd Na_2CO_3 (15 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (10–80%) to afford the relative benzimidazole products. In a solution of benzimidazole compound (0.5 mmol) in 5 mL DMF, Cs_2CO_3 (1.0 mmol) was added and the reaction mixture was treated in a microwave at 150 °C for 10 min. After the microwave vial was cooled to room temperature, the solvent was diluted with EtOAc (15 mL) and washed with brine (2 × 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 ethyl acetate/hexane (0–60%) to afford the relative fused benzimidazole–quinoxalinones. *Compound **7a**:* (yield 90%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74–8.50 (m, 2H), 7.99–7.89 (m, 2H), 7.92–7.84 (m, 1H), 7.49–7.35 (m, 3H), 7.27–7.15 (m, 2H), 7.00 (s, 1H), 6.73 (s, 1H), 6.24 (s, 1H), 1.81–1.61 (m, 2H), 1.58–1.41 (m, 2H), 1.39–1.22 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.6, 150.2, 143.6, 142.0, 131.1, 128.9, 127.3, 127.2, 125.1, 124.0, 123.7, 122.7, 120.7, 116.9, 111.4, 52.7, 31.5, 27.7, 22.2, 13.8. HRMS calculated for $C_{24}H_{23}N_4O$ $[M+H]^+$, 383.1866; found 383.1868. *Compound **12a**:* (yield 93%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 7.9, 1.7 Hz, 1H), 8.01–7.93 (m, 2H), 7.86–7.80 (m, 1H), 7.45–7.32 (m, 4H), 3.11–3.00 (m, 1H), 2.88 (dt, J = 18.0, 9.7 Hz, 1H), 2.71–2.58 (m, 2H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 154.6, 143.5, 131.6, 127.9, 126.0, 125.8, 124.1, 123.7, 123.5, 120.6, 116.4, 111.7, 60.5, 30.4, 25.0. HRMS calculated for $C_{18}H_{16}N_3O$ $[M+H]^+$, 290.1288; found 290.1287.