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Facile, novel two-step syntheses of benzimidazoles, *bis*-benzimidazoles, and *bis*-benzimidazole-dihydroquinoxalines

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Abstract

Three scaffolds of benzimidazoles, *bis*-benzimidazoles, and *bis*-benzimidazole-dihydroquinoxalines were synthesized via Ugi/de-protection/cyclization methodology. Benzimidazole forming ring closure was enabled under microwave irradiation in the presence of 10% TFA/DCE. The methodology demonstrates the utility of 2-(*N*-Boc-amino)-phenyl-isocyanide for the generation of new molecular diversity.

Keywords

UDC; Multi-component reactions (MCRs); Benzimidazoles; *Bis*-benzimidazoles; *Bis*-benzimidazole-dihydroquinoxalines

Introduction

Isocyanide-based multi-component reactions (IMCRs), and their applications, in which three or more starting materials combine to form a single highly functionalized product, have witnessed a resurgence of interest in recent years [1-5]. Indeed, IMCRs have been widely used in drug discovery circles for target-related high speed parallel synthesis and corporate deck file enhancement activities [6].

The Ugi 4-component condensation (Ugi-4CC) utilizes an amine, carbonyl compound, carboxylic acid, and isonitrile to produce α -acylaminoamides closely resembling dipeptides which can be further modified to access a rich array of skeletal diversity, in particular rigidified scaffolds [7-10]. Several years ago, this group introduced the concept of Ugi/de-protection/cyclization (UDC) which has proven to be an operationally friendly methodology for the generation of large libraries and has resulted in two reported Phase II clinical candidates to date [11-13]. Exploring this further, a masked internal amine was tethered to the isocyanide moiety in the form of 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (Scheme 1) to facilitate access to new benzimidazole, *bis*-benzimidazole and *bis*-benzimidazole-dihydroquinoxaline scaffolds. As such, benzimidazoles are a versatile structural motif seen in a multitude of biologically active molecules and interestingly several recent articles have described alternate, yet longer methods for their preparation via other MCRs [14-17]. Herein, we demonstrate that UDC methodology, mediated by 2-(*N*-Boc-amino)-phenyl-isocyanide, can produce a series of benzimidazole (via one internal amine nucleophile), *bis*-benzimidazole and *bis*-benzimidazole-dihydroquinoxaline derivatives (via two internal amine nucleophiles).

Results and discussion

Ugi product **2** was initially prepared by a four-component Ugi reaction involving an amine, carbonyl compound, carboxylic acid, and 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (Scheme 1) [18-20]. The above reaction solutions were concentrated in vacuo and the crude products dissolved in 10% TFA/DCE and exposed to microwave irradiation at 100 °C for 15 min. No purification of the intermediate condensation product **2** was required. On unmasking the internal Boc-protected amine, formation of intermediate **3** enabled cyclodehydration to afford the desired benzimidazole **4**, which in essence originated from the specific use of the designer isonitrile **1**. A study of the reactivity domain of the methodology was instigated before efforts at transitioning the methodology to scaled production readiness (Table 1). As such, all the starting materials used in the study are commercially available, and consist of six aldehydes (both alkyl and aromatic), eight primary amines, and nine carboxylic acids. All reagents proceed well in the condensation step with 2-(*N*-Boc-amino)-phenyl-isocyanide **1** and thus were pushed forward without purification. Alkyl aldehydes exhibited higher overall yields than aromatic aldehydes whereas the selection of carboxylic acids or primary amines had little effect on yield (isolated yields ranged from 57% **4f** to 78% **4i**).

As the methodology was robust, it was thought worthy to attempt the introduction of a second benzimidazole in the structure to afford *bis*-benzimidazoles of general structure **8** (Scheme 2). Thus, by applying of *mono-N*-Boc-phenyl-enediamine **5** in conjunction with 2-(*N*-Boc-amino)-phenyl-isocyanide **1**, the IMCR proceeded well to afford the Ugi product **6** in generally good yield. Strategically, it was hypothesized that the second internal amine, derived from the amine reagent input **5**, would undergo a ring closing cyclodehydration reaction onto the carbonyl group originally derived from the carboxylic acid reagent input. Indeed, upon treatment of the crude Ugi product **6** with 10% TFA in DCE and microwave irradiation (120 °C, 10 min), Boc groups were removed, thus unmasking the two primary amines, which subsequently performed ring closing cyclodehydration reactions onto both

carbonyl groups of the generic Ugi structure **7** giving the desired *bis*-benzimidazoles **8** (Scheme 2) [21–24]. It is noteworthy mentioning that the *bis*-benzimidazole procedure required slightly elevated temperatures relative to the mono-benzimidazole. Exploration of the new reactivity domain of this transformation was examined with five different aldehydes and nine different carboxylic acids producing ten *bis*-benzimidazole congeners (**8a–8j**) with isolated yields reported in Table 2. Encouragingly, overall isolated yields for the two-step process were similar to those for the single benzimidazole protocol (Table 1), ranging from 57 to 82% (Table 2). A variety of heterocyclic ring structures were amenable to the two cyclodehydration steps. Particularly noteworthy is congener **8d** (57%) which actually contains three benzimidazole moieties, with the third one emanating from the carboxylic acid input (Scheme 3).

Definitive structural elucidation was attained through X-ray crystallographic studies on crystalline **8f** (crystals grown in chloroform) (Fig. 1). The crystal structure provided interesting insight in that the two benzimidazole rings were not in the same plane and clear hydrogen bonding patterns were observed between coupled compounds. Detailed information about this crystal structure can be found in the Supplementary Material. An additional point of diversity was accessible through functionalization of the isocyanide-derived benzimidazole. Thus, utilizing *bis*-benzimidazoles **8a** and **8b** as starting materials, the isocyanide-derived benzimidazole was alkylated with a series of alkyl bromides, forming products **9a–9e** with excellent yields in Table 3.

Interestingly, a further novel *bis*-heterocycle—a *bis*-benzimidazole-dihydroquinoxaline was accessible via the use of glyoxylic acids **10** in combination with amine **11** and the high utility isonitrile **1**. The Ugi condensation proceeded well and subsequent product was used without any further purification (Scheme 4). Acid-mediated double deprotection enabled sequential or tandem ring closing events to afford **14**. Under the given reaction conditions, **15** was not observed at all. Ten examples are shown (**14a–14j**) with excellent overall yields for the two-step process in Table 4.

Definitive structural confirmation was obtained through X-ray crystallographic studies on **14c** (Fig. 2). Interestingly, the asymmetric unit of compound **14c** contains two chemically identical but crystallographically unique molecules. Detailed information about this crystal structure can be found in the Supplementary Material.

Conclusions

Concise synthetic routes have been established to three unique, pharmacologically relevant scaffolds, *mono*-benzimidazole **4**, *bis*-benzimidazole **8** (including alkylated analogs), and *bis*-benzimidazole-dihydroquinoxaline **14** utilizing very operationally friendly procedures. Production of these three chemotypes amounted to 125 compounds which were submitted to the MLPCN national repository for exhaustive biological evaluation. Due to the ease of synthesis and pharmacological relevance of the chemotypes, it is expected that these protocols will be embraced by the file enhancement community. It is hoped that this study will spur future studies on applications of this unique isonitrile.

Experimental section

¹H and ¹³C NMR were recorded on a Varian 400 spectrometer. HPLC-MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Restek Ultra C18 column (reverse phase, 3μm, 50 × 2.1mm); a linear gradient from 10% water and 90% acetonitrile to 95% acetonitrile and 5% water over 4.0min; flow rate of 1mL/min; UV photodiode array detection from 200 to 300 nm. All microwave irradiation experiments were

carried out in a CEM-Discover SP-D microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300W with utilization of the standard absorbance level of 220W maximum power. The reactions were carried out in 10mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to 40 °C with gas jet cooling.

General procedure for the synthesis of products

A solution of aldehyde (0.50mmol) and phenylenediamine (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10min. Then, acid (0.50mmol) and 2-(*N*-Boc-amino)-phenyl-isocyanide (0.50mmol) were added separately. The mixture was stirred continually at room temperature overnight. The reaction was monitored by TLC and when there was no 2-(*N*-Boc-amino)-phenyl-isocyanide present, the solvent was removed under reduced pressure. The residue was dissolved in 10% TFA/DCE (3mL) and microwave irradiated at 100 °C (120 °C for **8** and **14**) for 10min. After the microwave vial was cooled to room temperature, the solvent was diluted with EtOAc (15mL) and washed with saturated Na₂CO₃ (15mL). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by Teledyne Isco CombiFlash Rf (hexane/ EtOAc 20–100% or EtOAc/MeOH 0–20%) to afford the relative products.

(**4a**) ¹H NMR (400MHz, CDCl₃) δ 10.47 (s, 1H), 8.55 (d, *J* = 5.5Hz, 1H), 7.92 (s, 1H), 7.75 (t, *J* = 9.1Hz, 1H), 7.64–7.45 (m, 2H), 7.41 (t, *J* = 9.0Hz, 1H), 7.33–7.07 (m, 6H), 6.90 (s, 1H), 6.07 (q, *J* = 7.0Hz, 1H), 3.61 (m, 2H), 1.51 (d, *J* = 7.1Hz, 3H). ¹³C NMR (100MHz, CDCl₃) δ 171.45, 153.04, 150.36, 149.85, 140.73, 139.98, 138.02, 136.67, 134.69, 128.22, 124.49, 124.40, 124.09, 123.99, 122.84, 122.70, 122.59, 121.19, 48.95, 35.70, 15.93. LCMS calcd for C₂₄H₂₁N₄OS [M+H]⁺, 413; found 413.

(**8a**) ¹H NMR (400MHz, *d*-DMSO) δ 7.59–7.44 (m, 3H), 7.15 (dd, *J* = 5.9, 3.1Hz, 2H), 7.05 (dd, *J* = 7.3, 3.7Hz, 2H), 6.95 (t, *J* = 7.5Hz, 1H), 6.13 (q, *J* = 6.8Hz, 1H), 2.60 (s, 3H), 1.96 (t, *J* = 7.4Hz, 3H). ¹³C NMR (100MHz, *d*-DMSO) δ 152.58, 151.69, 142.75, 138.86, 133.70, 121.72, 121.40, 121.08, 118.41, 115.18, 110.46, 49.02, 17.27, 14.12. LCMS calcd for C₁₇H₁₇N₄ [M+H]⁺, 277; found 277.

(**14a**) ¹H NMR (400MHz, *d*-DMSO) δ 12.30 (s, 1H), 8.28 (d, *J* = 3.4Hz, 2H), 7.90 (d, *J* = 7.7Hz, 1H), 7.74–7.01 (m, 10H), 6.89 (s, 1H), 2.03 (d, *J* = 7.0Hz, 3H). ¹³C NMR (100MHz, *d*-DMSO) δ 154.10, 153.34, 153.06, 135.86, 133.10, 130.18, 130.03, 129.38, 127.79, 123.43, 121.58, 114.44, 46.99, 14.85. LCMS calcd for C₂₃H₁₉N₄O [M+H]⁺, 367; found 367.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
X-ray structure of compound **8f**

Fig. 2.
X-ray structure of compound **14c**

Scheme 1.
Synthetic pathway to functionalized benzimidazoles

Scheme 2.
Synthetic route to *bis*-benzimidazoles, **8**

Scheme 3.
Alkylation of *bis*-benzimidazoles

Scheme 4. Two-step synthesis of *bis*-benzimidazole-dihydroquinoxaline compound **14**

Table 1

Representative examples of benzimidazoles

Entry	Structure and yield ^a
1	<p>4a, 76%</p>
2	<p>4b, 61%</p>
3	<p>4c, 76%</p>
4	<p>4d, 77%</p>
5	<p>4e, 58%</p>
6	<p>4f, 57%</p>
7	<p>4g, 62%</p>
8	<p>4h, 73%</p>

Entry	Structure and yield ^a
9	 4i, 78%
10	 4j, 75%

All the reactions were conducted at 0.5mmol scale

^a Isolated yields over two steps

Table 2*Representative examples of bis-benzimidazoles*

Entry	Structure and yield ^a
1	<p>8a, 82%</p>
2	<p>8b, 71%</p>
3	<p>8c, 67%</p>
4	<p>8d, 57%</p>
5	<p>8e, 69%</p>
6	<p>8f, 65%</p>
7	<p>8g, 77%</p>
8	<p>8h, 81%</p>

Entry	Structure and yield ^a
9	8i , 66%
10	8j , 82%

All the reactions were conducted at 0.5mmol scale

^a Isolated yields over two steps

Table 3Alkylation of *bis*-benzimidazole compounds (9a–9e)

Entry	R ₁	R ₂	Product	Yield%
1	Me		9a	84
2	Me		9b	88
3			9c	93
4			9d	86
5			9e	80

Table 4

Representative examples of *bis*-benzimidazole-dihydroquinoxalines (**14a–14j**)

Entry	Structure and yield ^a
1	<p>14a, 82%</p>
2	<p>14b, 70%</p>
3	<p>14c, 78%</p>
4	<p>14d, 70%</p>
5	<p>14e, 79%</p>
6	<p>14f, 81%</p>
7	<p>14g, 76%</p>

Entry	Structure and yield ^a
8	14h , 86%
9	14i , 67%
10	14j , 72%

All the reactions were conducted at 0.5mmol scale

^a Isolated yields over two steps