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Two-step solution-phase synthesis of novel benzimidazoles utilizing a UDC (Ugi/de-Boc/cyclize) strategy†

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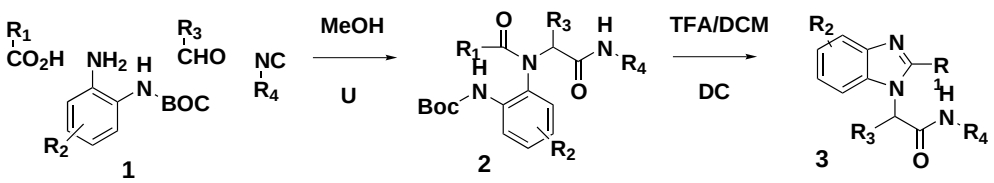
Abstract—The novel solution-phase synthesis of an array of biologically relevant benzimidazoles in a simple two-step procedure is revealed. Transformations are carried out in excellent yield by condensation of mono-Boc protected *ortho*-phenylene diamine and supporting Ugi reagents. Subsequent acid treatment and evaporation affords benzimidazoles in good to excellent yield. The described protocol represents a highly attractive solution-phase procedure for the rapid generation of benzimidazole libraries.

With the emergence of combinatorial chemistry and high-speed parallel synthesis in the lead discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest.[1] Easily automated one-pot reactions, such as the Ugi[2] and Passerini[3] reactions, are powerful tools for producing diverse arrays of compounds, often in one-step and high yield. Despite this synthetic potential, the Ugi reaction is limited by producing products that are flexible and peptidic, often being classified as 'non-drug-like'. Several novel intra-molecular variations on the reaction have been reported where more biologically relevant, constrained products result from interception of the intermediate nitrilium ion using a bifunctional input.[4] An alternative approach is to constrain the Ugi product via a post-condensation modification with an internal nucleophile.[5] This communication reports a novel extension of the latter methodology, describing a two-step procedure for producing benzimidazoles from *ortho*-phenylene diamines, **1**, via condensation in the Ugi reaction followed by acid treatment (Scheme 1).

The Ugi reaction proceeds in good yields with *ortho*-phenylene diamines to give the condensation product, **2** [60–80 area% (*A*%) as judged by LC/MS at UV 215 nm]. TFA-promoted Boc removal and cyclization, with a concomitant loss of water, affords benzimidazoles containing four points of potential diversity with the general structure, **3**. This transformation represents a novel and efficient extension of the UDC (Ugi/de-Boc/cyclize) methodology.[6] Benzimidazoles[7] have been shown to exhibit a wide range of biological function, including utility as Factor Xa inhibitors,[8] NPY 1 antagonists,[9] and proton-pump inhibitors.[10] Clearly, rapid and facile access to libraries of these biologically relevant molecules is of significance for new lead generation programs. The benzimidazole forming reaction was first identified as a side-product in the S_NAr/MCR reaction sequence, as shown in Scheme 2.[11] Thus, Ugi condensation of 2-fluoro-5-nitro benzoic acid, **4**, and *N*-Boc-*ortho*-phenylene diamine, **1**, followed by acid-mediated removal of Boc and polystyrene-supported base-catalyzed cyclization, led to the expected dibenzoazepinone, **8**, in 54% yield



Scheme 1. General reaction to benzimidazoles. *Reagents and conditions*: (i) **aldehyde**, **carboxylic acid**, **1**, **isonitrile**, rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-*N*-methylmorpholine (3 equiv.), THF:CH_2Cl_2, 24 h; (iii) 30% TFA/CH_2Cl_2, 12 h.

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† This paper is dedicated to Chloe P. Tempest on the occasion of her 2nd birthday.

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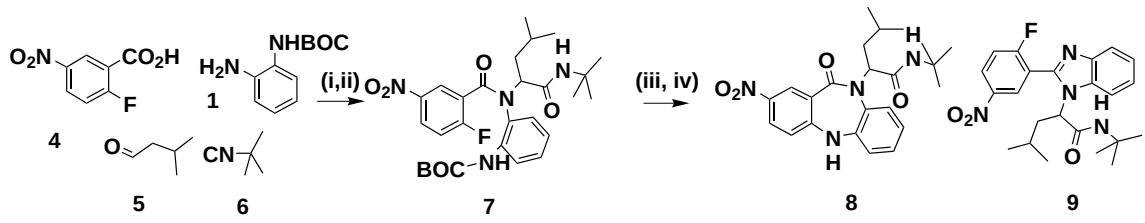

Scheme 2. *Reagents and conditions*: (i) **5**, **4**, **1**, **6**, rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-diisopropylethylamine (3 equiv.), THF:CH_2Cl_2, 24 h; (iii) 20% TFA/CH_2Cl_2, 4 h; (iv) PS-morpholine (3 equiv.), DMF, 36 h.

along with a side-product later identified as the benzimidazole, **9** in 34% yield.

Subsequent studies have demonstrated the generality of this reaction. The benzimidazole formation is improved with increased TFA concentration and prolonged evaporation. Area percent purities of 20 examples are reported in Table 1. The reaction appears general for a range of commercially available carboxylic acids, although sterically hindered acids seem to impede cyclization to the benzimidazole. This is exemplified by the use of diphenylacetic acid in which the expected product, **16**, is formed with only 35% purity. Interestingly, when a sterically hindered acid is used in conjunction with a relatively non-hindered isonitrile, an alternative reaction pathway giving dihydroquinoxalinones emerges. This is exemplified in Scheme 3, where the dihydroquinoxalinone, **13**, was obtained in 40% yield. In the majority of reactions, however, this pathway is insignificant, producing only trace amounts of dihydroquinoxalinones. Of note is a previously reported preparation of dihydroquinoxalinones[12] via cyclohexenyl (or 'convertible') isonitrile methodology.

Encouraged with the results shown in Table 1, the protocol was adapted to high throughput synthesis in a 96 well plate format. An array of 960 compounds was thus prepared using 1 (diamine)×8 (isonitriles)×10 (aldehydes)×12 (carboxylic acids). Unfortunately, *N*-Boc phenylene diamines, **1**, are not commercially available, and this proves to be a limiting factor in the array synthesis. The general procedure for plate level production of benzimidazoles is as follows (Fig. 1). Methanol solutions (200 μl) of the four inputs (0.1 M for amines, acids and isonitriles, 0.2 M for aldehydes) were added in order of their participation in the Ugi condensation yielding 20 μmol of final, theoretical product. Two equivalents of aldehyde were used to increase the yields of the initial Ugi condensation. Reagents were transferred into 2 ml square 96 well plates using a Quadra 96 (Tomtec), and the reaction proceeded at room temperature over 36 h. The methanol was stripped in vacuo at 65°C[14] for 2 h, which was followed by a one-pot double-scavenging step of unreacted aldehyde and acid with immobilized tosylhydrazine and *N*-methylmorpholine, respectively.[15] After resin filtering and evaporation, treatment with a 20% TFA/DCM solution over 24 h at room temperature and evaporation, afforded the array of 960 benzimidazoles. The purity distribution of the library is shown in Fig. 2. Purities of individual library members are comparable to scaled up procedures.[16]

In summary, a novel two-step procedure for the solution-phase synthesis of benzimidazoles has been reported. With final products containing four points of potential diversity and a facile and rapid protocol, access to thousands of diverse analogs of this physiologically important core is feasible. Current efforts are now focused on the development of potential solid-phase approaches.

Acknowledgements

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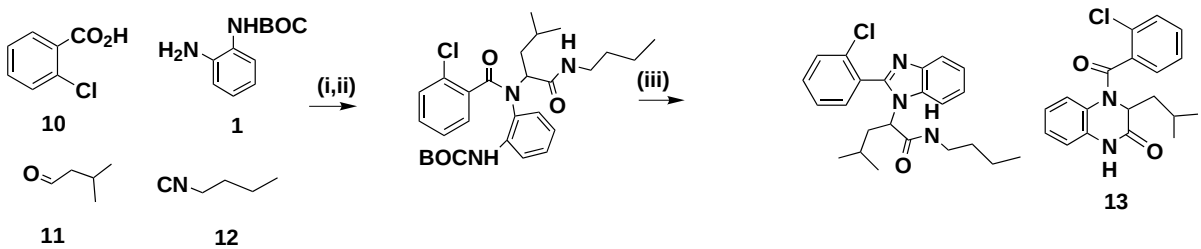

Scheme 3. *Reagents and conditions*: (i) **11**, **12**, **1**, **10**, rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-*N*-methylmorpholine (3 equiv.), THF:CH_2Cl_2, 24 h; (iii) 20% TFA/CH_2Cl_2, 4 h.

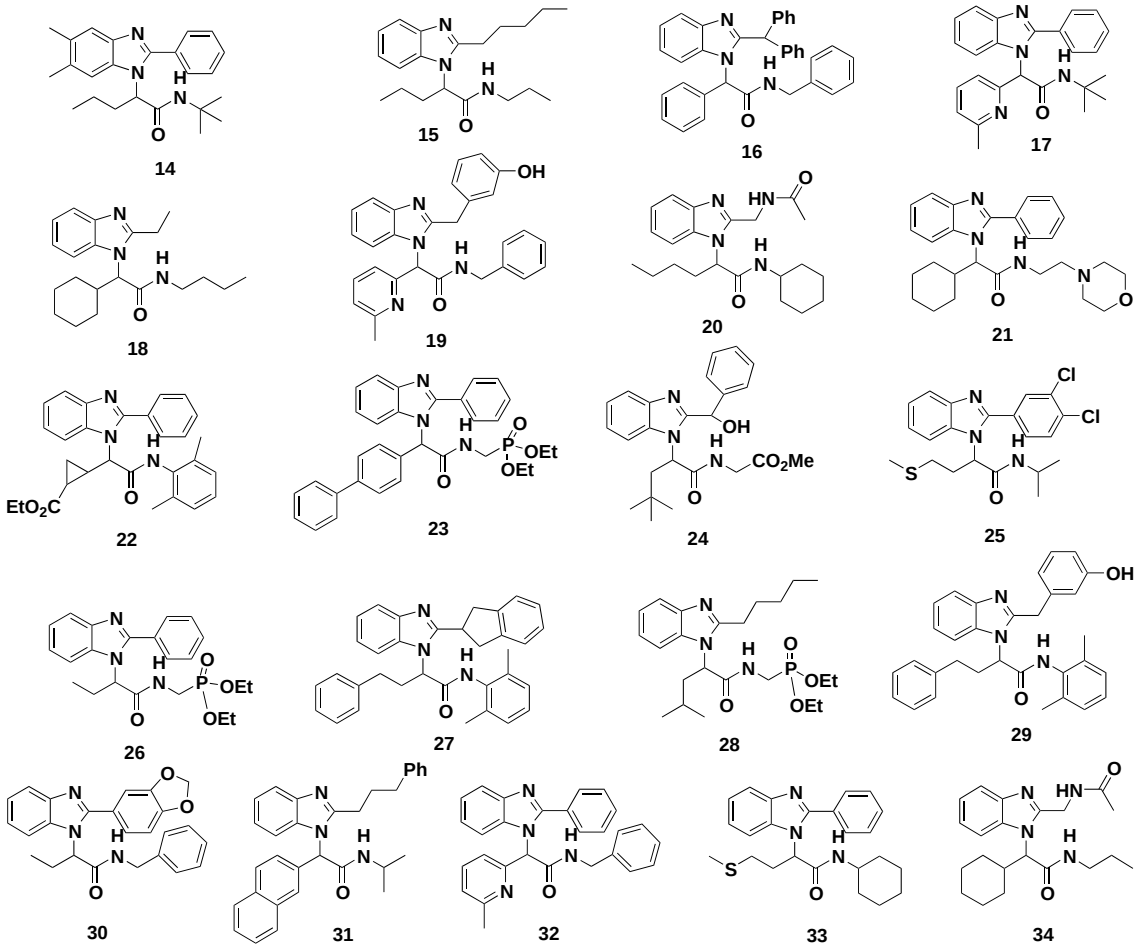

Figure 1. Specific benzimidazoles.

Table 1.

Cpd #	*A*%[a]	MH^+	Cpd #	*A*%[a]	MH^+	Cpd #	*A*%[a]	MH^+
14	67	378	**21**	73	447	**28**	41	452
15	72	330	**22**	59	468	**29**	63	490
16	35	508	**23**	20	554	**30**	80	414
17	86	399	**24**	49	424	**31**	53	462
18	84	342	**25**	62	435	**32**	66	432
19	86	454	**26**	60	430	**33**	84	408
20	94	385	**27**	47	500	**34**	74	357

[a] Area % purities by LC/MS UV220, LC/MS-HP1100 LC with LCQ, YMC-AM 4.6×150 mm column, ESI source.[13]

Lc/ms purity Distribution	
A%	**UV220**
76 - 100%	**30%**
51 - 75%	**44%**
26 - 50%	**18%**
0 - 25%	**6%**

Figure 2.

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13. LC/MS analysis was performed using a C18 Hypersil BDS 3μ 2.1×50 mm column with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 10 min. HPLC was interfaced with APCI techniques.
14. Performed in a SAVANT® evaporator for 2 h.
15. Tosylhydrazine resin purchased from Argonaut® technologies, *N*-methylmorpholine resin purchased from Novabiochem® technologies.
16. The following procedure was followed for the large-scale preparation of **27**: A mixture of 3-(methylthio) propionaldehyde (0.5 M, 800 μl in MeOH), *N*-Boc phenylene diamine (0.5 M, 400 μl in MeOH), *tert*-butyl isonitrile (0.5 M, 400 μl in MeOH) and benzoic acid (0.5 M, 400 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-morpholine were added and shaken for 4 h. The reaction was filtered and the solvent stripped. A 20% TFA/DCM solution (7 ml) was added, let stand for 18 h and stripped at 65°C for 4 h. The crude material was purified by column chromatography to yield **27** (68 mg, 88%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, m, C_6H_4), 7.76 (3H, 2×m, C_6H_4, C_6H_5), 7.59 (3H, 2×m, C_6H_4, C_6H_5), 7.47 (2H, m, C_6H_5), 5.38 (1H, m, CH), 2.66 (1H, m, CH_2), 2.41 (1H, m, CH_2), 2.17 (1H, m, CH_2), 2.03 (1H, m, CH_2), 1.80 (3H, s, CH_3), 1.35 (9H, s, 3×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 152.9, 135.3, 132.8, 132.2, 130.1, 129.9, 126.2, 126.0, 124.6, 117.5, 114.5, 60.9, 52.8, 30.8, 29.5, 28.9, 15.4. HRMS: theoretical value 382.1948; actual value 382.1950. dM/M = 0.5 ppm.