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Solid-Phase Synthesis of Substituted Benzimidazoles

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Abstract: A solid-phase synthesis of benzimidazoles, substituted on the aromatic ring by a variety of groups or atoms, is described. Intermediate **3**, derived from the acylation of a resin-bound secondary amine with Fmoc-glycine, was elaborated *via* nucleophilic displacement with substituted *o*-halo-nitroarenes to give **4**. Careful optimization of the subsequent nitro-group reduction and cyclization with aldehydes, followed by acidolysis gave the title compounds **7** in good yields and purities.

Combinatorial chemistry has become a powerful tool for accelerating the synthesis and screening of diverse collections of molecules.[1] One limitation of the solid-phase method, however, continues to be the requirement for linking the ligand being synthesized to the solid support in an appropriate way. This often necessitates the inclusion of an otherwise undesirable functionality into the target molecules. We have been investigating synthetic routes to the solid-phase synthesis of benzimidazoles for library production.[2] To date, all of the reported solid-phase routes to such compounds have resulted in final products that contain either a carboxyl, carboxamide or hydroxyl group attached to the aromatic ring as a result of their particular linking strategies.[3] We report here on an alternative route to substituted benzimidazoles, which does not rely on direct linker attachment *via* the aromatic ring. The procedure thus considerably extends the variety and position of groups that can be incorporated into the aromatic ring, without the need for specially designed linkers.

The solid-phase synthesis of the title compounds is shown in Scheme 1. The first step was the coupling of an amine onto ArgoGel-MB-CHO resin by reductive amination to provide the first diversity element.[4] An amine (6 equiv. in 0.5% MeOH/THF) was reacted with the resin for 5 h. at 50°C to form the imine followed by reduction with sodium cyanoborohydride (6 equiv.) in 0.5% AcOH/THF by further heating at 50°C for 12 h. to afford the resin-bound secondary amine **2**. Coupling of Fmoc-glycine using HATU/DIEA activation gave intermediate **3**. The loading of the initial amines ranged from 0.27-0.30 mmol/g by spectrophotometric determination of the piperidine/dibenzofulvene adduct (ε_{max} = 8100 l/mol/cm at λ = 302 nm) obtained during Fmoc deprotection of resin **3**. Incorporation of the R2 diversity element was achieved by reacting the deprotected resin with a variety of substituted *ortho*-fluoro- or chloro-nitroarenes (0.5M conc., 10 equiv.) and DIEA (5 equiv.) in DMSO for 12 h. at 60°C. Quantitative conversion to resin-bound, substituted *o*-nitro-anilines **4** was observed in all of the examples studied as determined by ninhydrin tests and LC-MS examination of the products from TFA cleavage of a small sample of resin. Optimization of the next two steps (**e** and **f** in Scheme 1) was crucial in obtaining good yields of the final products. Initially, we had observed

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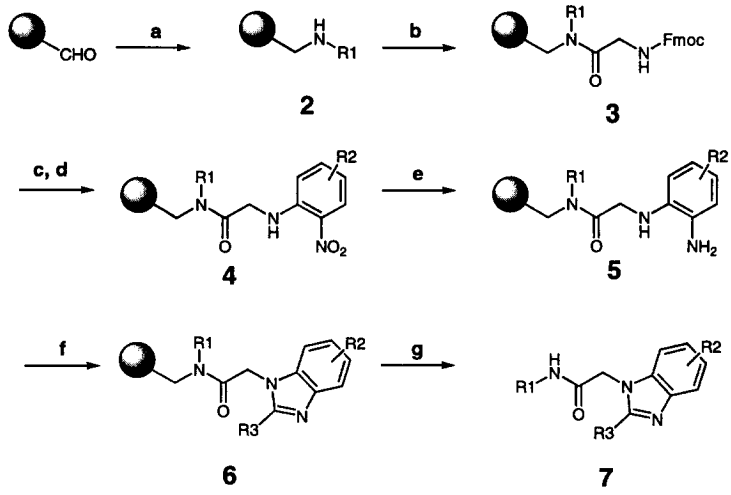
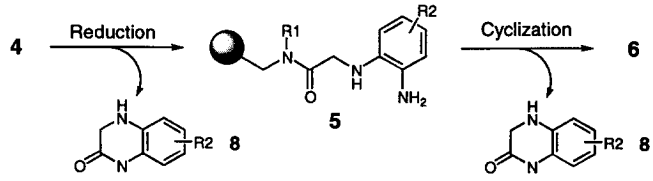
poor product yields when attempting benzimidazole formation using several previously published methods.[2,3(c)] We discovered that this was due to partial losses incurred from the internal cyclization of resin **5** intermediate to form a cyclic side-product (**8**), with concomitant loss of the intermediate from the resin, as illustrated in Scheme 2. The lowered yields occurred during the reduction and cyclization steps when using these methods.[5]



(a.) R1-NH_2, MeOH, THF; $NaCNBH_3$, AcOH, THF; (b.) Fmoc-Gly, HATU, DIEA, DMF; (c.) Piperidine, DMF; (d.) R2-*o*-(fluoro or chloro)-nitroarene, DIEA, DMSO; (e.) $SnCl_2.2H_2O$, NMP; (f.) R3-CHO, NMP; (g.) TFA, DCM.

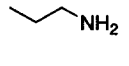
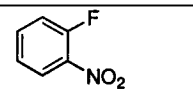
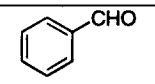
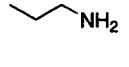
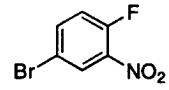
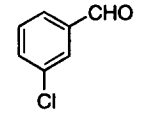
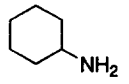
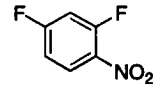
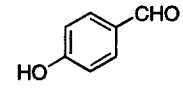
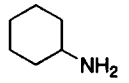
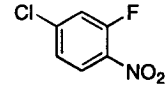
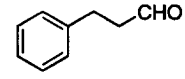
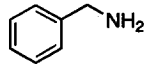
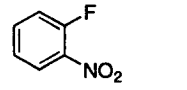
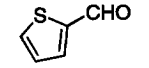
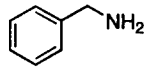
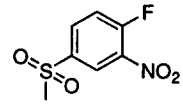
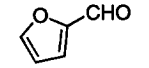
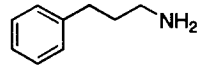
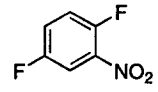
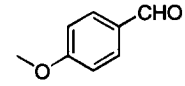
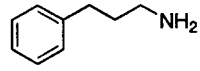
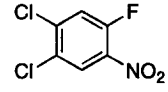
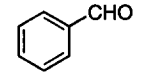
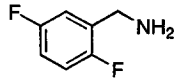
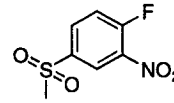
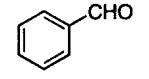
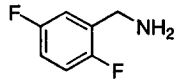
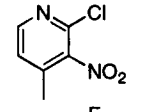
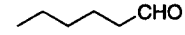
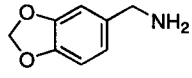
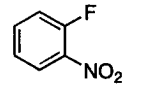
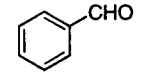
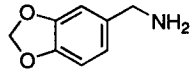
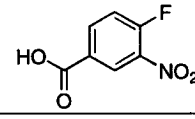
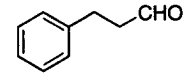
Scheme 1. Synthesis Route to Substituted Benzimidazoles



Scheme 2. Formation of side-product 8 during unoptimized reduction and/or cyclization steps

Additionally, when resin **5** was treated with TFA, **8** was the major product recovered, along with the R1 amine.[6] We therefore investigated whether or not milder conditions for the reduction and cyclization steps could result in improved yields of the target compounds. Accordingly, intermediate resins **4** were treated with tin(II) chloride dihydrate in NMP overnight at room temperature.[7] Each resin was washed then immediately treated with the R3 aldehyde in NMP for 5 h. at room temperature, followed by heating at 50°C for 8 h.[8] The crude products were released from the resin by TFA treatment for purification, analysis and quantitation. The synthetic scheme has proved successful in incorporating many different substituents at each of the R1, R2 and R3 positions, examples of which are shown in Table 1. All purified final products were characterized by RP-HLPC, LC-MS and ^{1}H- and ^{13}C-NMR.[9]

Table 1. Representative examples of substituted benzimidazoles

Compound	R1 monomer	R2 monomer	R3 monomer	Purity[a]	Yield[b]
7a				86	68
7b				68	55
7c				85	80
7d				71	60
7e				70	59
7f				70	45
7g				72	47
7h				83	53
7i				72	45
7j				75	55
7k				55	43
7l				70	55

[a] Purity based on peak integral of crude product peak at λ = 220 nm on RP-HPLC.

[b] Isolated, RP-HPLC-purified compounds, derived from cleavage of 250-300 mg of resin (see ref. 9 for details).

In summary, we have developed and optimized a solid-phase method for the synthesis of ring-substituted benzimidazoles from simple monomers. Further work extending this approach to the synthesis of encoded combinatorial libraries will be reported in due course.

Acknowledgements

The authors thank George Detre for NMR data and Drs. Mark A. Gallop and Ted A. Baer for useful comments.

References and Notes

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4. Obviously, the R1 amine, the amino acid component, the *o*-halo-nitroarene (providing R2) and the R3 aldehyde can each be varied to provide combinatorial diversity.
5. We determined separately that heating above 50°C during either of the reduction (ref. 2) or cyclization steps (ref. 3(c)) was the major contributing factor to reduced product yields using these methods.
6. Presumably, the products were first cleaved by acid then cyclized in solution. This further illustrates the propensity of intermediate **5** for cyclization as shown in Scheme 2. Glycine was, in fact, chosen for optimization studies as it could be expected to present the most problematical example in terms of these cyclative losses.
7. Intermediate **4** resin (2.0 g, approx. 0.6 mmol with respect to the nitro group) was reacted with 2.5M tin(II) chloride dihydrate in NMP (25 ml) in a 75 ml polypropylene filter tube (Alltech) for 12 h. at room temperature. The intermediate resin **5** was drained and washed with (30 ml each) NMP (x5), DCM (x3), MeOH (x5) then NMP again (x5). A batch of this solvated resin (equivalent to approx. 0.3 g dry weight) was immediately treated with 0.15M R3-aldehyde (6 ml, approx. 10 equiv.) in NMP for 5 h., with occasional stirring, then the resin/solution was transferred to a 20 ml glass vial and heated at 50°C with stirring for a further 8 h. The resultant resin **6** was transferred to a 25 ml filter tube, washed with (15 ml each) NMP (x5), DCM (x3), MeOH (x5) and Et_2O (x5) then dried overnight *in vacuo* prior to acidolysis.
8. We postulate that the intermediate imine formed by aldehyde addition under neutral conditions protects the reduced intermediate **5** from the previously observed cyclative losses, allowing subsequent benzimidazole formation *via* thermal cyclization (at 50°C).
9. The crude products were purified by preparative RP-HPLC to give final products of 99% purity (by peak integral at 220 nm). Yields were determined as the weight of purified product (which ranged from 13-25 mg for **7a-7l**) divided by the theoretical yield for that product. The theoretical yield was calculated as [M. Wt. of product] x [weight of resin used (0.25-0.30 g)] x [the loading of each R1 amine as determined by Fmoc loading (ranged between 0.27-0.30 mmol/g)] **7a:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (3H, m), 1.41 (2H, dd), 3.01 (2H, dd), 5.07 (2H, s), 7.50 (2H, d), 7.67 (3H, m), 7.70-7.80 (1H, m), 7.85 (3H, m), 8.54 (1H, t); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 11.4, 22.2, 30.7, 40.6, 47.5, 111.8, 116.3, 124.5, 125.5, 128.9, 129.4, 131.4, 134.3, 135.4, 151.8, 157.7, 158.1, 165.2; MS(ESI) = 294.1 (MH^+). **7c:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.14-1.30 (5H, m), 1.53-1.74 (5H, m), 3.56 (1H, broad), 5.00 (2H, s), 6.99 (2H, d), 7.34 (1H, t), 7.62-7.72 (3H, m), 7.80 (1H, m), 8.43 (1H, d); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 24.1, 25.0, 47.6, 98.6, 112.3, 115.6, 117.0, 130.9, 134.7, 152.9, 157.7, 158.0, 160.2, 164.1; MS(ESI) = 368.1 (MH^+). **7f:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.25 (3H, s), 4.33 (2H, d), 5.24 (2H, s), 7.02 (1H, s), 7.22-7.33 (5H, m), 7.84 (2H, d), 8.20 (1H, s), 8.30 (1H, s), 8.95 (1H, t); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 42.4, 44.2, 46.9, 110.3, 111.2, 115.5, 117.9, 120.8, 126.8, 127.1, 128.2, 134.6, 138.5, 139.3, 141.2, 143.1, 144.3, 149.6, 165.9; MS(ESI) = 410.1 (MH^+). **7g:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.70 (2H, m), 2.56 (2H, m), 3.13 (2H, m), 3.83 (3H, s), 5.03 (2H, s), 7.19 (5H, m), 7.26-7.33 (3H, m), 7.63 (1H, d), 7.70 (1H, m), 7.78 (2H, d), 8.55 (1H, t); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.7, 32.4, 38.4, 47.6, 55.5, 93.7, 102.9, 111.8, 112.5, 114.4, 118.5, 125.6, 128.0, 130.9, 131.6, 141.3, 153.6, 158.0, 160.3, 161.3, 165.5; MS(ESI) = 418.2 (MH^+).