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Solid phase synthesis of chiral 2-amino-benzimidazoles

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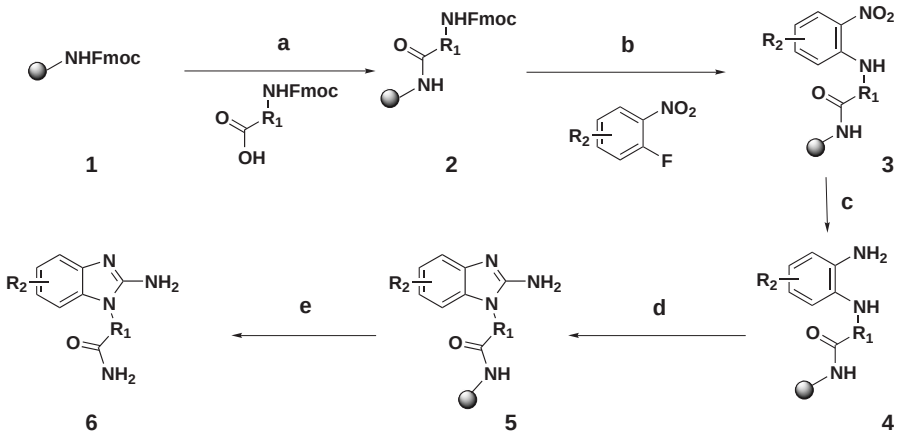
Abstract—A multi-step solid phase synthesis of 2-aminobenzimidazoles is described. The reaction sequence incorporates optically active α-amino acids to afford enantiomerically pure 2-aminobenzimidazoles with a chiral center adjacent to one of the heterocyclic nitrogens. This solid phase methodology has been further extended to prepare other chiral heterocyclic compounds such as benzimidazolones. © 2001 Elsevier Science Ltd. All rights reserved.

Compounds containing a 2-aminobenzimidazole group have been shown to exhibit a broad spectrum of pharmacological activities.[1] Clinical examples include mebendazole, albendazole (antihelmintics),[2,3] and astemizole (antihistamine).[1] In the past few years, the drug discovery process has witnessed a rapid development in the solid phase synthesis of potential therapeutics.[4–6] Benzimidazole-based compounds are being investigated by a number of groups for pharmacological activity.[7–13] However, the application of solid phase methodology in the synthesis of chiral benzimidazole derivatives has yet to be demonstrated, in particular chiral compounds containing a 2-aminobenzimidazole group. We report herein our solution to the synthesis of chiral 2-aminobenzimidazoles on solid support.

The reaction sequence began by deprotection of Fmoc-Sieber Amide resin using 20% piperidine in DMF (Scheme 1). Sieber Amide resin was selected as the polymer support because of its mild cleavage conditions (5% TFA in CH_2Cl_2).[14,15] Fmoc-amino acids (3 equiv.) were then coupled onto the resin using 1,3-diisopropylcarbodiimide (DIC, 3 equiv.) and *N*,*N*-diisopropylethylamine (DIPEA, 3 equiv.) in DMF. A ninhydrin test was performed on resin **2** to ensure complete loading of amino acids.[16] The Fmoc group was then removed with



Scheme 1. (a) 20% piperidine/DMF; FmocNHR$_1$COOH, DIC, HOBT, DMF; (b) 20% piperidine/DMF; R$_2$Ph(NO$_2$)F, DIPEA, DMSO; (c) $SnCl_2 \cdot 2H_2O$, DMF; (d) BrCN, DMF:EtOH (2:1); (e) 5% TFA/CH_2Cl_2.

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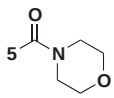
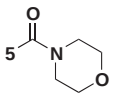
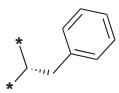
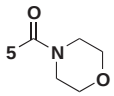
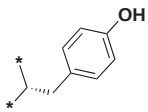
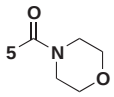
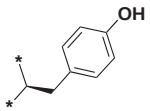
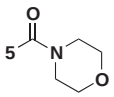
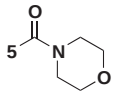
20% piperidine in DMF, followed by a nucleophilic aromatic substitution reaction (S_NAr) to incorporate a variety of *ortho*-fluoro-nitroarenes to give derivatives **3** (examples in Table 1). The S_NAr reaction was performed in DMSO with 10 equiv. of *ortho*-fluoro-nitroarene and 10 equiv. of DIPEA overnight at room temperature. The nitro group of **3** was then reduced with 1 M $SnCl_2{\cdot}2H_2O$ in DMF, following published procedures.[11,12] Cyclization of the aryldiamine on resin **4** with 10 equiv. of cyanogen bromide in ethanol/DMF (1:2) overnight at room temperature successfully provided the 2-amino-benzimidazole **5** on solid support for the first time. The final products **6** were cleaved from the Sieber Amide resin with 5% TFA in CH_2Cl_2.

This reaction sequence offers several advantages over alternative routes. First of all, it allows the solid phase synthesis of chiral 2-aminobenzimidazole derivatives for the first time. When chiral amino acids were used as the starting material, chirality was retained completely even after six to seven steps (including deprotection and cleavage) on solid support. The enantiomeric excess (*ee*) of 2-aminobenzimidazles was determined by chiral HPLC analysis. As an example, Fig. 1 shows the chiral HPLC traces of compound **7** (top trace) and **8** (middle trace), which were derived from Fmoc-(L)-alanine and Fmoc-(D)-alanine, respectively. In addition, a mixture of **7** and **8** (bottom trace) was also analyzed to ensure separation of enantiomers under the HPLC conditions.

Table 1. Typical examples of 2-aminobenzimidazoles

Compound	R_1[a]	R_2[a]	Yield (%)[b]	Purity(%)[c]	ee (%)[d]
7			99	92	>98
8			91	77	>98
9			93	83	>98
10			87	90	>98
11			84	76	>98
12			93	82	>98
13		5,6-di-Cl	99	98	>98
14		5-CF_3	99	69	>98
15		-H	91	78	>98

[a]The definition of R_1 and R_2 is the same as that in Scheme 1. The asterisks (*) in column 2 indicate the connection points of R_1 to the parent structure **6**. [b]Yield of crude products based on the original loading of Sieber Amide resin. [c]Purity determined by HPLC analysis of crude products (integration area @254 nm). All products show satisfactory ^{1}H NMR and MS (ESI) spectra. Physical data for selected compounds: Compound **7**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 1.62 (d, J = 7 Hz, 3H), 3.10–4.70 (m, 8H), 5.30 (q, J = 7 Hz, 1H), 7.25–7.35 (m, 2H), 7.44 (s, 1H), 7.60 (s, 1H), 7.80 (s, 1H), 8.86 (s, 2H). MS (ESI), m/z (M+H): 318.3. Compound **9**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.10–4.70 (m, 10H), 5.58 (m, 1H), 6.96 (m, 2H), 7.14 (m, 3H), 7.32 (d, J = 8 Hz, 1H), 7.36 (s, 1H), 7.49 (d, J = 8 Hz, 1H), 7.73 (s, 1H), 7.93 (s, 1H), 8.68 (s, 2H). MS (ESI), m/z (M+H): 394.3. Compound **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.10–4.70 (m, 10H), 5.38 (m, 1H), 6.49 (d, J = 8 Hz, 2H), 6.67 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 1H), 7.34 (s, 1H), 7.40 (d, J = 8 Hz, 1H), 7.69 (s, 1H), 7.84 (s, 1H), 8.55 (s, 2H), 9.25 (s, 1H). MS (ESI), m/z (M+H): 410.3. [d]Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralcel OD column, 4.6×250 mm) of the purified products.

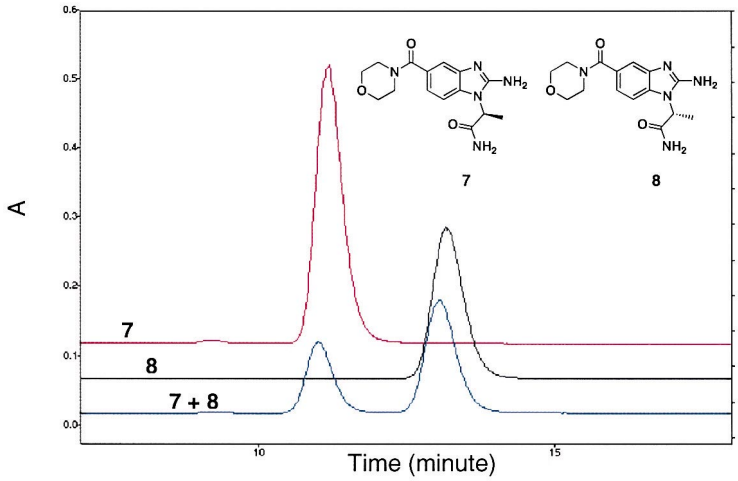


Figure 1. Chiral HPLC analysis of compound **7** (top trace), **8** (middle trace), and a mixture of **7** and **8** (bottom trace). Compounds were purified by preparative TLC (10–30% methanol and 2% NH_4OH in CH_2Cl_2 as developing solvents) prior to chiral HPLC analysis. HPLC conditions: Chiralcel OD column, 4.6×250 mm, 20% isopropanol in hexane, 1 mL/min for 25 minutes.

Indeed, the final products are enantiomerically pure after the multi-step reaction sequence. Additional examples **9**–**12** are shown in Table 1. Compounds **10** and **11** were derived from Fmoc-*O*-*t*-butyl-D-tyrosine and Fmoc-*O*-*t*-butyl-L-tyrosine, respectively. The *O*-*t*-butyl protecting group was concurrently removed during the cleavage step.

Many of the previous reports on solid phase synthesis of benzimidazoles involve attaching 4-fluoro-3-nitrobenzoic acid onto the solid support via an amide or an ester linkage.[11–13,17,18] Hence, all final products resulting from these reaction sequences have a carboxyl or a carboxamide group at the 5-position. The current reaction sequence overcomes this limitation by providing the opportunity to introduce various *ortho*-fluoronitroarenes using S_NAr reactions onto resin **2** (Scheme 1). As a consequence, functional groups (R_2) on the 2-aminobenzimidazoles **6** cannot only be of diverse structures but are also open for further modification on solid support (Table 1, **7**–**15**). When 4-fluoro-3-nitrobenzoic acid was the substrate of the S_NAr reaction, the carboxyl group of intermediate **3** could be further derivatized with various amines using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) as the coupling reagent. Compounds **7**–**12** result from this modification of the intermediate carboxy group with morpholine.

The solid phase methodology can be extended to synthesize other chiral heterocyclic compounds. Cyclization of the aryldiamine on resin **4** with 1,1′-carbonyldiimidazole (CDI) and trimethylorthoformate (TMOF) successfully afforded enantiomerically pure benzimidazolone and benzimidazole, respectively. Furthermore, additional structural diversity of 2-aminobenzimidazoles can be achieved by reacting acid chlorides, sulfonyl chlorides or isocyanates with the 2-amino group of resin **5**. These reactions are currently under detailed investigation and will be reported in due course.

In summary, we have developed a novel reaction sequence that allowed the first solid phase synthesis of chiral 2-aminobenzimidazoles in high yield and excellent enantiomeric excess. The versatility of this solid phase methodology can be extended to prepare other chiral heterocyclic compounds such as benzimidazolones.

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References

1. Nawrocka, W. *Bull. Chim. Farm.* **1996**, *135*, 18–23.
2. Winstanley, P. *Lancet* **1998**, *352*, 1080–1081.
3. Carpio, A. *J. Neurol., Neurosurg. Psychiatry* **1999**, *66*, 411–412.
4. James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
5. Lorsback, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549–1581.
6. Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443.
7. Tumelty, D.; Schwartz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185–6188.
8. Tumelty, D.; Schwarz, M. K.; Needles, M. C. *Tetrahedron Lett.* **1998**, *39*, 7467–7470.
9. Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668.
10. Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67–70.
11. Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655–6658.
12. Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201–204.

13. Wei, G. P.; Phillips, G. B. *Tetrahedron Lett*. **1998**, *39*, 179–182.
14. Chan, W. C.; Mellor, S. L. *J. Chem. Soc., Chem. Commun*. **1995**, 1475–1477.
15. Sieber, P. *Tetrahedron Lett*. **1987**, *28*, 2107–2110.
16. Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem*. **1981**, *117*, 147–157.
17. Smith, J. M.; Grad, J.; Cummings, W.; Kanizsai, A.; Krchnak, V. *J. Comb. Chem*. **1999**, *1*, 368–370.
18. Yeh, C.-M.; Sun, C.-M. *Synlett* **1999**, *6*, 810–812.