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Traceless Solid-Phase Synthesis of Substituted Benzimidazoles via a Base-Cleavable Linker

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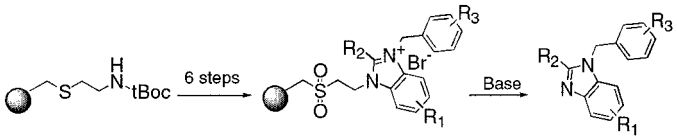
ABSTRACT



A solid-phase route to substituted benzimidazoles has been developed using a modified base-labile linker strategy to release the final products in a traceless manner. This approach permits the synthesis of diverse compounds in moderate yields and high purity.

Because of their relative ease of synthesis and precedence as bioactive molecules, benzimidazoles have been an obvious target for the development of solid-phase syntheses.[1] Recent reports have described routes where the cleavage of solid-phase-synthesized intermediates by acidolysis and their subsequent incubation in the cleavage solution effects the final cyclization step to form benzimidazoles with either two or three points of diversity.[2] The final products formed thus lack an obvious solid-phase-derived attachment point and may be described as "traceless".[3] This report describes the development of a traceless benzimidazole route in which a salt form of the desired compounds was synthesized on the resin and the desired final product was liberated by treatment with mild base. The synthetic design was such that only the final target compounds were released during the cleavage step, while unreacted intermediates remained resin-bound, allowing the synthesis of the desired products in moderate yield but high purity.

The fundamental linkage strategy has been described for simple tertiary amines and involves a final Hofmann elimination step to release the required products.[4] We have been able to extend this approach to demonstrate the combinatorial synthesis of substituted benzimidazoles by the route shown in Scheme 1. Tentagel-Br resin (**1**, 0.42 mmol/g loading) was treated with *tert*-butyl *N*-(2-mercaptoethyl)-carbamate, in the presence of base, to yield the tBoc-protected resin/linker **2**. After acidolytic removal of this protecting group and neutralization, a small sample of resin **3** was used to determine the loading of the linker.[5] Resin **3** was subjected to S_NAr displacement with a variety of *o*-fluoro- or -chloronitroarenes at elevated temperature, as previously described.[1a,6] Complete reaction of these mono-

(1) (a) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185−6188. (b) Tumelty, D.; Schwarz, M. K.; Needels, M. C. *Tetrahedron Lett.* **1998**, *39*, 7467−7470. (c) Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655−6658. (d) Sun, Q.; Yan, B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 361−364. (e) Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201−204. (f) Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37*, 4887−4890.

(2) (a) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67−70. (b) Smith, J. M.; Krchnak, V. *Tetrahedron Lett.* **1999**, *40*, 7633−7636. (c) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665−2668.

(3) In essence, this means that the benzimidazole products may lack the obligatory carboxyl/carboxamide group, which is usually left on the aromatic ring as a remnant of cleavage from acid-labile (or other) linkers.

(4) (a) Brown, A. R. *J. Comb. Chem.* **1999**, *1*, 283−285. (b) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288−3295. (c) Kroll, F. E. K.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573−8576. (d) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209−3212.

(5) By quantitative ninhydrin test: Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147−57. The amine was also reprotected using Fmoc-Cl/DIEA/DCM, the Fmoc removed with piperidine and quantified at 302 nm. The new loading was 0.35 mmol/g.

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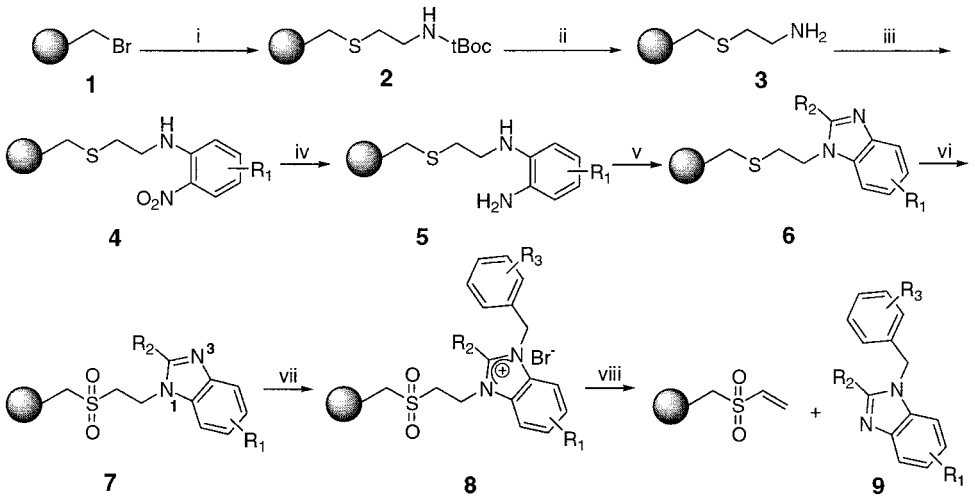
Scheme 1. Solid-Phase Synthesis of Traceless Substituted Benzimidazoles[a]



[a] Conditions: (i) *tert*-butyl *N*-(2-mercaptoethyl)carbamate (7 equiv), K_2CO_3 (4 equiv), NMP, 12 h, 60 °C, under N_2; (ii) TFA, dimethyl sulfide, DCM (9:1:10), 2 × 0.5 h, rt, then DIEA, DCM (1:5), 2 × 0.5 h, rt; (iii) *o*-nitrofluoro/-chloro-R_1-arene (20 equiv), DIEA (10 equiv), NMP, 12 h, 60 °C; (iv) $SnCl_2 \cdot 2H_2O$, NMP, 12 h, rt; (v) R_2-CHO (5 equiv), NMP, 12 h, 50 °C; (vi) aqueous Oxone, 12 h, rt; (vii) R_3-benzyl bromide (50 equiv) [or R_3-benzyl chloride (50 equiv.), NaI (5 equiv)], NMP, 18 h, 70 °C; (viii) triethylamine, DCM (1:19), 18 h, rt.

mers with the linker was conveniently determined by ninhydrin tests. Following nitro reduction of resins **4** with tin(II) chloride, the resin-bound secondary phenylene diamines **5** were cyclized by treatment with a variety of aromatic and aliphatic aldehydes. Under these conditions, no exogenous oxidants were necessary to form the ring-closed, resin-bound benzimidazoles **6**.

The efficient oxidation of the sulfide to the sulfone was crucial for the activation of the linker toward subsequent base cleavage. Resin **6** was thus washed in methanol; then a 0.4 M solution of Oxone in water was added and the resin/solution shaken overnight to produce resin **7**.[7] In model systems, these conditions had been shown to produce quantitative conversion of sulfides to the corresponding sulfones. The resin-bound intermediate **7** was subsequently converted to quaternary salt **8** by alkylation with substituted benzyl bromides. The reaction was quite slow for many benzyl bromides and had to be heated to 65−75 °C overnight for acceptable yields to be obtained. We were able to increase the rate and extent of alkylation by using large excesses of the reagents at high concentrations (at least 2 M in NMP). The addition of sodium iodide enabled both benzyl and alkyl chlorides to be used successfully in the alkylation step. Increasing the reaction temperature beyond 90 °C led to some premature release of the final products into the alkylating solution. Our studies indicated that the final product yield was largely determined by this step and was variable, depending mainly on the electronic properties of the alkylating species.

The final products **9** were released from the resin by an overnight treatment with 5% triethylamine/DCM. Other bases successfully released the products, e.g., DIEA, ammonia, and aqueous solutions of NaOH and NH_4OH. Also, 5% solutions of TEA and DIEA were effective in many other solvent systems, such as DMSO, acetonitrile, MeOH, acetone, and dioxane. Simple time-course cleavage studies were carried out on several small-scale samples of resin **8**. These indicated that 70% of the product material was released from the resin within the first 5 h of treatment with 5% TEA/DCM at room temperature. For preparative work, the resin samples were subjected to the cleavage conditions for 16 h in an attempt to maximize the product yield.

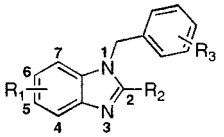
After cleavage, the resins were separated by filtration and washed with DCM and MeOH, and the filtrates were evaporated to dryness. The residue was taken up with EtOAc and extracted with 10% sodium bicarbonate solution to remove excess TEA salts, dried over sodium sulfate, and then evaporated under reduced pressure. The residue was taken up in DMSO and purified by semipreparative HPLC. Purified fractions were combined and lyophilized to give a white powder of at least 99% purity by HPLC.

The crude products were obtained with very good purity, although the yields varied, as expected, according to the steric and electronic characteristics of the monomers used for each combinatorial product. For the alkylation step, good to high yields of the final compounds were generally observed when benzyl bromide was used as the R3 monomer (Table 1, entries **9d**, **9e**, **9j**, **9p**, and **9q**). However, when electron-

(6) Of the many commercially available monomers of this type, around 20 proved to be useful in this synthetic scheme, some examples of which were used synthesize the final products shown in Table 1 and Scheme 2.

(7) Oxone (Aldrich) dissolves easily in water. Presolvation of the resin in MeOH aids its solvation by the aqueous solution. Previous oxidations of this type have also used MCPBA, e.g.: Garcia-Echeverria, C. *Tetrahedron Lett.* **1997**, *38*, 8933−8934.

Table 1. Purity and Yield of Traceless Benzimidazoles **9a**−**r**[a]



entry	R1	R2	R3	purity[b] (%)	yield[c] (%)
9a	5-Cl	-$(CH_2)_4$-Me	4-CN	81	22
9b	5-Cl	-Ph	2-CN	96	29
9c	5-Cl	3-F-C_6H_4	4-NO_2	84	27
9d	5-Cl	2-Cl-C_6H_4	-H	89	60
9e	5-Cl	-[4-CH(Me)$_2$]-C_6H_4	-H	84	58
9f	-7-F	-$(CH_2)_4$-Me	4-CO_2Me	93	44
9g	-7-F	-Ph	4-C(Me)$_3$	90	70
9h	-7-F	3-F-C_6H_4	-2-Me	91	55
9i	-7-F	2-Cl-C_6H_4	-4-OMe	93	10
9j	-7-F	-[4-CH(Me)$_2$]-C_6H_4	-H	87	75
9k	6-SO_2Me	-$(CH_2)_4$-Me	-4-Br	83	20
9l	6-SO_2Me	-Ph	-3,5-diMe	90	18
9m	6-SO_2Me	2-Cl-C_6H_4	-3-F	91	49
9n	6-SO_2Me	-[4-CH(Me)$_2$]-C_6H_4	-H	92	22
9o	-6-Br	-Ph	-3-OCF_3	91	40
9p	-6-Br	2-Cl-C_6H_4	-H	92	73
9q	-6-Br	-[4-CH(Me)$_2$]-C_6H_4	-H	83	49

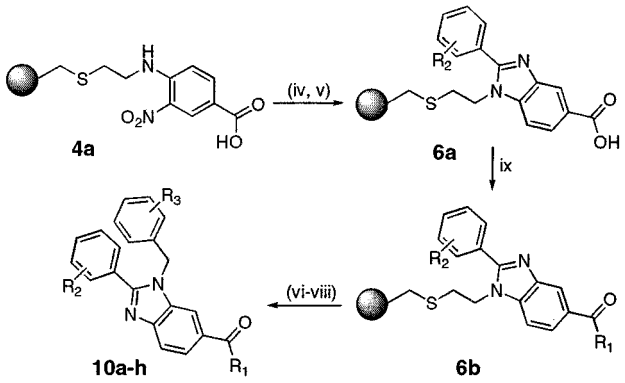
[a] All compounds were characterized by HPLC, LC-MS, and ^{1}H and ^{13}C NMR. Final compounds were obtained from the cleavage of 300 mg of resin, with the final weights obtained ranging from 10 to 50 mg. [b] Purity was determined by the HPLC integral of the product peak at 220 nm. The purity given is for the crude material directly after cleavage. [c] Yield was calculated as the weight of final compound obtained after HPLC purification (to 99% purity) divided by the theoretical yield. The latter was calculated from the original loading of resin **3**, corrected for weight gain due to the resin-bound compound (assuming 100% conversion in each of the subsequent reaction steps) × FW of compound × amount of resin used in cleavage step.

donating groups were present, low yields were obtained (entries **9i** and **9l**). After TEA treatment of the latter two resins, different products could be obtained by re-alkylating the resin with other benzyl bromides. Such experiments showed that the alkylation step with the original bromides was low yielding in these cases, rather than being caused by a low yield of resin intermediate **7**.

In an effort to extend the diversity available at the R1 position, the monomer 4-fluoro-3-nitrobenzoic acid was incorporated to give resin intermediate **4a** (Scheme 2). The acid functionality of resin **6a** was converted to a substituted amide **6b** and ultimately used to synthesize compounds **10a**−**h**. In contrast to previously described solid-phase routes,[8] this enabled tertiary carboxamides to be attached to the aromatic ring, some examples of which are shown in Scheme 2.

From inspection of the NMR spectra of samples **9a**−**q** and **10a**−**h**, it was apparent that a single, regioisomerically

Scheme 2. Carboxamide Formation To Give Compounds **10a**−**h**[a]



entry	R1	R2	R3	purity (%)	yield (%)
10a	-Nc(CH_2)$_5$	3,4-diO(CH_2)	-3-F	91	55
10b	-NH-CHc(CH_2)$_4$	-4-CH(Me)$_2$	-3-F	83	46
10c	-N(C_2H_5)CH_2-C_6H_5	3,4-diO(CH_2)	-3-F	90	50
10d	-N(C_2H_5)C_2H_5	-H	-3-F	92	65
10e	-NH-C_2H_5	-H	-3-F	84	66
10f	-NH-C_2H_5	-H	-H	95	82
10g	-NH-C_2H_5	-4-CH(Me)$_2$	-H	82	70
10h	-NH-C_2H_5	3,4-diO(CH_2)	-H	95	77

[a] Conditions: as in Scheme 1 (steps shown in parentheses), except (ix) diethyl cyanophosphonate (10 equiv), R1-amine (10 equiv), NMP, 12 h, rt.

pure compound had been obtained in each case. We expected that this followed alkylation at only the N3 position of resin **7**, as shown in Scheme 1. However, we were keen to obtain direct experimental evidence that this step formed the quaternary salt by alkylation solely at the N3 position rather than at the N1 nitrogen, the attachment point to the linker. Accordingly we devised a strategy, using an alternative solid-phase route, for synthesizing compounds which would correspond unequivocally to the products obtained from the traceless route if alkylation occurred exclusively at either the N1- or N3-nitrogen (Scheme 3).[9]

Tentagel-Wang resin was treated with triphenylphosphine dibromide in DCM, followed by displacement of the bromide with ethylamine in THF/NMP and finally coupled with either 3-fluoro-4-nitrobenzoic acid[10] or 4-fluoro-3-nitrobenzoic acid (via diisopropylcarbodiimide activation) to give resins **13** and **16**, respectively.

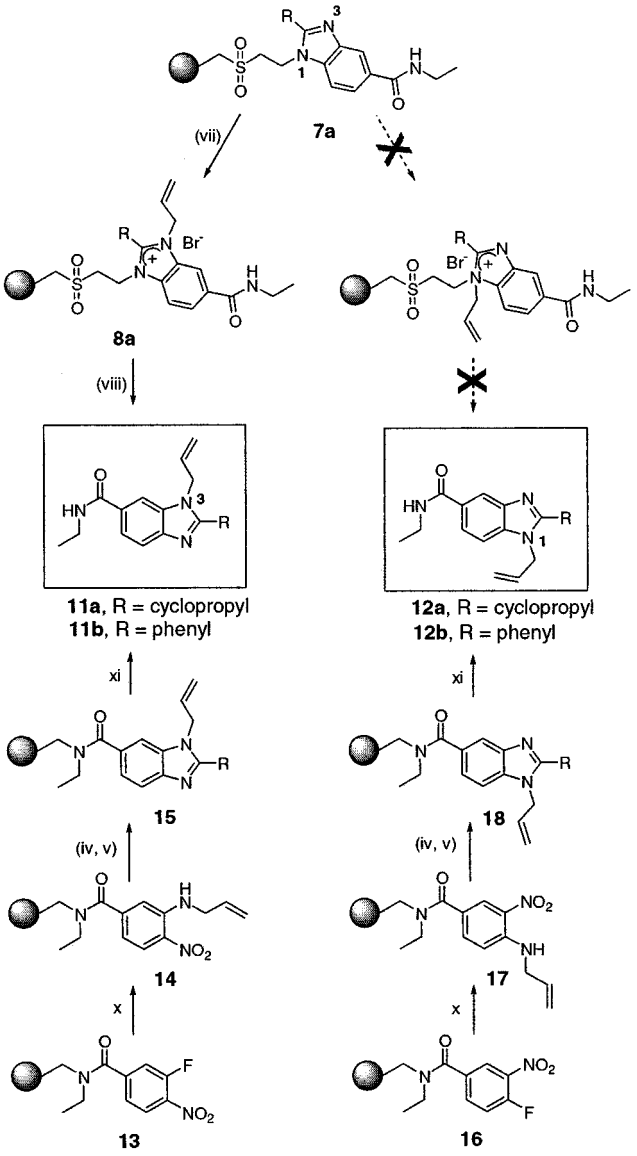
Nucleophilic substitution with allylamine in DMSO gave resins **14** and **17**. Nitro group reduction and cyclization with either cyclopropylaldehyde or benzaldehyde led to resins **15** and **18**. Final acidolysis released compounds **11a** and **11b** from the 3-F,4-NO_2-benzoic acid coupled resins and com-

(8) Primary carboxamides or, with the appropriate linker, secondary carboxamides have been described for previous solid-phase syntheses, where the carboxamide group was also the point of attachment to the linker/resin. With this new strategy, more diverse tertiary carboxamides are possible from the common resin intermediate, **6a**, as the carboxyl group is no longer required to be the point of attachment to the resin.

(9) The alternative route is derived from refs 1a−c, as well as the following: Tumelty, D.; Dong, L.-C.; Cao, K.; Le, Lanchi; Needels, M. C. Case Study 4−3. In *High Throughput Organic Synthesis*; Sucholeiki, I., Ed.; Marcel Dekker: New York, in press; pp 93−107.

(10) This acid was obtained by treating 3-fluoro-4-nitrotoluene with dichromate in aqueous sulfuric acid: Reynolds, D. W.; Cassidy, P. E.; Johnson, C. G.; Cameron, M. L. *J. Org. Chem.* **1990**, *55*, 4448−4454.

Scheme 3. Synthesis of Regioisomers **11a/b** and **12a/b**[a]



[a] Conditions: as in Scheme 1 (steps shown in parentheses), except (x) allylamine (10 equiv), DMSO, 18 h, 50 °C; (xi) TFA, H_2O (19:1), 1 h, rt.

pounds **12a** and **12b** from the 4-F,3-NO_2-benzoic acid coupled resins, respectively.

Using a combination of the chemistries shown in Schemes 1 and 2, two compounds were made using the traceless route, with either a cyclopropyl or phenyl group attached to the C2 position, such that they would correspond either to **11a/b** or **12a/b** depending on which nitrogen on resin **7a** had been alkylated, as shown in Scheme 3.

The crude compounds **11a/b**, **12a/b**, and those from the traceless route were each purified and compared by HPLC and ^{1}H NMR. The spectral evidence showed that compounds **11a** and **11b** were identical to the corresponding compounds obtained from the traceless route. Each was clearly different from **12a** and **12b**, respectively, confirming that alkylation occurred only at the N3 nitrogen of resin **7a** to form **8a** and, on cleavage, gave the same products as **11a** and **11b** (see Supporting Information for spectral information). We postulate that the same N3-substitution also occurred in compounds **9a**−**q** and **10a**−**h**.

It is interesting to note that in contrast to previously reported linkers of this type, the alkylation event that drives the Hofmann elimination, and hence leads to cleavage of the product from the resin, occurs at a nitrogen three atoms away from the point of attachment to the linker.

In conclusion, a traceless route has been developed for the synthesis of diverse benzimidazole compounds. The use of this strategy for the traceless synthesis of other heterocyclic compounds will be reported in due course.

Acknowledgment. We thank Dr. Stephen Raillard of Chemical Development Department at Affymax for synthesizing the 3-fluoro-4-nitrobenzoic acid monomer. We also thank Drs. Ted Baer, Randy Scheuerman, and Mike Needels for critically reading the manuscript.

Supporting Information Available: Experimental procedures for the synthesis of resin-bound intermediates **2**, **6b**, **7**, and **8**. ^{1}H NMR and HPLC spectra for comparison of compounds **11a/b** and **12a/b** from both routes. Spectral data (^{1}H NMR, LC-MS, and HPLC) for compounds **9a**−**q**, **10f**, and **10g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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