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Traceless Synthesis of Benzimidazoles on Solid Support†

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Abstract—Traceless solid-phase syntheses of benzimidazoles and 5-(benzimidazol-2-yl)benzimidazoles on 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene are described. No auxiliary functional groups are left in the products after ultimate cleavage and cyclization. © 1999 Elsevier Science Ltd. All rights reserved.

Solid-phase synthesis of small organic molecules has merged with medicinal chemistry in the last few years as a powerful method for time- and labor-efficient generation of both lead discovery and lead optimization libraries. Development of methodology for the synthesis of pharmacologically relevant scaffolds has become one of the practical goals of combinatorial chemistry. Many of the published works rely upon direct application of known solution phase chemistry utilizing Wang and Rink resins. As a result, extraneous functional groups left in the products after cleavage alter physico-chemical and biological properties and also limit investigation of structure–activity relationships. Therefore, one of the important challenges in solid-phase combinatorial synthesis remains the development of so-called traceless synthetic methodologies where structures of compounds have no vestige of their solid-phase origin. Herein, we describe the traceless synthetic methodology employing 4-formyl-3-methoxyphenoxy linker. To our knowledge, the traceless synthesis of aromatic heterocycles on an aldehyde functionalized resin has not been published before. The acid sensitive 4-formyl-3-methoxyphenoxy linker and its derivatives have been applied for solid-phase preparation of *N*-substituted amides, ureas, sulfonamides, carbamates,[1] and lactams.[2–4]

The benzimidazole ring represents an important pharmacophore in drug discovery.[5–8] Reported solid-phase routes to benzimidazoles are based mostly on Wang resin[9–11] or Rink resin.[12–14] Application of these supports results in ultimate isolation of carboxy- or carbamoyl-benzimidazoles. Using a 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin, we have developed a traceless synthesis of benzimidazoles **6** and **12** from both primary amines and carboxylic acids (Schemes 1 and 2). Traceless synthesis of benzimidazoles on carbonate resin has been published recently.[15]

Synthesis of 1,2-disubstituted benzimidazoles is outlined on Scheme 1. Commercially available primary amines were tethered to 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene using reductive amination. Complete conversion of alkyl amine functionalized resin into *o*-nitroaniline bound support was achieved after treatment with *o*-fluoronitrobenzene at 50 °C.

This reaction required the use of *N*,*N*-diisopropylethylamine both as a base and as an appropriate solvent. The aryl nitro group was then reduced by a 1 M solution of tin (II) chloride dihydrate in *N*-methylpyrrolidin-2-one (NMP) in the presence of *N*-methylmorpholine (NMM). NMP was used instead of the commonly used DMF to avoid formation of (*N*-formyl)phenylenediamine which was detected as a side product. (*N*-formyl)phenylenediamine cyclized partially into 1-substituted benzimidazole after cleavage. Formylation of amino group during reduction in DMF has been reported recently.[14] The ability of tin chloride to partially cleave aniline derivatives from acid sensitive resins was neutralized by addition of NMM. Acylation was carried out by using symmetric anhydrides which were generated in situ from *N*,*N*′-diisopropylcarbodiimide (DIC) and corresponding carboxylic acids. Release of *o*-(*N*-acyl)phenylenediamine **5** with trifluoroacetic acid (TFA) did not occur with concomitant ring closure except of the acetyl intermediate.

Exposure of compound **5** in TFA even at elevated temperature overnight was insufficient to complete conversion, however, heating of the cleaved product in

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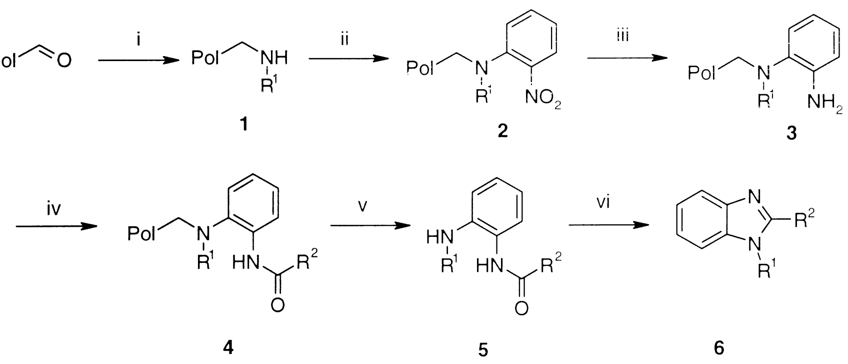
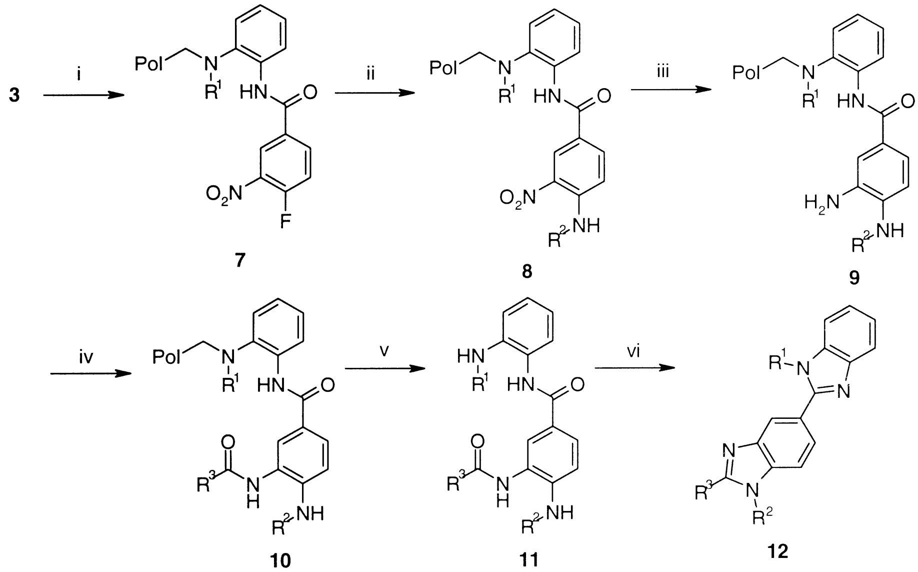


Scheme 1. (i) R^1NH_2, $HC(OEt)_3$, $NaCNBH_3$; (ii) 2-F-$C_6H_4NO_2$, *i*-Pr_2NEt; (iii) $SnCl_2{\cdot}2H_2O$, NMM; (iv) R^2CO_2H, DIC; (v) $CF_3CO_2H/CH_2Cl_2/Et_3SiH$ (10/30/1); (vi) 4 N HCl/dioxane-MeOH (2/1), 50 °C.



Scheme 2. (i) 4-F-3-NO_2-$C_6H_3CO_2H$, DIC; (ii) R^2NH_2; (iii) $SnCl_2{\cdot}2H_2O$, NMM; (iv) R^3CO_2H, DIC; (v) $CF_3CO_2H/CH_2Cl_2/Et_3SiH$ (10/30/1); (vi) 4 N HCl/dioxane-MeOH (2/1), 50 °C.

mixture HCl/MeOH/dioxane at 50 °C for 3 h was found to be an optimal condition for formation of various benzimidazoles.

To expand the diversity of the benzimidazole library, we have developed a synthesis of 5-(benzimidazol-2-yl)benzimidazole scaffold **12** with three points of diversity (Scheme 2).

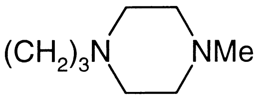
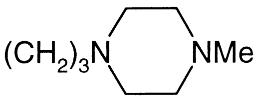
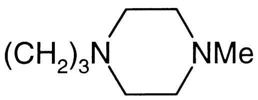
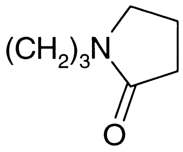
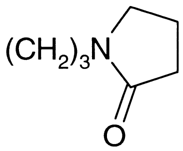
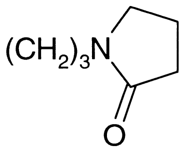
Resin bound *o*-phenylenediamine **3** was acylated by symmetrical anhydride obtained from 4-fluoro-3-nitrobenzoic acid. Nucleophilic aromatic substitution of the fluorine group with primary amines was carried out in DMF at room temperature. Following reduction of the nitro group, selective acylation of primary aromatic amino moiety in compound **9**, and cleavage were accomplished in the same reaction conditions as those in Scheme 1. Finally, acydolitic tandem cyclization of compound **11** yielded product **12**. Structures, yield and purity data obtained for a representative set of benzimidazoles **6**, **12** are summarized in Table 1. Compounds were characterized by ^1H NMR and LC/MS.[16]

In summary, we have demonstrated an application of developed traceless synthetic methodology for the preparation of pharmacologically relevant scaffold benzimidazoles. This method allows for the introduction of chemical diversity in combinatorial libraries of benzimidazoles through the utilization of commercially available building blocks, namely amines and carboxylic acids. Versatility of the methodology for syntheses of other heterocyclic libraries will be reported in due course.

General procedure for the synthesis of 1,2-disubstituted benzimidazoles 6. N_2 was bubbled into a mixture of 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene[‡] (50 mg), was mixed with $HC(OEt)_3$ (1 mL) and 1 M primary amine (1 mL) in 1,2-dichloroethane for 2 h. Solution was removed by suction, and the resin was treated with 1 M $NaCNBH_3$/THF (1 mL) and 1%

[‡] The resin with loading capacity 0.5 mmol/g was purchased from Calbiochem-Novabiochem Corp.

Table 1.

Entry	R^1	R^2	R^3	Yield, %[a]	Purity, %[b]
6a	CH_2Ph	3,4-$F_2C_6H_3$		96	95
6b	CH_2Ph	CH_2Ph		95	95
6c	CH_2Ph	Me		98	95
6d		CH_2Ph		77	92
6e		Cyclohexyl		89	93
6f		3-ClC_6H_4		86	89
6g		CH_2Ph		85	88
6h		3-pyridyl		97	79
6i		Me		98	95
12a	CH_2Ph	CH_2Ph	CH_2Ph	95	95
12b	CH_2Ph	$CHMMe_2$	Me	93	95
12c	CH_2Ph	CH_2-2,5-$F_2C_6H_3$	3-ClC_6H_4	94	92
12d	CH_2Ph	$(CH_2)_2SCH_2Ph$	3-ClC_6H_4	88	90

[a] Yields based on the original loading of the resin.

[b] Purity of the compounds are based on the integration area on HPLC (215 and 254 nm).

AcOH/DMF (1 mL) overnight under N_2. After washing of the resin, the procedure was repeated. The resin was washed five times with DMF, MeOH, CH_2Cl_2 after each reaction step. 1 M *o*-$FC_6H_4NO_2$/*i*-Pr_2NEt (2 mL) was added to the dry resin. The slurry was heated at 50 °C overnight. The support bound nitroaniline (**2**) was reduced with 1 M $SnCl_22H_2O$ and 1 M *N*-methylmorpholine in *N*-methylpyrrolidin-2-one (2 mL) overnight at rt, 2 mL of 0.25 M carboxylic anhydride (prepared in situ from an carboxylic acid and DIC in DMF) was added to the resin bound *o*-phenylenediamine (**3**). N_2 was bubbled into the slurry overnight, and then *N*-acyl-*o*-phenylenediamine (**5**) was cleaved from the resin by treatment with 2 mL of $CF_3CO_2H/CH_2Cl_2/Et_3SiH$ (10/30/1) for 1 h. The solution was collected, and the resin was washed with MeCN (2 mL). The combined filtrates were collected and concentrated in vacuum. The residue was dissolved in 1 mL of 4 N HCl/dioxane–MeOH (2/1). The solution was kept at 50 °C for 3 h and concentrated in vacuum to give benzimidazole **6**.

General procedure for the synthesis of 5-(benzimidazol-2-yl)benzimidazoles 12. 4-Fluoro-3-nitrobenzoic anhydride (0.25 M) (2 mL, prepared in situ from acid and DIC in DMF) was added to resin bound *o*-phenylenediamine **3** (50 mg). N_2 was bubbled into the slurry overnight. The resin was washed five times with DMF, MeOH, CH_2Cl_2 after each reaction step. After addition of 1 M amine/DMF (2 mL), N_2 was bubbled into the mixture. Nitroaniline **8** was reduced with 1 M $SnCl_2{\cdot}2H_2O$ and 1 M *N*-methylmorpholine in *N*-methylpyrrolidin-2-one (2 mL) overnight at rt, 0.25 M carboxylic anhydride (2 mL, prepared in situ from an carboxylic acid and DIC in DMF) was added to the resin bound *o*-phenylenediamine **9**. N_2 was bubbled into the slurry overnight. *N*-Acyl-*o*-phenylenediamine **11** was obtained from resin **10** by treatment with 2 mL of $CF_3CO_2H/CH_2Cl_2/Et_3SiH$ (10/30/1) for 1 h. The solution was collected, and the resin was washed with MeCN (2 mL). The combined filtrates were collected and concentrated in vacuum. The residue was dissolved in 1 mL of 4 N HCl/dioxane-MeOH (2/1). The solution was kept at 50 °C for 3 h and concentrated in vacuum to give benzimidazole **12**.

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16. For example, analytical data for compound **6g**: ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 8.01 (1H, d, $J=7.0$ Hz), 7.91 (1H, d, $J=8.0$ Hz), 7.60 (2H, m), 7.42 (5H, m), 4.69 (2H, s), 4.44 (2H, t, $J=7.5$ Hz), 3.38 (2H, m), 3.18 (2H, m), 2.17 (2H, t, $J=7.5$ Hz), 1.82 (4H, m); *m/z* 334.4 $(M+H^+)$. For compound **6h**: ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 9.10 (1H, s), 8.97 (1H, d, $J=5.0$ Hz), 8.41 (1H, d, $J=8.0$), 8.13 (1H, d, $J=7.5$ Hz), 7.92 (1H, d, $J=8.0$), 7.84 (1H, m), 7.65 (2H, m), 3.19 (2H, m), 3.15 (2H, m), 2.04 (4H, m), 1.76 (2H, m); *m/z* 321.3 $(M+H^+)$.