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A solid phase traceless synthesis of 2-arylaminobenzimidazoles

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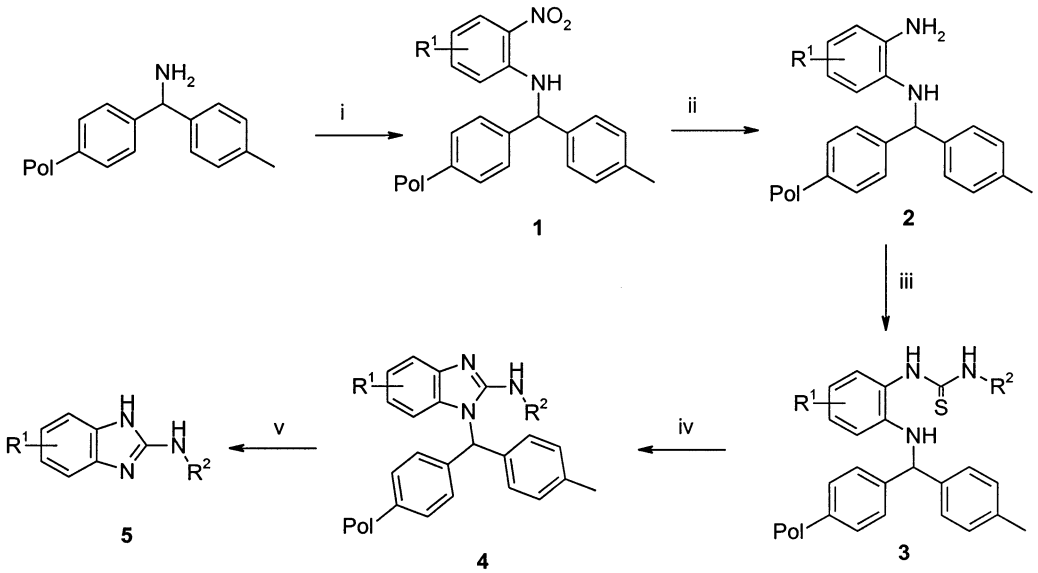
Abstract—A solid phase traceless synthesis of 2-arylaminobenzimidazoles in three combinatorial steps is reported that is based on acid lability of *N*-benzylanilines. MBHA resin was reacted with *o*-nitrobenzenes, the nitro group was reduced by tin(II) chloride, the resin-bound *o*-phenylene diamine was treated with isothiocyanates, and the resulting thiourea cyclized by carbodiimide. 2-Arylaminobenzimidazoles were further derivatized with alkyl halides. Target compounds were cleaved from the solid support by TFA or gaseous HF.

In continuation of our efforts to exploit synthetic routes for solid phase traceless synthesis (SPTS) of heterocyclic compounds, we have developed a straightforward method for the preparation of 2-arylaminobenzimidazoles in combinatorial fashion. The concept takes advantage of the acid lability of an electron-rich resin-bound benzyl group attached to an aryl amino group, and we have successfully applied this approach to the synthesis of benzimidazoles,[1] quinoxalinones,[2] and tetrahydroquinoxalines.[3] We have already described the solid phase synthesis of 2-arylaminobenzimidazoles; however, the target compounds were biased by the presence of a carboxamide moiety.[4] The synthesis in solution was reported numerous times.[5]

The synthesis was developed on *p*-methylbenzhydrylamine (MBHA) resin according to Scheme 1. Aromatic nucleophilic substitution of fluorine in *o*-fluoronitrobenzenes by the resin-bound amino group of MBHA resin provided *o*-nitroaniline **1**. The nitro group was



Scheme 1. Traceless synthesis of 2-arylaminobenzimidazoles. *Reagents*: (i) 1 M *o*-fluoronitrobenzene in NMP, 75°C, overnight; (ii) 2 M $SnCl_2$ dihydrate in NMP, rt, 2 h; (iii) 1 M isothiocyanate in NMP, rt, overnight; (iv) 1 M DIC in NMP, rt, overnight; (v) HF, rt, 2 h or TFA, overnight.

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reduced by tin(II) chloride dihydrate in *N*-methylpyrrolidone (NMP) to yield **2** and then reacted with isothiocyanates to form polymer supported thioureas **3**. Cyclization to 2-arylaminobenzimidazoles **4** was accomplished by diisopropylcarbodiimide (DIC). The target compounds **5** were cleaved from the resin by overnight exposure to TFA or by gaseous HF.[6] We have also applied the same synthetic scheme to SynPhase Lanterns (Mimotopes, Clayton, Victoria, Australia, www.mimotopes.com) with similar results. SynPhase Lanterns are modular grafted solid phase support with loading 15 or 35 μmol/Lantern. For the synthesis the aminomethyl-derivatized Lanterns were acylated with the Fmoc-4-methoxy-4′-(γ-carboxypropyloxy)benzhydrylamine (Bachem Bioscience, King of Prussia, PA).

We have synthesized numerous target 2-arylaminobenzimidazoles in manually operated Domino Blocks.[7] Structures of representative examples are shown in Fig. 1. The purity of the products, evaluated by analytical HPLC,[8] was consistently high and ranged from 84 to 95%; the isolated yield was 40–50%. Products were characterized by LC/MS data (Table 1) and NMR.[9]

The resin-bound 2-arylaminobenzimidazoles **4** were further derivatized by alkylation with an electrophile. The alkylation occurred on either the ring nitrogen or on the nitrogen in position 2 (Scheme 2) and was influenced by the type of base. We prepared the resin-bound 2-arylaminobenzimidazoles **4a** and **4b** from 2,4-difluoronitrobenzene and 2,5-difluoronitrobenzene, respectively. Following the alkylation with 4-methylbenzyl bromide using K_2CO_3 as a base and cleavage from the resin,[10] the HPLC retention times of the products **6a** and **6b** were very close but non-identical (two peaks on co-injection). We therefore concluded that alkylation occurred on the ring nitrogen, since alkylation of the exocyclic nitrogen would have given identical products (**7a**=**7b**). When phosphazene base P1-t-Bu-tris(tetramethylene) was used at low concentration (10 uL of the P1 base in 1 mL of 0.5 M alkyl bromide per 50 mg of resin), products **7a**=**7b** were predominantly obtained (less than 10% of products **6a** and **6b**, respectively). At higher concentration of the P1 base (100 uL per 1 mL of the alkylating solution), both alkylated products were obtained and three components were separated on HPLC of co-injected samples (Fig. 2). A convenient diagnostic signal in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) was the singlet of methylene protons of the benzyl group (δ: 5.078, 5.060, and 4.967 for compounds **6a**, **6b**, and **7a**=**7b**, respectively).

As independent chemical evidence of the structure, we synthesized compounds **6a** and **6b** using an alternative route. The route was based on a modification of our previously described traceless synthesis of benzimidazoles[1] using 4-methylbenzylamine (R^1=4-MeBn) and 4-chlorophenyl isothiocyanate (R^2=4-ClPh) as building blocks (Scheme 3). The resin-bound dianiline was reacted with isothiocyanate to form the thiourea **8**, which was cleaved by TFA and cyclized in solution by DIC[11] to yield 2-arylaminobenzimidazoles

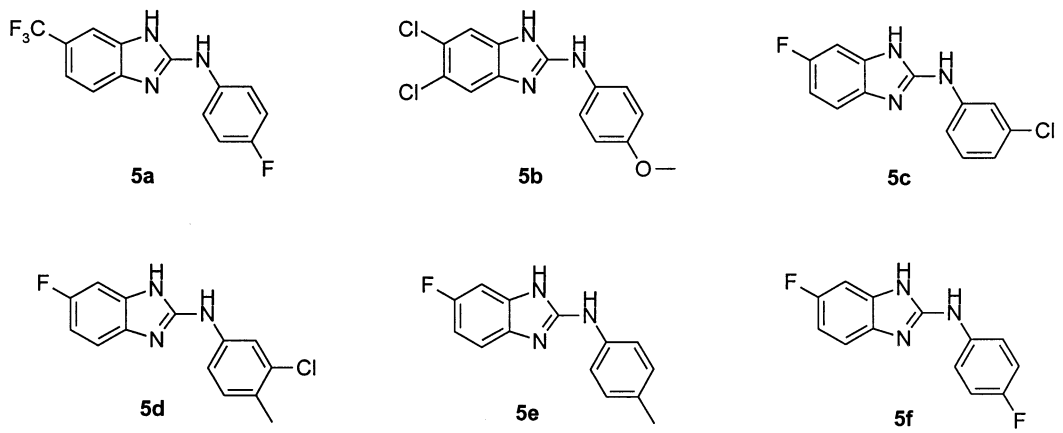
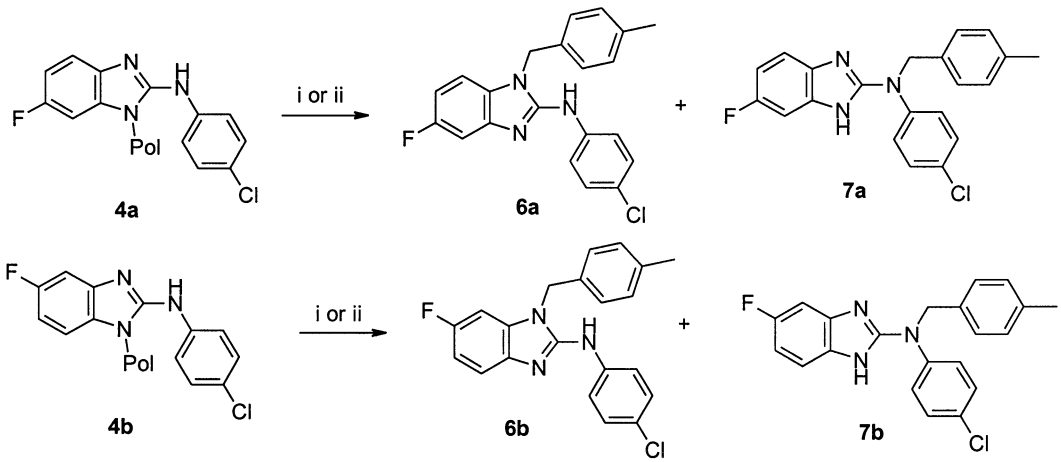


Figure 1. Structure of representative 2-arylaminobenzimidazoles.

Table 1. Analytical data of 2-arylaminobenzimidazoles

Compound	Rt (min)	Purity TFA[a] (%)	Purity HF[a] (%)	M_w	$[M+H]^+$
5a	4.4	89	91	295.1	296.1
5b	4.6	79	87	307.1	308.1
5c	4.2	81	98	261.1	262.1
5d	4.4	81	84	Nt[b]	Nt
5e	4.3	92	95	241.1	242.1
5f	4.4	87	93	261.1	262.1

[a] Indicates method of cleavage.
[b] Nt stands for not tested.



Scheme 2. Alkylation of 2-arylaminobenzimidazoles. *Reagents*: (i) 1 M alkyl halide, K_2CO_3, in DMF, 75°C, overnight; (ii) 0.5 M alkyl halide, 1% phosphazene base P1-*t*-Bu-tris(tetramethylene), DMF, rt, overnight.

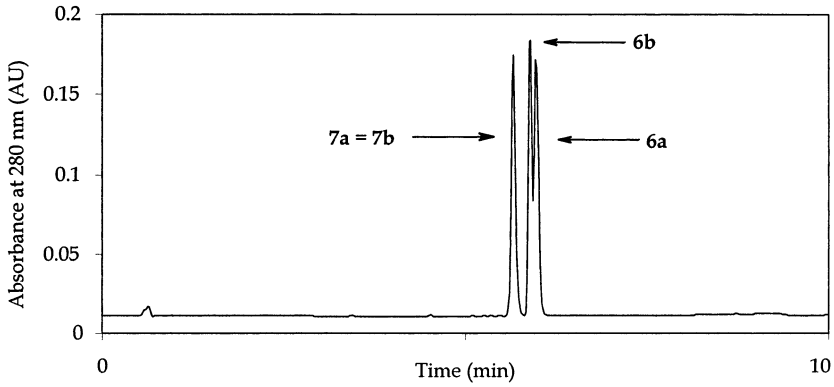
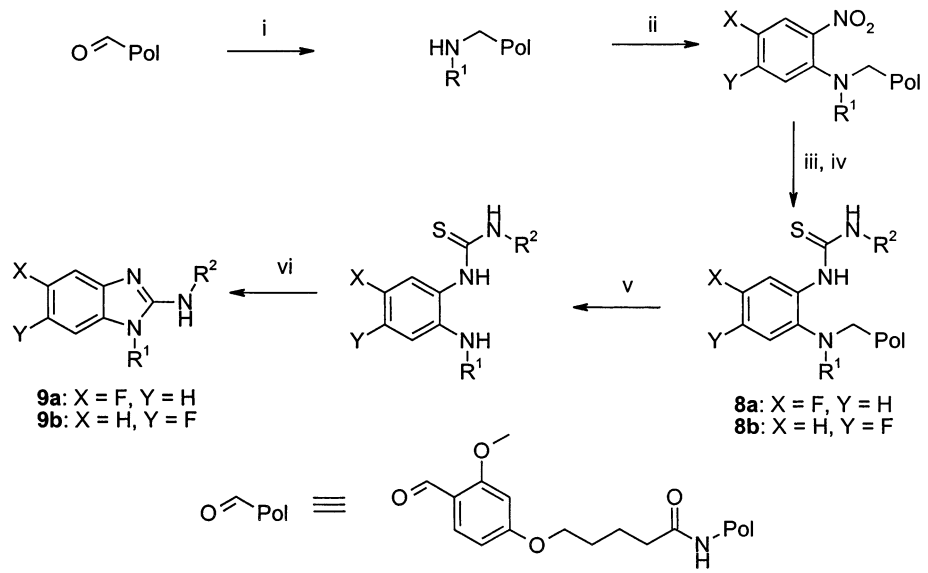


Figure 2. Analytical gradient profile of co-injected alkylated products **6** and **7**.



Scheme 3. Alternative synthesis of *N*-alkylated 2-arylaminobenzimidazoles. *Reagents*: (i) 4-Methylbenzylamine/$NaBH(AcO)_3$ in DMF/AcOH; (ii) 2,5-difluoronitrobenzene (series **a**) and 2,4-difluoronitrobenzene (series **b**), DMSO, 75°C, overnight; (iii) $SnCl_2 \times 2H_2O$ in NMP, rt, overnight; (iv) 4-chlorophenyl isothiocyanate in DMF, rt, overnight; (v) TFA, rt, 2 h; (vi) DIC, ethyl acetate, rt, overnight.

9. The corresponding products from both syntheses were found to be identical on HPLC co-injection and LC/MS (**9a**=**6a** and **9b**=**6b**).

In summary, we have developed a straightforward synthetic route for solid phase traceless synthesis of 2-arylaminobenzimidazoles with three combinatorial steps. The traceless character is achieved through the acid lability of *N*-arylbenzylamines and utilizes standard commercially available derivatized resins.

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7. Domino Block (Torviq, Tucson, AZ, www.torviq.com) is a simple manual solid phase synthesizer that allows parallel synthesis of up to 48 compounds using plastic syringes equipped with a frit as reaction vessels. Krchňák, V.; Padera, V. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3261–3264.
8. Analytical gradient HPLC profile was run on a ProC18 4.6×50 mm analytical column (YMC, Wilmington, NC), gradient 0–70% of ACN in 7 min. The purity was estimated based on analytical traces at 280 nm.
9. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of compound **5a** δ: 7.27 (t, 2 H), 7.44 (d, 1H), 7.49 (d, 1H), 7.61 (s, 1H), 7.67 (q, 2H); compound **5c** δ: 7.11 (t, 1H), 7.26 (m, 1H), 7.34 (d, 1H), 7.4 (m, 2H), 7.50 (m, 1H), 7.63 (s, 1H); compound **5d** δ: 2.33 (s, 3H), 7.06 (t, 1H), 7.23 (d, 1H), 7.34 (d, 2H), 7.38 (q, 1H), 7.43 (d, 1H), 7.66 (s, 1H). All compounds were measured as TFA or HF salts.
10. Cleavage of alkylated 2-arylaminobenzimidazoles from the resin was carried out in TFA. Exposure to gaseous HF partially cleaved the benzyl group having electron-donating substituents.
11. A 10 mg sample of the resin was cleaved by TFA, TFA was evaporated by a stream of nitrogen, and the product was extracted into ethyl acetate. The ethyl acetate was extracted three times with 5% K_2CO_3 in water, DIC was added, and the reaction mixture was kept at rt overnight.