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Solid Phase Synthesis of Benzimidazoles

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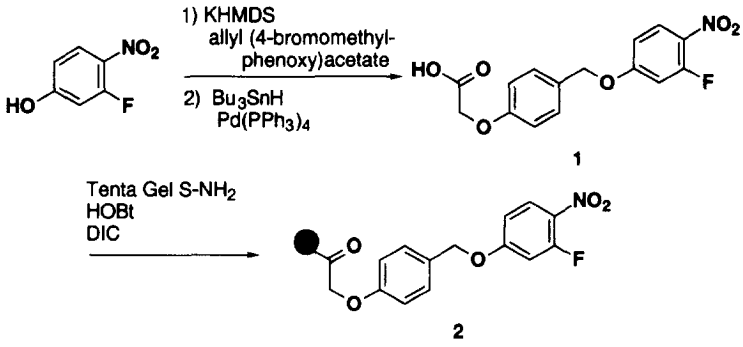
Abstract: An efficient solid phase synthesis of benzimidazoles is described. Polymer bound o-fluoronitroaromatic compound **2** was treated with an amine to give o-nitroaniline derivative **3**. Reduction of **3** with $NaBH_4$-$Cu(acac)_2$ followed by cyclization with an aryl imidate and cleavage with TFA gave **5**. A library of benzimidazoles has been prepared in three steps in 70-95 % crude yield and 70-98 % purity. Final purified yield ranged from 54-93 %. Extension of this synthesis to the split/pool method is also reported. Copyright © 1996 Elsevier Science Ltd

The preparation of small organic molecules on solid phase is emerging as an expedient method and is being utilized for generating compounds for screening against biological systems and enhance the drug discovery effort.[1] In addition, the preparation of compounds combinatorialy to prepare libraries is important for the large numbers of compounds required of effective high capacity screening. Methodologies that are useful in solid phase synthesis and library preparation have been reported.[2] Herein, we report the efficient solid phase synthesis of a library of benzimidazoles from a versatile intermediate.

The planned method of preparing the benzimidazoles was to introduce one of the nitrogens by nucleophilic addition of a primary amine to an o-fluoronitrobenzene. Following reduction of the nitro group, the diamine would be cyclized with an acid equivalent to give the benzimidazole. There are many standard preparations of benzimidazoles.[3] Unfortunately, many require high temperatures and acidic conditions for the ring closure. Because of questions about the stability of the solid support, we perceived high temperatures and in general, forcing conditions as a potential problem. To circumvent the high temperatures, the cyclization of a diamine with an imidate was utilized.[4] The two steps that would be used to introduce diversity into the library are the primary amine addition and the cyclization with an acid equivalent, both of which have many commercially available or easily accessible precursors.

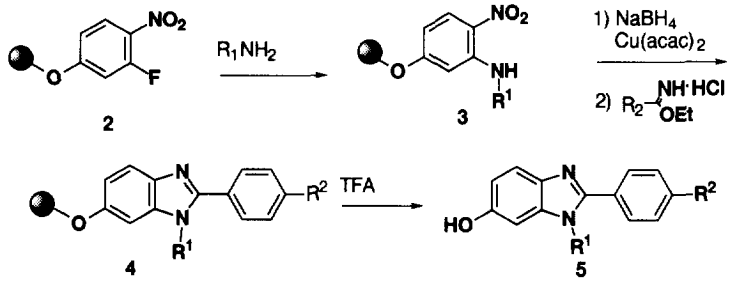
For this study the o-fluoronitrobenzene was linked to a TentaGel S-NH_2 resin through a linker strategy reported previously (Scheme 1).[5] Reaction of 3-fluoro-4-nitrophenol with allyl (4-bromomethylphenoxy)acetate under standard conditions gave the ether. This intermediate may also be obtained through the coupling reaction of the phenol with allyl (4-hydroxymethylbenzyloxy)acetate under standard Mitsonobu conditions in good yield.[2a, 6] Deesterification with Bu_3SnH and $Pd(PPh_3)_4$ in CH_2Cl_2 and coupling with TentaGel S-NH_2 in DMF with HOBT and DIC gave **2**. The substitution loading level was determined to be >90 % by treatment of **2** with TFA and purification.

The benzimidazole synthesis is illustrated in Scheme 2.[7] Reaction of **2** with amines proceeded at ambient temperature to give nitroanilines **3** in high purity and yield (>95 %).[8] Reduction with Tin(II) in this case gave inconsistent results, but reduction with $NaBH_4$-$Cu(acac)_2$ gave the diamine.[9] Treatment with the ethyl



Scheme 1

benzimidate hydrochloride in n-BuOH and DMF at 90 °C for 24 h gave the benzimidazole **4,** which was cleaved from the support with 95:5 TFA/H_2O to afford the benzimidazoles, **5.** The final choice of using the imidate for the cyclization was important. Normal conditions for cyclization are high temperatures and/or acidic media. By employing more mild conditions, we were able to obtain crude yields of 70-95 %. This purity of the crude material was typically between 70-98 % the desired compound as determined by HPLC. The final purified yields of the various benzimidazoles are reported(Table 1). Utilizing the same reaction conditions in solution phase and a unsubstituted benzyl group for protection of the phenol, **5a** was obtained in 40 % purified yield after hydrogenation to remove the benzyl group.



Scheme 2

The solid phase synthesis described was extended to split/pool combinatorial synthesis. Compound **2** was split into five pools, as before and reacted with five different primary amines, (*n*-butylamine, *i*-butylamine, *i*-propylamine, cyclohexylamine and benzylamine). The corresponding five pools were combined, reduced, cyclized with ethyl 4-hydroxybenzimidate hydrochloride, and cleaved with TFA to give the five benzimidazoles. Theses five products were analyzed by LC/MS and determined to be a mixture of the five expected products prepared individually. Each compound prepared individually had the same retention time as a component of the mixture by RPHPLC[10] (Figure 1) and each component of the mixture had a consistent molecular ion.

Table 1: Benzimidazole synthesis products

Compound	R^1	R^2	Yield[a] (%)
5a	n-Bu	H	70
5b	n-Bu	Me	62
5c	n-Bu	Cl	63
5d	i-Bu	H	82
5e	i-Bu	Cl	54
5f	i-Pr	H	68
5g	i-Pr	OH	68
5h	Bn	H	62
5i	Bn	Me	57
5j	C_6H_{11}	H	93
5k	C_6H_{11}	Me	84

[a]Isolated yield by column chromatography[7]

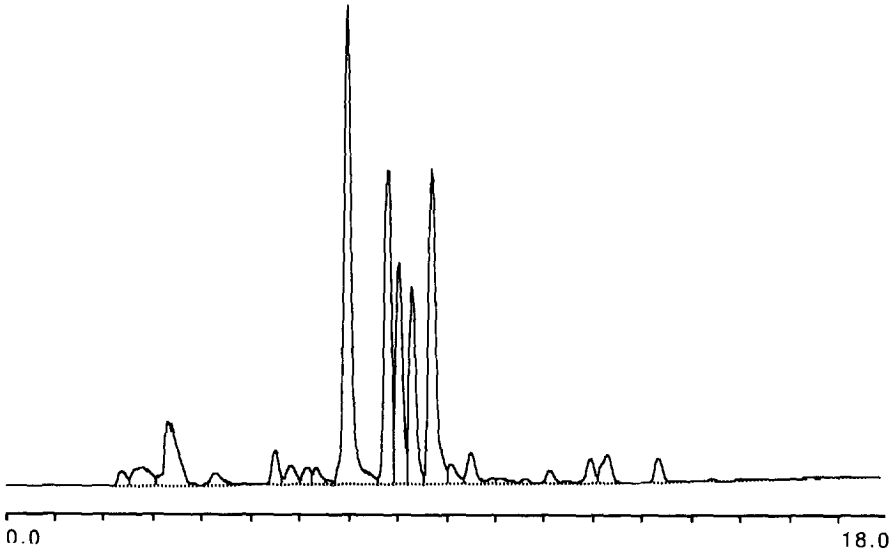


Figure 1: RPHPLC of mixed pool

The efficient preparation of benzimidazoles on solid support in high yield and purity has been illustrated. In the future, we plan to further illustrate the versatility of this chemistry and the intermediates **2** and **3** in the preparation of other heterocycles and libraries.

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7. Compound **2** (400 mg, 0.09 mmol) was mixed with DMSO (2 mL) and vortexed for 1h at r.t. To the slurry was added the amine (20 mmol) in DMSO (2 mL). After vortexing for 24 h at r.t., the solvent was removed by suction and the resin was washed with DMSO (5X10 mL), EtOH (5X10 mL), and CH_2Cl_2 (5X10 mL). To **3** was added DMF (3 mL), the preformed mixture of $Cu(acac)_2$ (60 mg, 0.23 mmol) and $NaBH_4$ (40 mg, 1.1 mmol) in EtOH (4 mL), and $NaBH_4$ (90 mg, 2.4 mmol) in EtOH (3 mL). The reaction mixture was vortexed for 24 h. The solvent was removed by suction and the resin was washed with 50% aqueous EtOH (3X10 mL), DMF (3X10 mL), and EtOH (3X10 mL). The reduction reaction was repeated. To the resin was added n-BuOH (6 mL) and DMF (5 mL) and an ethyl benzimdate hydrochloride (30 equiv.). The reaction mixture was shaken at 55 to 90 °C for 24 to 40 h. The solvent was removed by suction and the resin washed with 50% aqueous EtOH (5X10 mL), DMF (5X10 mL). EtOH (5X10 mL), and CH_2Cl_2 (5X10 mL). The support bound benzimidazole **4** was treated with TFA/H_2O (95:5, 8 mL) for 3-12h.[5] The solvent was collected and the resin was washed with $MeOH/CH_2Cl_2$ (3X10 mL). The combined organic solvents were collected, evaporated, diluted with toluene and ethyl acetate, and evaporated to dryness. Twenty-five compounds were prepared and the crude yield was typically >70 % and > 70 % pure. The material could be purified by column chromatography with ethyl acetate/hexane (1/4) and ethyl acetate to give benzimidazole **5**. Only the purified compounds are reported (Table 1). All purified compounds gave consistent ^1H NMR, ^{13}C NMR, and mass spectral data. The data for compound **5a** is as follows: 17.3 mg as a yellow solid, m. p. 201-203°C; IR (KBr) 3436, 2934, 1624, 1489, 1474, 1370, 1235 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) d 9.33 (s, 1H), 7.71 (m, 2H), 7.55 (m, 3H), 7.46 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.73(dd, J = 8.8, 1.5 Hz, 1H), 4.16 (t, J = 7.0 Hz, 2H), 1.61(p, J = 7.0 Hz, 2H), 1.11 (m, 2H), 0.75(t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) d 153.8, 151.8, 136.4, 136.1, 130.8, 129.3, 128.9, 128.6, 119.5, 111.7, 95.8, 43.6, 30.9, 19.2, 13.3; HRMS(FAB) calcd for $C_{17}H_{19}N_2O$ (MH^+) 267.1497, found 267.1499.
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10. RPHPLC were run on a Dynamax-60A C18 column with a 20-80 % acetonitrile in water gradient.

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