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Solid Phase Synthesis of Benzimidazolones

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Abstract: An efficient solid phase synthesis of benzimidazol-2-one-5 carboxylic acid is described. Polymer bound o-fluoronitroaromatic compound **2** was treated with an amine to give o-nitroaniline derivative **3**. Reduction of **3** with $SnCl_2$ followed by cyclization with DSC gave the benzimidazolone **5**. Reaction with NaH and an alkyl bromide followed by cleavage with TFA gave **7**. A library of 13 benzimidazolones has been prepared in three steps in 90-100 % crude yield and 91-95 % purity.

The preparation of organic molecules on solid phase has become a standard tool of the drug discovery process due to the speed and versatility at generating large numbers of compounds and methodologies that are useful in solid phase synthesis and library preparation have been reported.[1] To increase the diversity present in each library, we have been involved in the preparation of different heterocyclic systems from single solid bound intermediates. Herein, we report the efficient solid phase synthesis of a library of benzimidazolones from a versatile intermediate to complement our previously reported preparation of benzimidazoles.[2] In addition, to further demonstrate the versatility of the methodology and increase the diversity of compounds that can be prepared, an alternate linking strategy was employed.

We prepared the benzimidazolones under standard conditions[3] with the nitrogens containing the two points of diversity. One was introduced with an amine and the other with an alkyl halide, both of which have many commercially available or easily accessible precursors. The first point of diversity was introduced by nucleophilic addition of a primary amine to an o-fluoronitrobenzene. Following reduction of the nitro group to the diamine, cyclization with an appropriate reagent and alkylation of the free nitrogen with an alkyl halide gave the 1,3 differentially substituted benzimidazolone.

The benzimidazolone synthesis is illustrated in Scheme 1. o-Fluoronitrobenzene **1** was linked to a Wang resin through a linker strategy reported previously (Scheme 1).[4] Reaction of 4-fluoro-3-nitrobenzoic acid with the Wang resin under standard conditions gave the polymer bound ester. Nucleophilic addition of amines with **2** proceeded at ambient temperature to give nitroanilines **3** in high purity and yield.[2,5] In the benzimidazole synthesis, we tried many reagents to effect the reduction of the nitroaromatics to the aniline, but found only $NaBH_4$-$Cu(acac)_2$ to give consistent results.[6] With this system, $NaBH_4$-$Cu(acac)_2$ gave low conversion, but more standard means, using Tin(II) chloride gave the diamine in good yields and purity. Cyclization to the benzimidazolone with standard reagents (eg. Im_2CO, phosgene, triphosgene, etc) gave low conversion and inconsistent results, regardless of the quantity of reagent used. Benzimidazolone formation with

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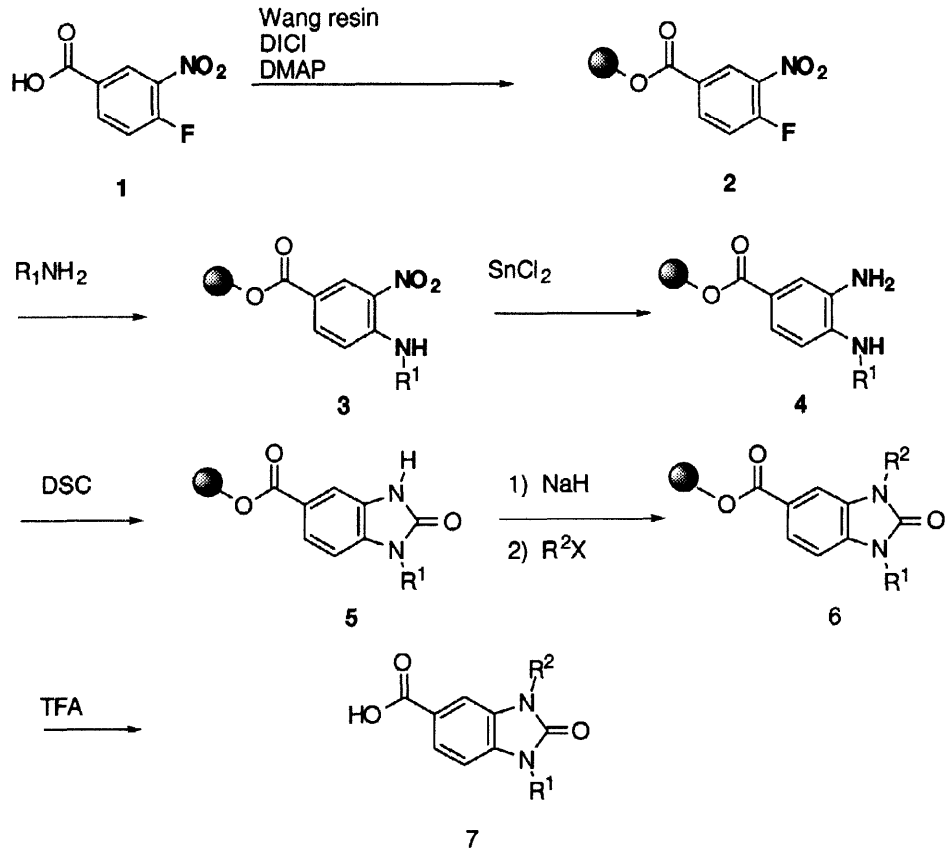
disuccinimidocarbonate (DSC) gave consistently high yields of benzimidazolone (**5**) with high purity.[7] Alkylation proceeded smoothly by deprotonation with sodium hydride followed by quenching with an alkyl halide to give the fully functionalized benzimidazolone **6**. Cleavage from the resin with TFA gave the acid **7**. The final crude yields are reported (Table 1). The purity of crude compounds was typically excellent (>90 % as determined by HPLC and $_1$H NMR).[8]



Scheme 1

Reactions of **5** with primary halides gave a single regioisomer. NOESY NMR experiments indicated that the exclusive product was the alkylated on both nitrogens. The spectrum of **7a** indicated an NOE effect between the methyl singlet at 3.36 ppm with an aromatic singlet at 7.66 ppm and a downfield triplet at 3.85 ppm with an aromatic doublet ar 7.26 ppm. Reaction of **5** with 2-iodopropane gave two compounds in a 9:1 ratio. NMR indicated that the O-alkylated product was the minor isomer.

The efficient preparation of benzimidazoles and benzimidazolones on solid support in high yield and purity has been illustrated. The versatility of the methodology has been extended to tetrahydroquinoxalin-2-ones from a Rink bound intermediate of 4-fluoro-3-nitrobenzoic acid by Lee, et. al.[9] 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.

Table 1: Benzimidazolone synthesis products

Compound	R^1	R^2	Yield[a] (%)
7a	*n*-Bu	Me	100
7b	*i*-Bu	*i*-Bu	98
7c	cyclohexyl	*i*-Bu	96
7d	Bn	*i*-Bu	95
7e	*n*-Bu	*i*-Bu	100
7f	*i*-Bu	Bn	99
7g	cyclohexyl	Bn	92
7h	*i*-Pr	Bn	90
7i	Bn	Bn	90
7j	*n*-Bu	Bn	100
7k	cyclohexyl	allyl	99
7l	*i*-Pr	Ally	96
7m	Bn	*i*-Pr	90[b]

[a] Isolated yield based on resin-bound starting material **2**. [b] Ratio of N-alkylated product to O-alkylated product; 9:1 determined from ^{1}H NMR.

General procedure for the synthesis of benzimidazol-2-one-5-carboxylic acids: Fluoride **2** (200 mg, 0.2 mmol) was mixed with a primary amine (20 mmol) in DMSO (2 mL). After vortexing at ambient temperature for 24 h the resin was filtered and washed with DMSO (5x10 mL) and EtOH (5x10 mL). The resin was mixed with 1.0 M $SnCl_2 \cdot 2H_2O$ in DMF (10 equivalent) and vortexed for 30 h followed by washing with 50% aqueous DMF (5x10 mL), DMF (5x10 mL), EtOH (5x10 ml), and CH_2Cl_2 (3x10 mL). The diamine was treated with 2 eq. DSC in THF-CH_2Cl_2-DMF (8:2:1, 11 mL). After vortexing for 24 h the reaction was washed with DMF (5x10 mL) and THF:CH_2Cl_2 (1:1; 5x10 mL). The washed resin was treated with 20 eq. NaH in DMF (6 mL) and vortexed for 50 min. A solution of alkylating reagent (40 eq.) in 1 mL of DMF was added. After vortexing for 24 h the resin was washed with 50% aqueous DMF (5x10 mL), DMF (5x10 mL), EtOH (5x10 mL), and CH_2Cl_2 (5x10 mL). The support bound benzimidazol-2-one-5-carboxylic acids **6** were cleaved from the resin by treatment with TFA/ CH_2Cl_2 (1:1, 6 mL) and vortexing for 1 h. The solvents were collected and the remaining resin was rinsed with the same solvents (2 mL). The combined solvents were evaporated under reduced pressure and the crude product was dried under vacuum to give the desired products **7**.

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8. All the compounds listed in Table **1** gave satisfactory ^{1}H NMR ^{13}C NMR and MS data. The data for benzimidazol-2-one-5-carboxylic acid is as follows: **7a,** ^{1}H NMR (300 MHz, DMSO-d_6) d, 11.05 (s, 1H), 7.71 (d, J = 8.06 Hz, 1H), 7.66 (s, 1H), 7.26 (d, J = 8.06Hz, 1H), 3.85 (t, J = 6.96 Hz, 2H), 3.36 (s, 3H), 1.59 (p, J = 6.96 Hz, 2H), 1.28 (m, 2H), 0.87 (t, J = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) d, 167.4, 153.9, 132.7, 129.5, 123.3, 123.2, 108.5, 107.2, 40.3, 29.9, 26.9, 19.3, 13.5; LSIMS, m/z for $C_{13}H_{16}N_2O_3$ (MH^+): 249.
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