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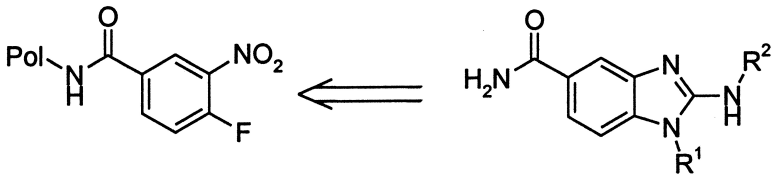

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Necklace-Coded Polymer-Supported Combinatorial Synthesis of 2-Arylaminobenzimidazoles

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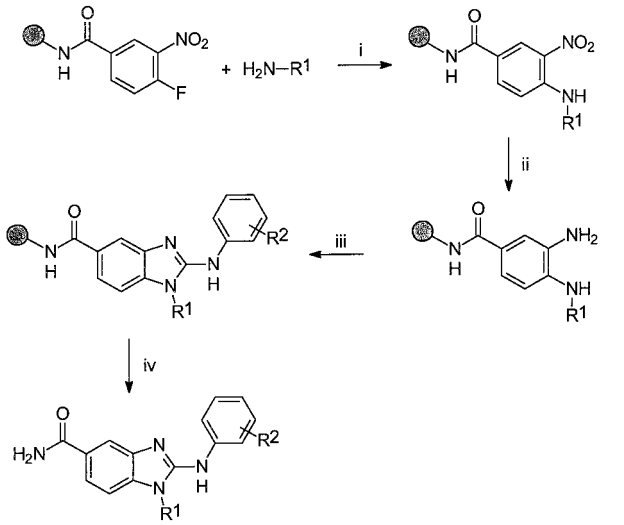
Combinatorial synthesis of benzimidazole and its derivatives has been described several times.[1] Synthetic routes leading to 2-arylaminobenzimidazoles in solution phase are known.[2] However, a solid-phase synthesis of 2-arylaminobenzimidazoles has not been reported yet. In this contribution we wish to describe a straightforward solid-phase synthesis of diverse 2-arylaminobenzimidazoles (Scheme 1) using commercially available building blocks, as well as a novel "low-tech" coding concept for tracking chemical history during split and mix synthesis on SynPhase crowns.

The synthesis was developed on polystyrene−1% divinylbenzene MBHA resin (Chem-Impex, Chicago, IL), and the optimized protocol was later applied to Rink derivatized SynPhase crowns (Chiron Technologies, Clayton Victoria, Australia). A SynPhase crown is a 2 cm long, injection molded, polypropylene piece. Its surface is grafted with polystyrene and then functionalized for solid-phase synthesis (www.chirontechnologies.com). Both *p*-methylbenzhydrylamine (MBHA) and Rink linkers were developed for the synthesis of peptide amides, and both also allow cleaving of compounds using gaseous reagents such as HF and HCl. The beads and crowns can be handled after cleavage, and the compounds are released into solution only when the extracting solvent is applied. We have used gaseous cleavage successfully on different occasions in the past.[3]

The synthesis of 2-arylaminobenzimidazoles begins with acylation of the resin by 4-fluoro-3-nitrobenzoic acid and continues with displacement of the fluorine by primary amines and reduction of the nitro group by tin chloride. The same reaction sequence leading to polymer-supported *o*-phenylenediamines has already been used several times.[1c,1d,4] We occasionally observed incomplete reduction of the nitro group, an issue already reported in the literature[4d] that we are currently trying to address. The resin-bound *o*-phenylenediamine was exposed to isothiocyanates in the presence of carbodiimide. Initially formed thiourea cyclized to the desired 2-arylaminobenzimidazoles. We tested several different reaction conditions for the cyclization step. Reacting overnight in DMF at ambient temperature provided the best results. Resin-bound products were exposed to gaseous HF at ambient temperature for 2 h, and cleaved 2-arylaminobenzimidazoles were extracted into methanol. The purity and identity of final products were assessed by analytical HPLC,[5] NMR,[6] and MS.

Scheme 1. Polymer-Supported Synthesis of 2-Arylaminobenzimidazoles[a]



[a] Reagents and conditions: (i) 1 M amine in DMF, rt, overnight; (ii) 2 M $SnCl_2$ in NMP, rt, overnight; (iii) 1 M isothiocyanate, 1 M DIC in DMF, rt, overnight; (iv) HF (MBHA linker) or HCl (Rink linker), rt, 2 h.

We have synthesized a sizable library (more than 10 000 compounds) of 2-arylaminobenzimidazoles with three combinatorial steps using the "split only" technique.[3c] The additional diversity point was introduced by acylation of the resin with an amino acid, followed by coupling of the 4-fluoro-3-nitrobenzoic acid. The synthesis was performed in polypropylene syringes on Domino Blocks.[7] The Domino Block is a reaction block for manual and semiautomatic parallel solid-phase organic synthesis that simplifies liquid exchange and integrates common synthetic steps. The last combinatorial step was done in 96-well plates.[8] The library was synthesized using 48 primary amines. We used both acyclic and cyclic aliphatic amines, benzyl and phenethyl amines, and aminomethyl and aminoethyl heterocyclic compounds. The carboxyl groups of the amino acids were protected by a tBu group. Amino alcohols were used unprotected, and we have not observed formation of a thiocarbamate. Twenty-four phenylisothiocyanates were used in the last combinatorial step, and they contained both electron-donating and electron-withdrawing substituents in ortho, meta, or para position to the isothiocyanate. The overall yield of target compounds exceeded 80%.

Solid-phase synthesis on SynPhase crowns provides distinct advantages, particularly with respect to handling large numbers of compounds. While crowns were designed for attachment to a holder and individual use in a 96-well plate format, they can be handled in batches for reactions in large vessels. To know the structure of a final compound after the "split and mix" combinatorial synthesis, the solid-phase particle has to carry the information about the chemical history (type of building block reacted with specific particle), or the solid phase support needs to be tracked. This has been achieved by chemical coding in the case of beads, labeling the T-bags, inserting a radio frequency chip into a porous

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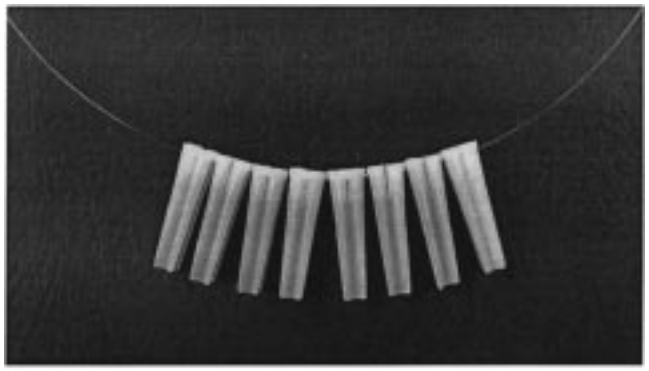

Figure 1. A necklace of eight SynPhase crowns.

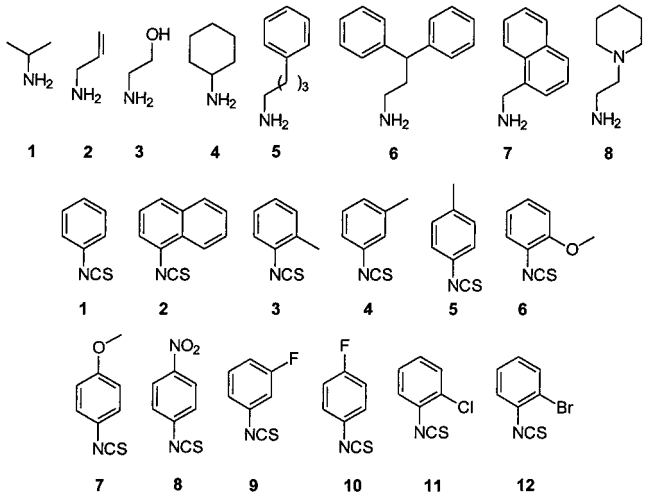

Figure 2. Eight amines and 12 isothiocyanates used to synthesize 96 2-arylaminobenzimidazoles.

container, or color coding.[9] The crowns offer a simple low-tech solution: the information can be conserved by organizing crowns into a sequence, practically achieved by arranging them on a string (Figure 1). Each string of crowns, referred to as a "necklace", is reacted with a different synthon. The position on the string determines the building block reacted with this particular crown. There are as many necklaces as there are building blocks in the second combinatorial step, and there are as many crowns on each necklace as there were building blocks in the first combinatorial step.

The concept of necklace tracking was proven on a synthesis of 96 2-arylaminobenzimidazoles from 8 amines and 12 isothiocyanates.[10] The structures of amines and isothiocyanates used on the first plate are shown in Figure 2. The purity of the products was analyzed by HPLC and ranged from 56 to 99%, average being 83%.[5] The correct molecular weight was confirmed by mass spectrometry (PE-Sciex API III+ with an articulated ion spray sample inlet system). The average yield (gravimetric estimation) was 77%.

The purity of products synthesized on MBHA resin and SynPhase crowns was comparable. However, handling the crowns was much easier than handling the resin, a distinct advantage, appreciable particularly during synthesis of large libraries. The price per compound favors resin synthesis.

In summary, we have described a straightforward solid-phase synthesis of 2-arylaminobenzimidazoles from resin-bound *o*-phenylenediamines and isothiocyanates. The reaction conditions are amenable to synthesis of large combinatorial libraries, and the purity of final product is good to excellent. A novel tracking protocol, referred to as necklace coding, was used to trace chemical history during combinatorial synthesis on SynPhase crowns.

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(5) Analytical gradient HPLC profile was run on a ProC18 4.6 × 50 mm analytical column (YMC, Wilmington, NC), gradient 0−70% of acetonitrile in 7 min. The purity was estimated based on analytical traces at 254 nm.

(6) A sample of dry resin-bound product in a polypropylene syringe with a porous polypropylene disk was exposed to gaseous HF for 2 h. The crude product was extracted by adding DMSO-d_6 to the syringe and filtering the solution into an NMR tube. Compound synthesized using isopropylamine and *p*-methoxyphenylisothiocyanate provided the following ^{1}H NMR spectrum: (500 MHz, DMSO-d_6) δ 1.56 (d, J = 7.0 Hz, 6 H), δ 3.45 (s, 1 H), δ 3.74 (s, 3 H), δ 6.97 (d, J = 8.5 Hz, 2 H), δ 7.17 (s, 1 H), δ 7.53 (d, J = 10.0 Hz, 1 H), δ 7.60 (d, J = 10.0 Hz, 1 H), δ 7.67 (d, J = 9.0 Hz, 2 H), δ 7.85 (s, 1 H), δ 7.89 (s, 1 H). Isopropylamine and *p*-methylphenylisothiocyanate: δ 1.56 (d, J = 7.0 Hz, 6 H), δ 2.27 (s, 3 H), δ 3.48 (s, 1 H), δ 7.14 (d, J = 8.0 Hz, 2 H), δ 7.18 (s, 1 H), δ 7.56 (d, J = 5.0 Hz, 1 H), δ 7.62 (d, J = 5.0 Hz, 1 H), δ 7.64 (d, J = 8.5 Hz, 2 H) δ 7.88 (s, 1 H), δ 7.92 (s, 1 H). Isopropylamine and *p*-chlorophenylisothiocyanate: δ 1.59 (d, J = 7.0 Hz, 6 H), δ 3.44 (s, 1 H), δ 4.97 (m, 1 H), δ 7.22 (s, 1 H), δ 7.65 (d, J = 10.0 Hz, 1 H), δ 7.69 (d, J = 10.0 Hz, 1 H), δ 7.92 (s, 1 H), δ 7.99 (d, J = 10.0 Hz, 2 H), δ 8.07 (s, 1 H), δ 8.25 (d, J = 9.0 Hz, 2 H).

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(10) Eight 20 mL syringes were charged with 12 Rink linker derivatized SynPhase crowns (Chiron Technologies, Clayton Victoria, Australia, loading 33 μmol/crown) each and attached to the Domino Block (Torviq, Tucson, AZ).[7] The Fmoc group was removed with piperidine/DMF, and the amino group was acylated with 4-fluoro-3-nitrobenzoic acid in DMF upon DIC/HOBt activation. Each syringe was then charged with a 1 M solution of amine in DMF to replace the fluorine and produce eight different resin-bound *o*-nitroanilines. The crowns were then placed on a stainless steel string to form a necklace. A knot was tied at one end, the second end was left open. Twelve identical necklaces were made, each containing eight crowns

with different *o*-nitroanilines. Each necklace was placed into a 20 mL syringe, the nitro group was reduced and *o*-phenylenediamines were reacted with 1 M isothiocyanate and 1 M DIC solution in DMF at ambient temperature overnight. The crowns were washed, the necklaces were disassembled, and the crowns were transferred into a 96-well plate so that crowns from one necklace were placed into the same column of a 96-well plate. The plate with 96 crowns was exposed to gaseous HCl for 2 h, and products were extracted by methanol. (The necklaces can also be disassembled after the gaseous cleavage.)

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