Pergamon

Tetrahedron Letters 39 (1998) 6655–6658

TETRAHEDRON LETTERS

Solid-Phase Synthesis of Benzimidazoles

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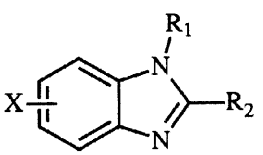
Received 22 May 1998; revised 2 July 1998; accepted 6 July 1998

Abstract. A readily automated solid-phase approach to the synthesis of diverse benzimidazoles is described. The procedure utilizes polymer supported 4-fluoro-3-nitrobenzoic acid and a wide range of commercially available amines and aldehydes. The key heterocyclization step is achieved under mild conditions and was found to be general for a large number of diverse inputs.

Keywords: solid-phase, benzimidazole, combinatorial chemistry

One of the major challenges for combinatorial chemistry is the acceleration of the lead generation and optimization phases of drug discovery.[1] Despite impressive advances to date the combinatorial practitioner continues to face a number of hurdles in reducing this concept to routine use. These include the difficulties of adapting established solution-phase precedents to polymer supported reactions and consistently reproducing conditions such as anhydrous and/or inert atmosphere or extreme temperature ranges while remaining within the constraints of a miniaturized, robotic format. While automation capability continues to improve, it is frequently desirable to avoid or minimize demanding synthetic conditions when planning a combinatorial library.



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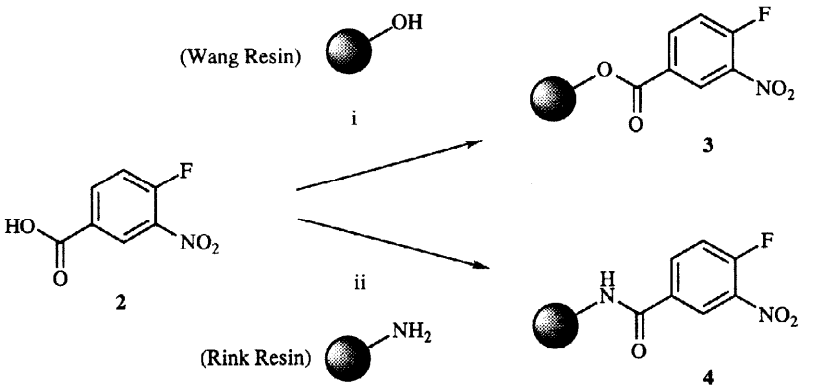
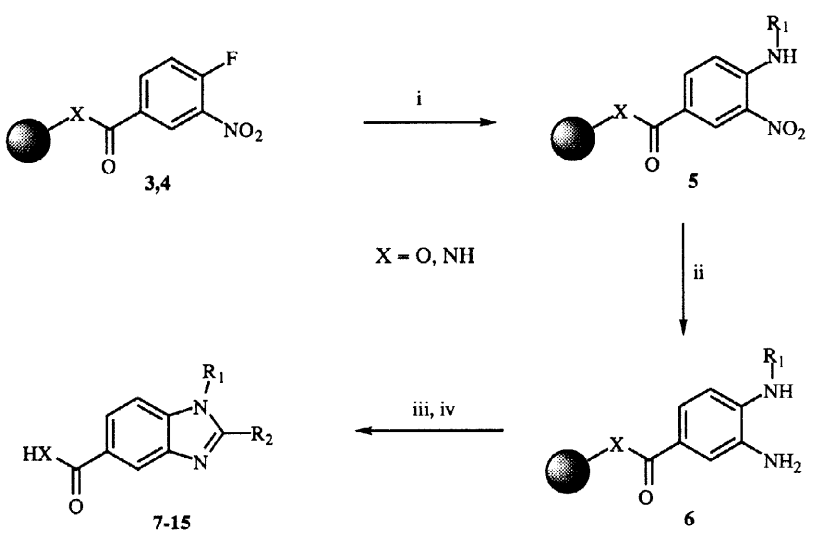
The benzimidazole **1** is an important heterocyclic nucleus which has seen extensive use in medicinal chemistry, with the antihistamine Astemizole[2] and the antiulcerative Omeprazole[3] being notable clinical examples. In addition, benzimidazole based compounds have shown such diverse biological activities as inhibition of phophodiesterase IV[4] and antagonism of angiotensin 1[5,6] and neuropeptide Y binding.[7] As part of our continuing effort to adapt heterocyclic methodologies to a high speed synthesis format we examined a solid-phase synthesis of this pharmacophore.[8,9] Our strategy emphasized flexibility, maximal use of commercially available inputs and mild reaction conditions which could be readily adapted to polymer support and automated operation. The procedure outlined in Schemes 1 and 2 was utilized for the synthesis of a representative library. The starting material, 4-fluoro-3-nitrobenzoic acid **2** was tethered to Wang[10] or Rink[11] derivatized polystyrene resin in multi-

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01427-0

gram quantities. Initial attempts to carry out the loading step using the 1-hydroxybenzotriazole (HOBt) ester of **2** were unsuccessful due to the unanticipated ipso-fluoride displacement by the nucleophilic hydroxyl group of HOBt.[12] The coupling in both cases was subsequently carried out using the corresponding diisopropylcarbodiimide (DIC) generated symmetrical anhydride, with 0.1 equivalents of N,N-dimethylaminopyridine (DMAP) added to catalyze the esterification of Wang resin. Following the loading step the resins **3** and **4** were treated with



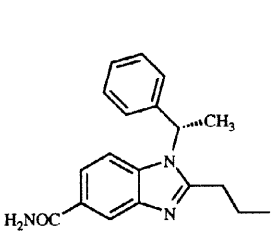
Scheme 1. Legend : i) 4.0 eq. 4-fluoro-3-nitrobenzoic acid, **2**, 2.0 eq DIC, 0.1 eq. DMAP in DMF, 12 hours, ii) 3.0 eq. 4-fluoro-3-nitrobenzoic acid, **2**, 1.5 eq. DIC in DMF, 3 hours.



Scheme 2. Legend : i) 5.0 eq. amine, 5% DIEA in NMP or DMF, O/N, ii) 3.0 M $SnCl_2$ in DMF, 5 hours, iii) 4.0 eq. aldehyde, 2.0 eq. DDQ in DMF, 5 hours, iv) 50% trifluoroacetic acid in DCM, 2 hours.

5.0 equivalents of selected primary amines in a 5% solution of N,N-diisopropylethylamine (DIEA) in DMF or N-methylpyrrolidone (NMP) overnight at room temperature. The reaction proceeded efficiently with a wide range (>100) of primary aliphatic, benzyl and 2-alkylbenzyl amines, anilines were not included. Displacements by benzylamine inputs with either electron donating or withdrawing substituents proceeded to completion within the overnight time frame. Reduction of the polymer supported nitroanilines **5** was achieved by treatment with 3.0M $SnCl_2$

in DMF for 5 hours.[13] The quality of the resultant intermediate could be assessed by cleavage and analysis of a portion of the resin bound *o*-phenylenediamine **6**, prior to splitting the resin to perform the discrete cyclization reactions. The published procedure of Phillips and Wei[8] was handicapped by the limited availability of the requisite aryl imidates and by the prolonged heating required for the transformation. We therefore sought an alternative strategy which could not only utilize a large number of commercial inputs but offer milder reaction conditions. The one-pot method of Vanden Eynde *et al.*,[14] featuring a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated cyclocondensation of an *o*-phenylenediamine and an aldehyde, presented an attractive alternative. Solid phase application of this procedure involved the addition of 4.0 equivalents of an aldehyde and 2.0 equivalents of DDQ to **6** in DMF for 5



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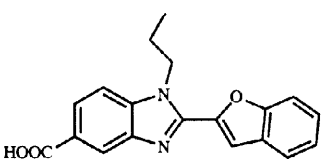

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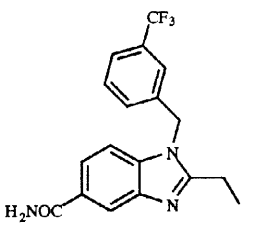

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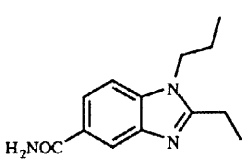

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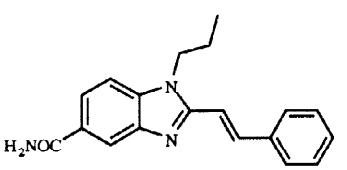

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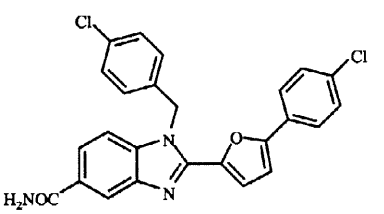

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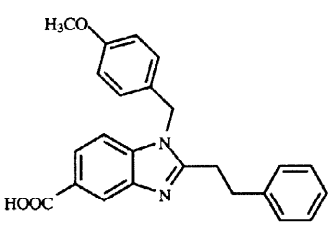

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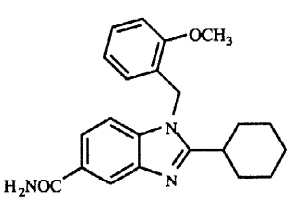

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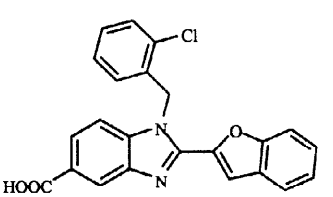

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Table 1. Representative products and results from a validation library. The first number refers to the crude yield, the number in parentheses to purity as assessed by integration of HPLC peak areas.

hours at room temperature and was successfully demonstrated for 160 aldehydes. Following DMF and DCM washes, the resins were subjected to cleavage with 50% trifluoroacetic acid in DCM for 2 hours. The structures, yield[15a] and purity[15b] data obtained for a representative set of compounds (**7-15**) are summarized in Table 1. Additionally, products from validation libraries were characterized by ^{1}H NMR and electrospray mass spectrometry.[16]

In summary, the benzimidazoles represent an excellent combinatorial scaffold and our method allows for the introduction of chemical diversity through the use of commercially available inputs with additional expansion possible by use of resins preloaded with natural and unnatural amino acids. The methodology is ideally suited for automated application since the entire synthetic sequence can be carried out in DMF at room temperature.

Acknowledgment

We thank Dr. Leszek Poppe for NMR data, Mr. Doug Lenz for mass spectral analysis, Dr. William S. Marshall for critical reading of the manuscript and Dr. Lawrence S. Melvin and Dr. Theodore Jones for their support.

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[15] a) Yields were calculated from the weight of crude material and the initial loading level of starting resin. b) Analysis was carried out by HPLC (Vydac C_{18} column, 4.6 x 250mm, 0-50% acetonitrile/water containing 0.1% TFA with integration of peak areas at 220nm).
[16] Analytical data for compound **8**, ^{1}H NMR (400MHz, $CDCl_3$) δ 8.97(d, 1H, J=2Hz), 8.45(m, 1H, J=5.3Hz), 8.11(d, 1H, J=9.0Hz), 8.05(s, 1H), 7.80(d, 1H, J=7.8Hz), 7.63(d, 1H, J=1Hz), 7.50(t, 1H, J=8.3Hz), 7.39(t, 1H, J=7.3Hz), 6.91(d, 1H), 3.37(m, 2H, J=7.3Hz), 1.8(m, 2H, J=7.3Hz), 1.1(t, 3H); mass spectrum (ESI) m/z 321 ($M+H^+$).