Pergamon

Tetrahedron Letters 40 (1999) 2665–2668

TETRAHEDRON LETTERS

A New "Traceless" Solid-phase Synthesis Strategy: Synthesis of a Benzimidazole Library

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Received 30 December 1998; revised 22 January 1999; accepted 1 February 1999

Abstract: A new strategy to achieve "traceless" solid-phase synthesis has been developed. Using this strategy, a "traceless" benzimidazole library with diversity on the benzene moiety was synthesized efficiently in high yield with high purity. During the final step of this new synthetic sequence, cleavage and cyclic nucleus elaboration take place by a series of substitution and elimination reactions on the solid phase followed by release to the solution phase.
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Keywords: solid-phase synthesis, Traceless, benzimidazole, combinatorial chemistry

Merrifield solid-phase synthesis methods have been successfully applied in peptide synthesis for more than three decades.[1] Since natural peptides and proteins generally contain free carboxylic acids or amides at their carboxyl-terminus, most of solid-phase peptide chemistry has focused on attachment of the carboxyl-terminal acid or amide to the support. While Merrifield solid-phase synthesis method has been applied to synthesis of small organic compounds especially for combinatorial libraries, during the last few years, a considerable effort has focused on developing chemistry for specific attachment to the solid support.[2] Libraries of compounds synthesized on solid phase, in general, leave the polar support attachment functionality, such as COOH, $CONH_2$, OH, SH and NH_2 covalently attached to the structure. These invariable functional groups may limit SAR studies and structural optimization. To this end, increasing number "traceless" solid-phase synthesis strategies have been developed. These strategies include i) molecular elaboration by intermolecular substitution,[3] ii) cyclization by intramolecular substitution,[4] and iii) substitution or elimination on a preformed nucleus (with so-called traceless linkers).[5] In this paper, we wish to introduce a new strategy with somewhat more comprehensive features which affords an important class of compounds useful in drug discovery.

Substituted benzimidazoles are widely used in medicinal chemistry.[6] A number of groups are working on solid-phase synthesis of benzimidazole libraries.[7] To our knowledge, all of the reported strategies have left the support attachment functionality (OH, $CONH_2$ or COOH) with little substituent diversity introduced on the benzene ring of the benzimidazole nucleus. To improve on these limitations, we wished to design a synthesis that allows for solid support attachment through the N-1 nitrogen of the precursor to the imidazole ring with the

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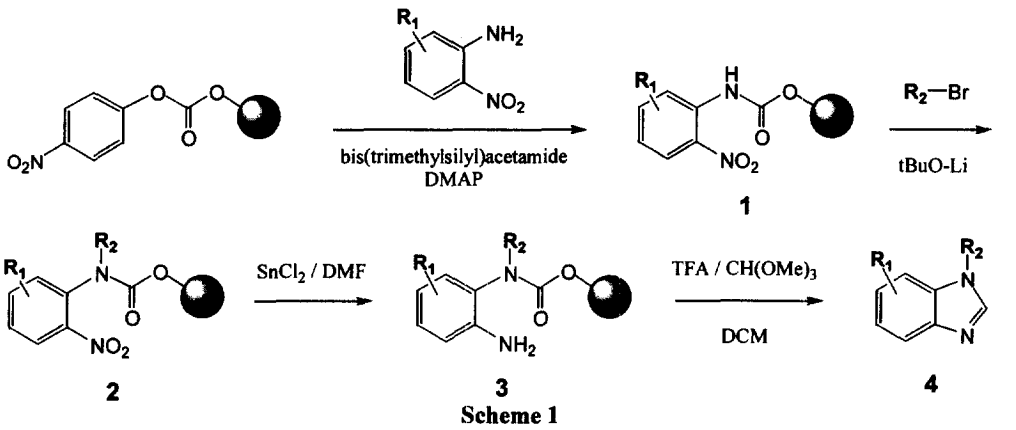
PII: S0040-4039(99)00293-2

ability to introduce significant diversity on the benzene ring. Our "traceless" synthesis of benzimidazoles **4** comprises four steps shown in Scheme 1.



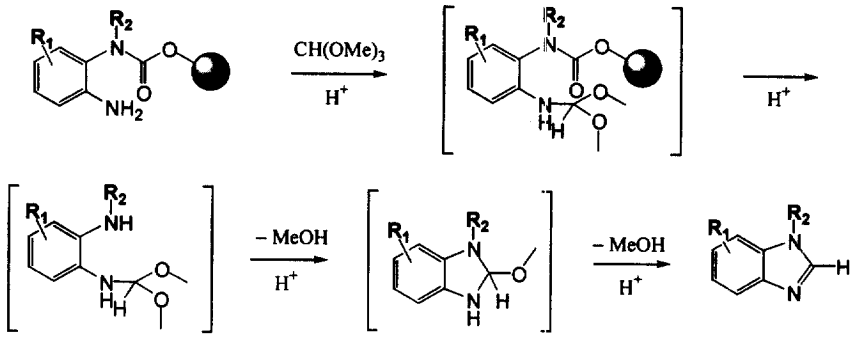
1 **2** **3** **4**

Scheme 1

All reactions were run at ambient temperature and gave near quantitative yield, which was monitored by cleavage of a small quantity of compound-bound resin at each step. The first group of building blocks, substituted 2-nitroanilines were attached to p-nitrophenyl carbonate Wang resin in DMF with bis(trimethylsiyl)-acetamide[8] and DMAP for 20-24 hours to afford carbamates **1**. The completion of loading can be monitored by absence of the released p-nitrophenol with RP-HPLC. Alkylation of the carbamate nitrogen of **1** with benzylic bromides using lithium t-butoxide in THF/DMSO for 5 hours gave the substituted carbamates **2**. Reduction of nitro groups of **2** with $SnCl_2$ in DMF for 3 hours furnished the anilines **3**.[9]

The final step is a key step in our sequence. The resin-bound **3** was treated with a solution of trimethylorthoformate/TFA/DCM (1/1/2, 1 mL/50 mg of resin) for 3 hours and gave quantitatively the product benzimidazoles **4** upon evaporation, which did not require further purification (Figure 2). Here the TFA not only cleaves compounds from the resin, but also elaborates the imidazole ring. It is interesting to note that the purity of the products decreased, if the concentration of TFA increased. In addition, if stepwise cleavage of the diamines from the resin with TFA, evaporation of TFA, followed by treatment with trimethylortho-formate/TFA/DCM was performed, a complex mixture of compounds was observed by RP-HPLC. This is consistent with the reported acid-catalyzed ring closure of dianilines with orthoformates in solution, which gives moderate yields of benzimidazoles upon heating[10]. Therefore, we propose that initially the trimethylorthoformate specifically reacts with the aniline functionality, yielding an intermediate dimethylformamidine[11], which is subsequently reactive with the secondary amine slowly released from the resin following diluted TFA catalyzed cleavage. Further elimination of methanol yields the desired benzimidazoles **4**. (Scheme 2) As a result, the solid support attachment site N-CO bond has been converted to N-C bond of the benzimidazole nucleus and has left no evidence of solid-phase synthesis. In fact, the new bond formation presumably took place in solution-phase. In this traceless solid-phase synthesis, the carbon fragment was added

to the free amino group followed by cleavage, cyclization and elimination (aromatization) in one pot. This represents a variation from all the current approaches.



Scheme 2

With four efficient steps, we have been able to introduce subsequently two building blocks (R_1-2-nitroanilines and R_2Br), for which there is a large number of diverse substitutions and which are readily available. Using the same protocol, a mini library was synthesized. For building blocks R_1-2-nitroanilines: R_1 = 4-methoxyl (**I**), 3-chloro (**II**), and 3-methoxyl (**III**) were used, while for building blocks R_2Br, R_2 = benzyl (**A**), 4-cyanobenzyl (**B**), and 4-methyloxycarbonylbenzyl (**C**) were selected. All nine product benzimidazoles (Figure 1) were characterized by RP-HPLC, UV, IR, ^{1}H-NMR and MS. The typical four-step overall yield and purity was 80-95%, which was detected by RP-HPLC (Figure 2). IR spectra showed significant bands at 2229 cm^{-1} for the cyano group and 1717 cm^{-1} for the ester group of compounds **I-IIIB** and **I-IIIC** respectively. ^{1}H-NMR[12] and MS spectra were satisfactory for all the compounds.

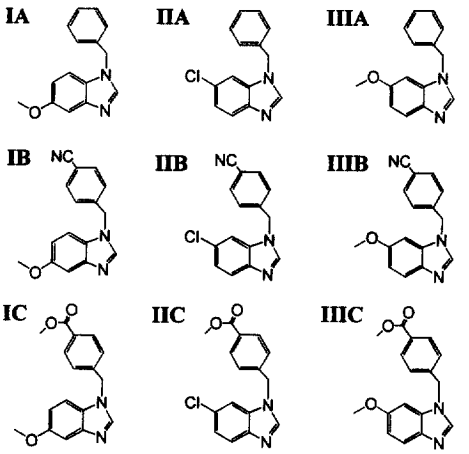


Figure 1: Structures of the mini library.

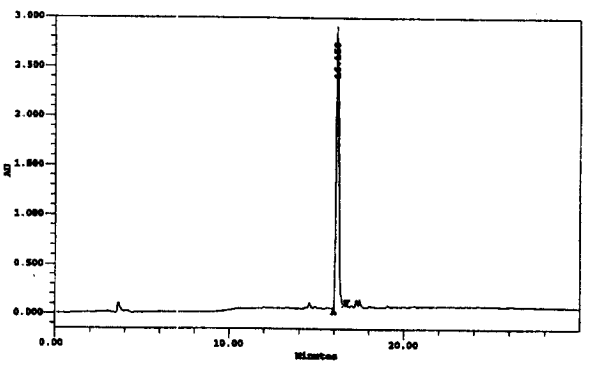


Figure 2: RP-HPLC trace for compound **IA.**

Column: C_{18} (4.6 x 250 mm); gradient: 0-100 % CH_3CN in H_2O with 0.1% TFA; UV: 214 nm; Flow rate: 1 mL/min.

In the present mini library synthesis, we chose only benzylic bromides for the building blocks R_2Br. The use of other classes of alkylating agents as well as the introduction of alternate carbon fragments into the C-2 position of the imidazole nucleus would greatly expand the structural diversity of this approach and are the subject of further investigation.

In conclusion, a new "traceless" solid-phase synthesis strategy for a cyclic nucleus elaboration has been demonstrated. During the final step of the synthesis of benzimidazoles, a reactive carbon fragment is added followed by stepwise cleavage and cyclization/elimination in solution. As demonstrated, a "traceless" benzimidazole library with diversity on the benzene moiety was synthesized in efficient steps, with high yield and high purity.

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