Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1001–1003

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Liquid-Phase Combinatorial Synthesis of Aminobenzimidazoles

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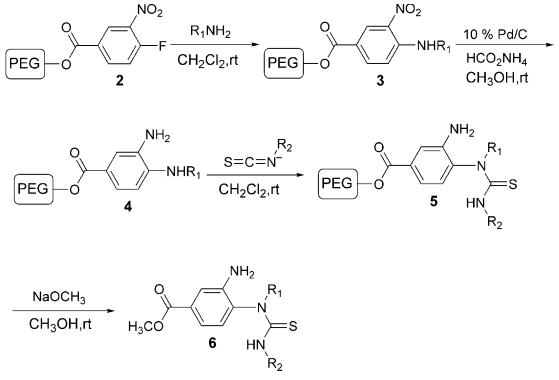
Received 12 December 2001; accepted 2 February 2002

Abstract—Liquid-phase synthesis of 2-arylaminobenzimidazoles using soluble polymer support strategy is first described. The key step to benzimidazole skeleton is achieved in the presence of diisopropylcarbodimide (DICDI) and isothiocyanates. A mechanism study for one-pot cyclodesulfurization is also investigated on the support. A wide range of benzimidazole derivatives is synthesized in excellent yield and purity just by simple wash and precipitation. © 2002 Elsevier Science Ltd. All rights reserved.

Combinatorial solid-phase synthesis of small organic molecules is emerging as a powerful tool for both lead discovery and lead optimization.[1–2] Development of efficient methods for the rapid generation of pharmacological scaffolds has become a practical goal of combinatorial chemistry.[3–4] Direct application of known solution chemistry to develop synthetic sequences on solid support could be a difficult and time-consuming process.[5,6] In an effort to develop a method for the rapid parallel synthesis of chemical libraries, we have been exploring liquid-phase combinatorial synthesis (LPCS) by the use of soluble polymer support-poly (ethylene glycol) monomethyl ether to generate libraries.[7–12] Unlike an insoluble matrix, the soluble polymer support-PEG is soluble in many organic solvents and tends to precipitate in diethyl ether or ethanol. In each step of the reaction sequence, the PEG bound products are precipitated selectively for isolation and purification purposes. Excess reagents and by-products are removed by simple filtration. It is also worthy of note that biological assay could be directly evaluated on the PEG linked libraries which is a particular attractive feature for the PEG supported library synthesis.[13–14]

The benzimidazole ring is a crucial pharmacophore in drug discovery.[15,16] Benzimidazole-based compounds have shown diverse biological activities, including antiulcer, anticancer and antiviral effects.[17–19] Therefore, a practical method for accelerating synthesis of diverse collection of benzimidazoles would be of great value for drug discovery. To date, several solid-phase synthesis of *N*-substituted benzimidazoles have been published.[20–23] However, liquid-phase synthesis of 2-(arylamino)benzimidazoles using different synthetic protocol has not yet been reported. As part of our continuing effort to adapt heterocyclic methods to a high-throughput synthesis format, we report here our preliminary study in soluble polymer-supported synthesis of 2-(arylamino)benzimidazoles. The synthetic route to the targeted molecule is outlined in Scheme 1. According to our previous results, acylation of the PEG is accomplished with 4-fluoro-3-nitrobenzoic acid and continues displacement of fluorine by commercially available primary amines.[24–26] Aromatic nitro group of **3** is then reduced with 10% Pd (C) and ammonium formate in methanol at room temperature.[27] This reaction condition is particularly useful to prepare polymer bound nitroanilines when rapid and mild reduction is necessary.[28] Following the treatment of PEG-supported *o*-phenylenediamine **4** with isothiocyanate in methylene chloride provides *N*-(2-aminophenyl)-*N*′-substituted thioureas **5**. In order to check regioselectivity at this stage, compound **6bb** is



Scheme 1. Synthesis of *N*-(2-aminophenyl)-*N*′-substituted thioureas on the support.

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PII: S0960-894X(02)00091-4

liberated from the support to confirm that 1-napthyl isothiocyanate is only attached to a more nucleophilic, secondary aniline nitrogen (Fig. 1).[29]

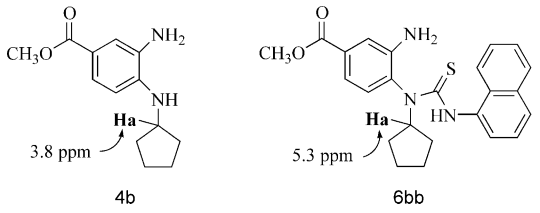
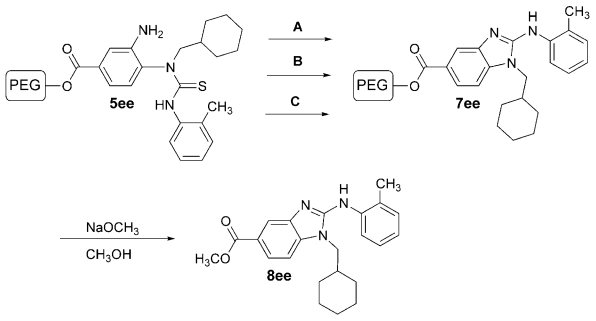


Figure 1. Comparison of chemical shift (**Ha**) in **4b** and **6bb**.

As a further expansion of our previous experience of synthesing *N*,*N*′-di(Boc)-protected guanidine, we think those reaction conditions for guanidinylation could be applied to current heterocyclic formation (Scheme 2).[11,12] To investigate the efficiency of cyclodesulfurization, we carried out reactions of **5ee** with various reagents under several conditions (Scheme 2, entries A–C). Treatment of immobilized thiourea **5ee** with DICDI results in complete cyclization in 10 h at room temperature (entry A). Progress of reaction is easily followed by conventional ^{1}H NMR analysis without any polymer support cleavage. A different protocol is adopted for ring-closure reaction of *N*′-(2-aminophenyl)-*N*′-phenylthiourea derivatives by methyl iodide activation. Subsequent cyclization of polymer bound *S*-methylisothiourea in the presence of triethylamine provides a very efficient route for the benzimidazole formation (entry B).

Cyclodesulfurization is also proceeded well using mercury(II) chloride to give final product in excellent yield and purity (entry C). The insoluble mercuric sulfide formed is easily removed by using fluted filter paper before precipitation and washing of polymer bound intermediate. Although the exact intermediates for the mercuric chloride or DICDI-promoted benzimidazole formation (entries A and C) are not clear, the possible in situ generated highly electrophilic carbodimide may be the reactive species. Indirect evidence of a mechanistic pathway is the isolation of *N*,*N*′-diisopropylthiourea after using DICDI for cyclization.

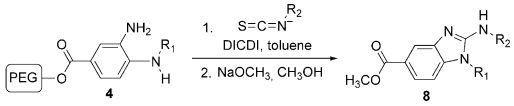
In the present study, one-pot cyclodesulfurization provides a more efficient route to 2-arylbenzimidazoles. We next turn our attention to explore scope and generality of reaction conditions for direct cyclization to **8**. We



Entry	Conditions	Time (h)	Crude yield (%)	Crude purity (%)
A	DICDI CH_2Cl_2, rt	10	90	90
B	CH_3I, Et_3N CH_2Cl_2, rt	10	85	87
C	$HgCl_2$, Et_3N CH_2Cl_2, rt	10	74	85

Scheme 2. Synthesis of 2-arylbenzimidazoles on the support.

find PEG bound *o*-phenylenediamine **4** reacts well with DICDI and isothiocyanates in toluene (Scheme 3). Following ether and ethanol washes after precipitation in a fritted Buchner funnel, immobilized benzimidazoles are subjected to a facile cleavage from the PEG with sodium methoxide to deliver targeted molecules in 85–98% overall yield. Each crude product is analyzed by HPLC and ranges from 80 to 99% (Table 1). By employing the desired reaction sequence, we are able to introduce two diverse substitutions that have a large number of building blocks readily available. We have screened four kinds of amines and four kinds of isothiocyanates to assemble a small library. The structures, yields and purities of compounds are summarized in Table 1.

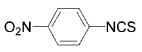
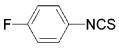
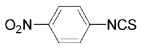
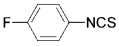
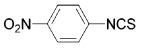
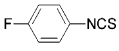
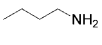
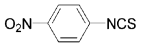
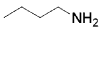
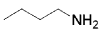
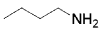
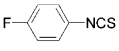


Scheme 3. One-pot cyclization to 2-arylbenzimidazoles.

It is worth noting that, in contrast to the various restrictions on the analysis of reaction development in solid-phase synthesis, liquid-phase synthesis allows routine analytical instruments (UV, IR, NMR, TLC) to monitor reaction progress without following cleave-and-analyze technique.

Products from validation libraries are characterized by mass spectrometry and ^{1}H NMR, confirming that in each reaction the major compound has a molecular ion corresponding to the appropriate product. This liquid-phase methodology provides a nice complement to the widely employed procedures of solid phase reactions involving benzimidazole heterocycles. It should decrease difficulties of adapting established solution-phase precedents to polymer-supported reactions. The focusing library synthesis and results from its screening for the identification of active compounds will be reported in the near future.

Table 1. Representative products and results of benzimidazole

Entry	R_1NH_2	R_2NCS	Crude yield[a]	Crude purity[b]
1			91	80
2			98	94
3			95	99
4			98	91
5			98	81
6			98	83
7			98	96
8			95	89
9			98	91
10			88	94
11			85	88
12			95	93
13			98	80
14			92	80
15			98	86
16			95	93

[a]Determined based on weight of crude sample (%).
[b]Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm) of crude products (%). Products show satisfactory ^{1}H NMR and MS data.

Acknowledgement

This study was supported by grant from the National Science and Technology Program in Pharmaceuticals and Biotechnology (NSC 89–2323-B-259–001).

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