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Soluble polymer-supported synthesis of 2-(arylamino)benzimidazoles

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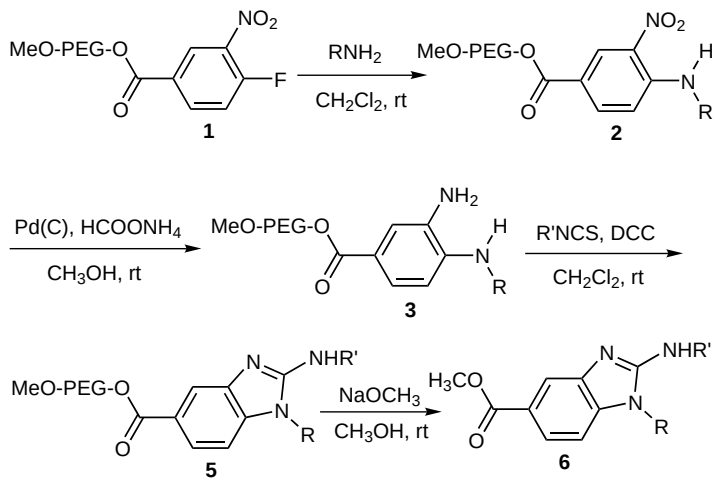
Abstract—A novel liquid-phase method for the construction of biologically important benzimidazoles has been developed. A library of *N*-substituted 2-aminobenzimidazoles was readily assembled utilizing S_NAr reactions, reduction of the nitro group and a one-pot cyclization with isothiocyanate as the key step in the synthesis. The crude benzimidazoles were obtained in 80–99% yields with 78–95% HPLC purity.

In recent years applications of combinatorial chemistry have increased rapidly for the discovery of pharmaceutical lead compounds. Much of the work in this area has focused on solid-phase synthesis due to advantages including the easy and fast purification separating excess reagents and side products from the desired compounds, which are attached to an insoluble carrier.[1–4] However, several disadvantages are associated with solid-phase chemistry, such as heterogeneous reaction conditions, reduced rate of reactions, solvation of the bound species and mass transport of reagents were also observed.

We have been interested in employing liquid-phase combinatorial technology as a means of efficiently constructing diverse multifunctional libraries.[5] Polyethylene glycol mono-methyl ether (MeO-PEG-OH) is a quite unique polymer carrier because it is soluble in many organic solvents and is selectively precipitated in other solvents.[6–8] This soluble polymer support is also readily functionalized with different spacers and linkers. Furthermore, the progress of the polymer-supported reactions can be easily monitored by using conventional analytical techniques such as ^1H, ^{13}C NMR, IR and TLC.

It is well known that the benzimidazole moiety is an important structural element in drug discovery and shows a broad spectrum of biological activity.[9–11] Sev-



Scheme 1. One-pot synthesis of 2-aminobenzimidazoles.

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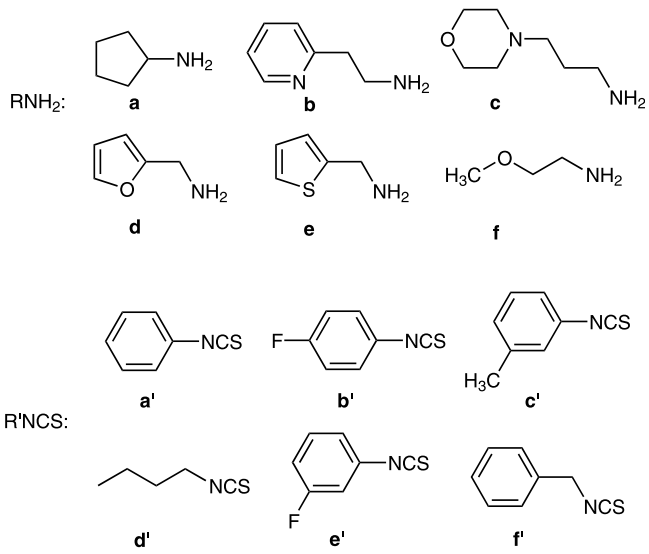
eral compounds from this class have been used as antihistaminic, antiparasitic and antiviral agents.[12,13] Several reports have appeared in the literature describing benzimidazole synthesis using solid-phase chemistry.[14–18] During our study we felt that substituted benzimidazoles are worthy of further study and therefore we decided to investigate the as yet, unreported liquid-phase synthesis of 2-arylaminobenzimidazoles.

Here we present our first results on the liquid-phase synthesis of *N*-substituted 2-aminobenzimidazoles. For our studies, commercially available MeO-PEG-OH was esterified with 4-fluoro-3-nitrobenzoic acid through DCC/DMAP coupling in dichloromethane. The building blocks used for the synthesis of the benzimidazoles are illustrated in Scheme 1.

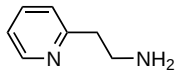
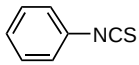
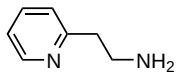
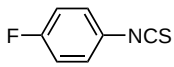
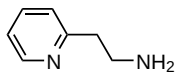
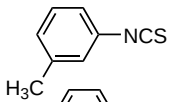
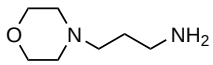
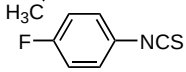
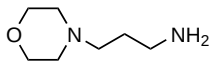
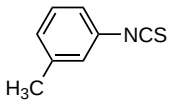
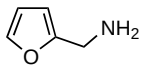
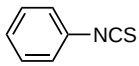
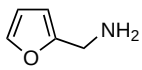
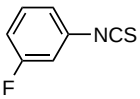
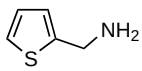
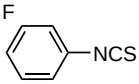
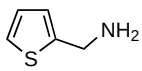
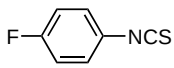
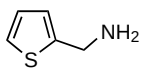
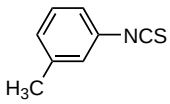
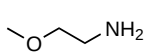
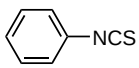
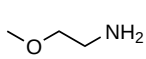
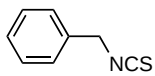


In the first step of the reaction sequence, polymer bound 4-fluoro-3-nitrobenzoic acid **1** was reacted with several heterocyclic amines. The *ipso*-fluoro displacement reaction proceeded smoothly at room temperature. We tried various reducing agents to reduce the aromatic nitro group and observed that the Zn-NH_4Cl[19] and Pd/C-$HCOONH_4$[20] reagents reduced the nitro group to the corresponding amine at room temperature, whereas other reducing agents such as Al-NH_4Cl[21] and 2 M $SnCl_2$[22,23] failed to reduce the immobilized nitro group. Upon completion of the reaction, the heterogeneous material was removed by filtration and the PEG-bound diamine was purified by a precipitation method. We next turned to study the one-pot cyclization reaction to give the target molecules. We observed that PEG-bound diamines **3** cyclized with isothiocyanates directly at ambient temperature in the presence of DCC to yield PEG-bound benzimidazoles **5** (Scheme 1). Progress of the cyclization reaction was easily monitored by regular proton NMR spectroscopy. No trace of the uncyclized compounds was observed by NMR after 24 h of stirring. Upon completion of reaction, insoluble DCU (dicyclohexyl thiourea) was removed first by filtration, and the PEG-bound benzimidazoles **5** were precipitated selectively by adding diethyl ether to the reaction mixtures. The precipitated PEG-bound benzimidazole was then filtered through a sintered glass funnel and thoroughly washed with diethyl ether until all the unreacted isothiocyanate and DCC were removed. Following solvent washes after precipitation, the immobilized benzimidazoles were subjected to an efficient cleavage from the support with sodium methoxide to provide the desired compounds. Complete cleavage of the PEG was verified by the observation of a downfield shift for the α-methylene protons of the polymer attachment site from δ 4.4 to δ 3.6 ppm. If the peak of the α-methylene protons were still present after checking by NMR, the recovered PEG bound products could be resubmitted to the reaction conditions until complete cleavage was reached. In most cases, the cleavage reactions were carried out overnight.

The MeO-PEG-OH was removed from the homogeneous solution by a precipitation and filtration method to give the corresponding analytically pure products in 80–99% yield with 78–95% crude purity, as assessed by HPLC. All the desired products were characterized by NMR and mass spectrometry. Table 1 data summarizes the crude yields and purities from the set of representative compounds. Fig. 1 shows a typical HPLC spectrum of the crude product **6aa′** with 96% purity. In order to understand mechanistic details, the reduced PEG-bound diamines **3a** were reacted with isothiocyanate to afford the corresponding thiourea product in quantitative yield (Scheme 2). In the case of the unsymmetrical 1,2-diaminobenzene **3a**, two possible regioisomers can result, depending on which of the ring nitrogen atom was acylated with the isothiocyanate. During our mechanistic studies, it was found that the cyclization reactions took place via formation of the thiourea intermediate **4ad′**, as shown in Scheme 2. We observed that only the more nucleophilic secondary amine reacted with *n*-butylisothiocyanate to give a substituted thiourea intermediate **4ad′**, as confirmed by proton NMR spectroscopy, since the methine proton (CH) of the cyclopentyl substituent was shifted from 3.8 (**3a**) to 5.3 ppm (**4ad′**).[†] The same compound **4ad′** was also obtained when polymer bound *o*-nitroaniline **2a** was first reacted with *n*-butylisothiocyanate to give **7ad′** and then reduced to provide the aromatic nitro group of **7ad′** (Scheme 2). The resulting thiourea **4ad′** was then subjected to intramolecular cyclization with

[†] Analytical data for cleaved compound from **4ad′**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.24 (d, J=8.4 Hz, 1H), 5.30 (m, 1H), 3.89 (s, 3H), 3.70–3.64 (m, 2H), 2.25–2.22 (m, 2H), 2.11–2.01 (m, 4H), 1.88–1.85 (m, 2H), 1.77–1.67 (m, 2H), 1.41–1.33 (m, 2H), 0.79 (t, J=7.3 Hz, 3H).

Table 1. Liquid phase synthesis of benzimidazoles **6**

Entry	RNH_2	R'NCS	Yield[a](%)	purity[b](%)
1			80	88
2			93	80
3			99	87
4			99	92
5			93	87
6			83	78
7			88	93
8			89	95
9			90	81
10			90	91
11			83	84
12			86	95

a. Determined based on weight of crude sample.

b. Purity was determined by the HPLC integral of the product peak at 254 nm.

The purity given is for the crude product directly after cleavage.

Products show satisfactory ^1H NMR and MS(MH^+, FAB) data

DCC and reaction smoothly proceeded at room temperature to give **5ad**′. Although the exact intermediates involved in the DCC-catalyzed benzimidazole cyclization are not known, a possibly in situ generated highly reactive carbodimide may be one of the species.

In summary, we describe a straightforward liquid-phase synthesis of benzimidazoles from commercially available building blocks. In each step of the reaction sequence, the immobilized intermediates were purified by simple precipitation and washing. This synthetic design permits the introduction of a diverse array of substituents into both the 1 and 2 positions of the benzimidazole skeleton. All reactions were performed at room temperature to give the desired molecules in high yield and high purity. This synthetic methodology is versatile and produces compounds with known pharmacophoric scaffolds, and is amenable for iterative combinatorial library generation.

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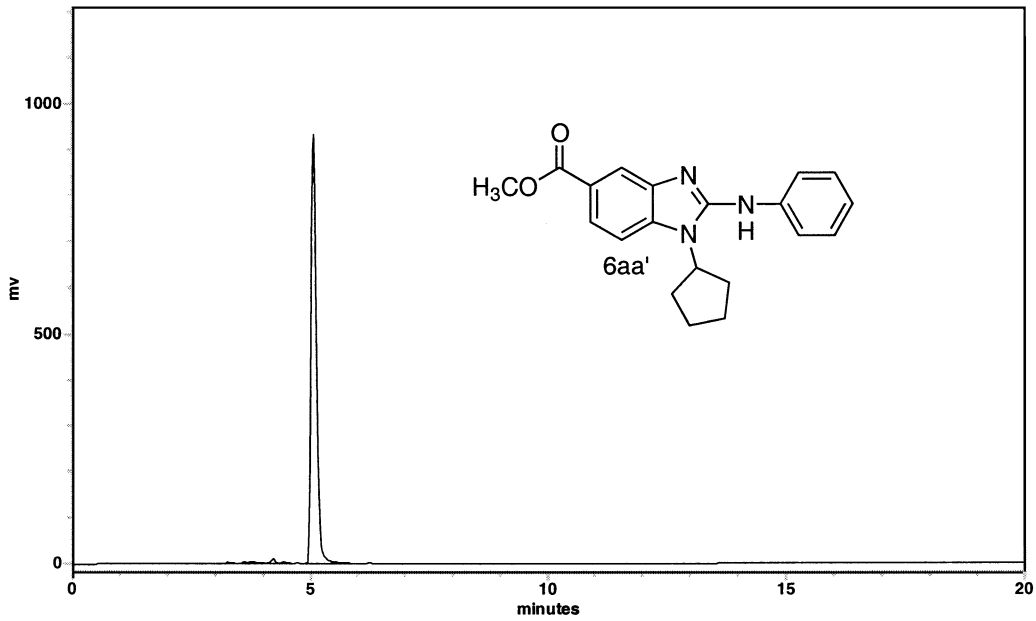
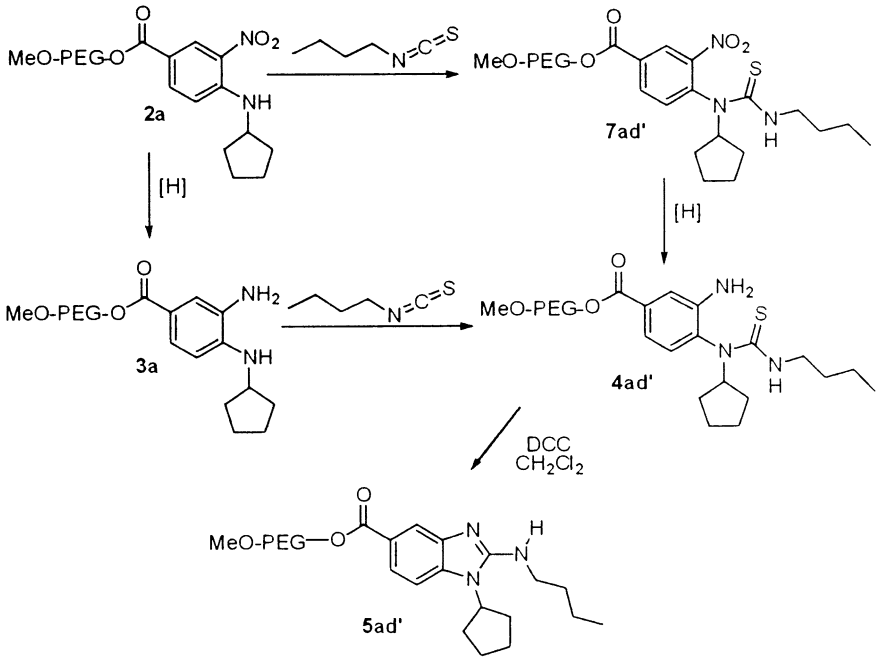


Figure 1. HPLC analysis of crude product **6aa**′, with UV detection at $\lambda = 254$ nm. Column: Sphereclone 5u Si (250×4.6 nm); gradient: 50% EA/hex.; flow rate: 1 mL/min.



Scheme 2. Mechanistic studies for the synthesis of 2-aminobenzimidazoles.

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