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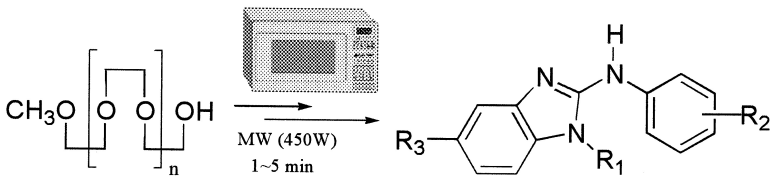

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Rapid Microwave-Assisted Liquid-Phase Combinatorial Synthesis of 2-(Arylamino)benzimidazoles

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An efficient, facile, and practical liquid-phase combinatorial synthesis of benzimidazoles under microwave irradiation is described. In the first step of reaction sequence, polymer-bound activated aryl fluoride was condensed with selective primary amines via an ipso-fluoro displacement reaction. Reduction of the polymer-bound nitro group followed by cyclization with isothiocyanates afforded immobilized benzimidazoles. The desired products were obtained in high yield with high purity after detaching from the soluble matrix. All reactions involved (S_NAr reaction, reduction, cyclization, and support cleavage) were performed completely within a few minutes under microwave irradiation. The coupling of microwave technology with liquid-phase combinatorial synthesis constitutes a novel and particularly attractive avenue for the rapid generation of structurally diverse libraries.

Combinatorial chemistry and high-throughput parallel synthesis have emerged as a powerful technique for the generation of structurally diverse druglike compounds.[1] Although the solid-phase synthesis technique has been successfully applied in the preparation of a large variety of heterocyclic molecules and a number of review articles have appeared in this area, insoluble polymer-supported synthesis needs unambiguously vast development time and effort.[2−4] Soluble-polymer-supported syntheses have recently emerged as an alternative and powerful technique for the preparation of small heterocyclic libraires.[5,6] Liquid-phase combinatorial synthesis offers several unique advantages. For example, reactions may be carried out in homogeneous solution, but convenient product purification such as that of a solid-phase method can be achieved by simple filtration and washing. The large excess of reagents typically used in solid-supported synthesis is normally not required in liquid-phase synthesis. Characterization of immobilized intermediates is also straightforward because the polymer support does not interfere with spectroscopic methods.

Microwave-assisted organic synthesis (MOREs) has received much attention in recent years because of its faster chemistry and formation of cleaner products compared with conventional heating.[7] It is clear that the application of microwave technology to rapid synthesis of biologically significant molecules on the solid support would be of great value for library generation.[8] This technology has recently been recognized as a useful tool for a drug-discovery program.[9] In conjunction with our continuous interest in developing new protocols in liquid-phase combinatorial synthesis, we explore the use of microwave irradiation as a heating source in conformational rigid heterocycles synthesis.

In our effort to develop a multistep route to diversely substituted druglike scaffolds, we have targeted the benzimidazole system. It is well-known that the benzimidazole pharmacophore is an important structural element in medicinal chemistry and that it shows a broad spectrum of pharmacological activities.[10] Several compounds from this class have been used as antihistaminic, antiparasitic, and antiviral agents.[11,12] Many classical[13] and solid-phase[14] methods have been reported for the synthesis of benzimidazole compounds. To the best of our knowledge, application of microwave technology to liquid-phase combinatorial multistep synthesis has not been demonstrated.[15] We herein report the first microwave-assisted 2-(arylamino)benzimidazole library synthesis on soluble polymer support, which can deliver high yield and purity of products after a few minutes reaction time.

In our previous study, we have shown the usefulness of a versatile building block, PEG-bound *o*-fluoronitrobenzene (**1**), for the construction of medicinally interesting heterocycles such as arylpiperazine,[16] benzimidazolone,[17] and 2-(alkylthio)benzimidazole.[18] The reaction sequence for the synthesis of a representative library is shown in Scheme 1. The first point of diversity was incorporated by nucleophilic aromatic substitution (S_NAr) of primary amines with PEG-bound activated aryl fluoride **1** under domestic microwave irradiation in chloroform. Irradiation with 450 W was suitable to provide more than 99% conversion of the starting material within a few minutes, and no decomposition of polymer support was observed. The ipso-fluoro displacement reaction with various amines proceeded very quickly under microwave heating and was completed within 1 min to deliver uneventfully PEG-bound *o*-nitroaniline **2** in 95% yield. In each step of the following reaction sequence, the PEG-bound products were precipitated selectively from a suitable

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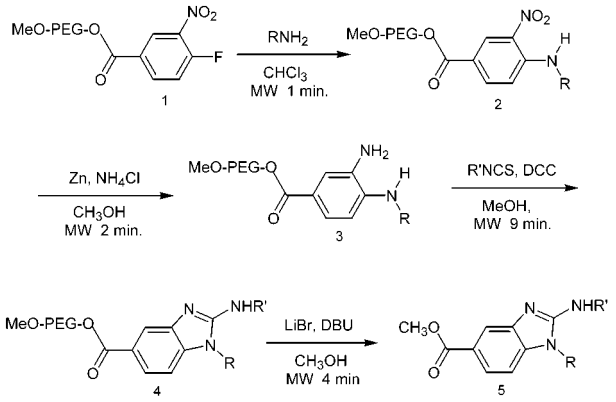
Scheme 1



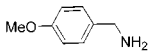
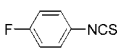
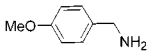
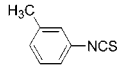
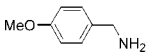
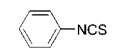
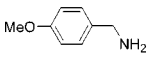
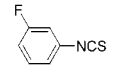
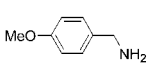
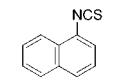
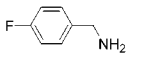
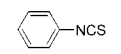
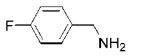
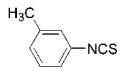
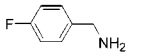
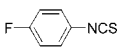
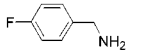
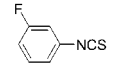
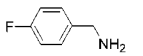
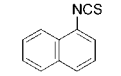
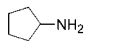
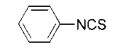
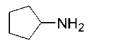
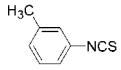
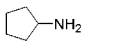
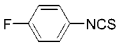
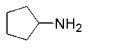
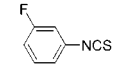
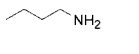
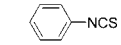
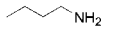
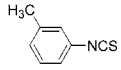
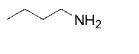
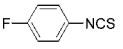
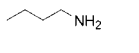
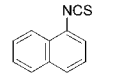
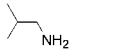
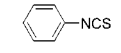
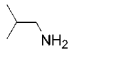
combination of solvents such as methylene chloride and ether for isolation and purification purposes.

Reduction of PEG-bound *o*-nitroaniline **2** in a microwave cavity was tested using various reducing agents. We observed that Zn−NH_4Cl selectively converted nitro to the corresponding amine **3** within 2 min under microwave exposure in methanol. However, other reducing agents such as Al−NH_4Cl failed to reduce such an immobilized nitro group, even in prolonged heating in a microwave cavity. We used conventional ^1H NMR as an essential tool for direct reaction monitoring and optimization on the soluble polymer support.[19] Arylnitro to arylamino transformation was confirmed by the utilization of proton NMR. Upon completion of the reaction, the heterogeneous material was filtered out to ensure high recovery of the products.

Toward this end, subjection of the resulting PEG-bound diamines **3** to microwave irradiation by treatment with various aromatic isothiocyanates in the presence of DCC and methanol provided the corresponding cyclized products **4** in quantitative yield. Progress of one-pot cyclization was easily monitored by regular proton NMR spectroscopy and showed that optimized reaction conditions for cyclization was completed within 10 min (450 W) under microwave exposure. During the workup, insoluble dicyclohexylurea (DHU) was removed first by filtration to ensure the final purity of the library and the PEG-bound benzimidazole was purified by precipitation. For the sake of comparison to conventional thermal heating, cyclization reactions were also performed in refluxing methanol for 10 min, using identical stoichiometry. However, after cleavage, we obtained only unreacted diamine. It has been observed that quantitative conversion of PEG-bound diamine **3** to the cyclized products **4** required around 4 h of refluxing reaction time. When both microwave results and conventional preheated oil bath results were compared, we observed a clear improvement in yield and reaction time with microwave heating. A similar enhancement was also observed in the S_NAr reaction and in the reduction step.

The removal of the substituted benzimidazoles from the polymer support was then studied under microwave heating. It was found that transesterification of immobilized benzimidazoles with LiBr and DBU in methanol was performed well when the reaction mixture was irradiated in a microwave cavity (450 W) for 4 min.[20] Upon completion of the reaction, MeO−PEG−OH was removed from the homogeneous solution by precipitation and filtration to provide the corresponding crude products **5** in 86−96% yield with 65−91% purity as assessed by HPLC (Table 1).[21] Products from the validated libraries are characterized by mass spectrometry and proton NMR, confirming that in each reaction the major compound has a molecular ion corresponding to the appropriate product.

Table 1. Microwave-Accelerated Liquid-Phase Combinatorial Synthesis of Benzimidazoles **5**

Entry	RNH_2	R'NCS	Crude purity (%)	Crude yield (%)
1			86	92
2			76	87
3			67	86
4			87	96
5			82	96
6			75	92
7			87	94
8			80	91
9			77	94
10			82	90
11			65	94
12			79	95
13			86	86
14			77	90
15			91	92
16			83	86
17			84	97
18			89	95
19			87	93
20			88	95
21			91	90
22			86	90
23			91	91

In summary, we have successfully combined the advantages of microwave technology with liquid-phase combinatorial chemistry to facilitate the rapid synthesis of benzimidazoles from commercially available building blocks. Microwave irradiation is a powerful tool for accelerating dramatically the reaction rate of the liquid-phase synthesis of 2-(arylamino)benzimidazoles. Compared to conventional thermal hearting, microwave irradiation decreased the reaction time on the support from several hours to several minutes. It is worth noting that all polymer-supported intermediates and the polymer support itself remained stable under microwave exposure as determined by proton NMR and MS. All reactions involved are highly efficient to give the desired compounds in high yield and high purity. The versatility of this methodology can be extended to develop a streamlined approach to other druglike heterocycles in a combinatorial fashion.

Acknowledgment. We are thankful of the general financial support from the National Science Council of Taiwan.

Supporting Information Available. Spectra of various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Czarnik, A. W.; DeWitt, S. H. *A Practical Guide to Combinatorial Chemistry*; American Chemical Society: Washington, DC 1997. (b) Fenniri, H. *Combinatorial Chemistry*; Oxford University Press: New York, 2000. (c) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wileys & Sons: New York, 2000.

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(21) All microwave-assisted reactions were performed in a 100 mL round-bottom flask (attached to the reflux condenser) with a Sharp domestic microwave oven at a frequency of 2450 Hz (900 W). A typical procedure for the synthesis of **5** (Table 1, entry 15) is the following. A mixture of polymer-supported diamine (510 mg), DCC (5 equiv), 10 mL of methanol, and 5 equiv of phenyl isothiocyanate was irradiated in a microwave cavity with an output at 50% (450 W) for 10 min. Upon completion of the reaction, cold diethyl ether (20 mL) was added to the reaction mixture to precipitate the PEG-bound benzimidazole. The precipitate was then collected on a sintered glass funnel and thoroughly washed with diethyl ether (20 mL × 3). PEG-bound benzimidazole was then dried under vacuum to yield the cyclized benzimidazole in quantitative yield. Finally, the resulting PEG-bound benzimidazole was cleaved in a microwave cavity by using LiBr (5 equiv) and DBU (3 equiv) in 10 mL of methanol. After 4 min of reaction, the detached MeO−PEG−OH was precipitated by adding cold diethyl ether. The polymer was filtered, and the combined filtrate was passed through an SPE (solid-phase extraction) short cartridge to remove a trace amount of PEG and DBU. The final compound was dried to offer the corresponding crude product in 92% yield with 91% HPLC purity.

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