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Mercury chloride assisted cyclization toward benzimidazoles by focused microwave irradiation

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This article is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—An efficient, microwave-assisted method for the mercury chloride mediated synthesis of 1,2-disubstituted benzimidazoles has been developed. Biologically interesting benzimidazoles were readily assembled utilizing S_NAr reactions, reduction, and followed with mercury(II) mediated cyclization under microwave irradiation. The desired products were then liberated from the soluble matrix in excellent yield and purity after cleavage.

The application of microwave irradiation to the combinatorial chemistry becomes a powerful tool in accelerating the pace of library synthesis.[1] Domestic microwave oven is most popularly used in synthesis because of its low cost and ready availability. However, specially fabricated mono-mode microwave reactors provide homogeneous heating, temperature control, and more importantly improved safety features. Major aim of this integrated technology is to exploit high degree of molecular diversity and high-throughput organic synthesis to rapid access greatly expanded drug-like compound collection without tedious or time-consuming processes.[2] Convergent, polymer-supported microwave synthesis of discrete chemical entities provides an attractive lead optimization method for the refinement of biological activity. This approach may result in a marked reduction of the drug development timeline compared to that of conventional solution-phase synthesis. The use of soluble polymer support in combinatorial synthetic methodologies facilitates the library synthesis and overcomes the experiencing difficulty on solid phase reactions.[3] It serves as a chemically robust macromolecular protecting group and is carried over along with molecular modifications in multi-step synthesis until intentional cleavage at proper stage. Soluble polymer supported reactions are easily monitored progress using routine analytical techniques like TLC, IR, and ^1H NMR.[4]

Benzimidazole moiety is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including antiulcer, antitumor, and antiviral effects.[5] Therefore a general method of rapidly synthesizing benzimidazoles would be greatly advantageous and warrants further investigation in drug discovery. Although a number of solid-phase approaches for benzimidazole synthesis[6] have been reported, mercury chloride catalyzed one-pot cyclization toward benzimidazole on soluble polymer support by microwave irradiation is unknown.[7]

Convergent synthesis toward the targeted compounds was first to ligate 4-fluoro-3-nitrobenzoic acid to the support HO-PEG-OH **1** using microwave-assisted dehydrative esterification in dichloromethane (Scheme 1). The PEG bound *ortho*-nitro aryl fluoride **2** was subjected to facile aromatic nucleophilic substitution with various primary amines to introduce the first diversity. The proton NMR showed the complete conversion of **2** to **3** in 5 min under microwave irradiation. Polymer immobilized *o*-nitrophenylamino ester **3** was treated with a suspension of Zn/NH_4Cl in methanol for 6 min in a microwave cavity to afford immobilized diamine **4**.[8] Synthesis of potential scaffold intermediates was performed successfully under multi-step microwave irradiation in open vessel system. We found that no cleavage of

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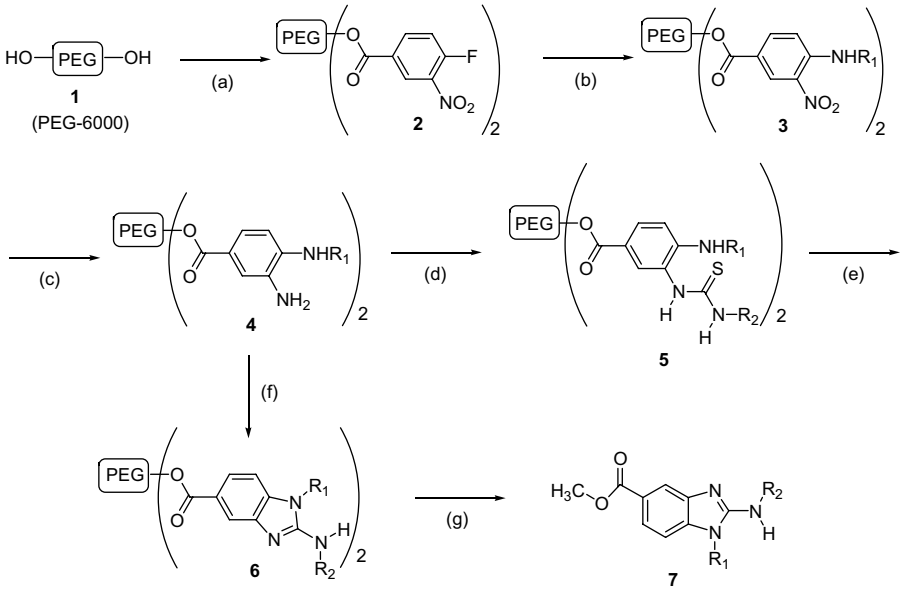
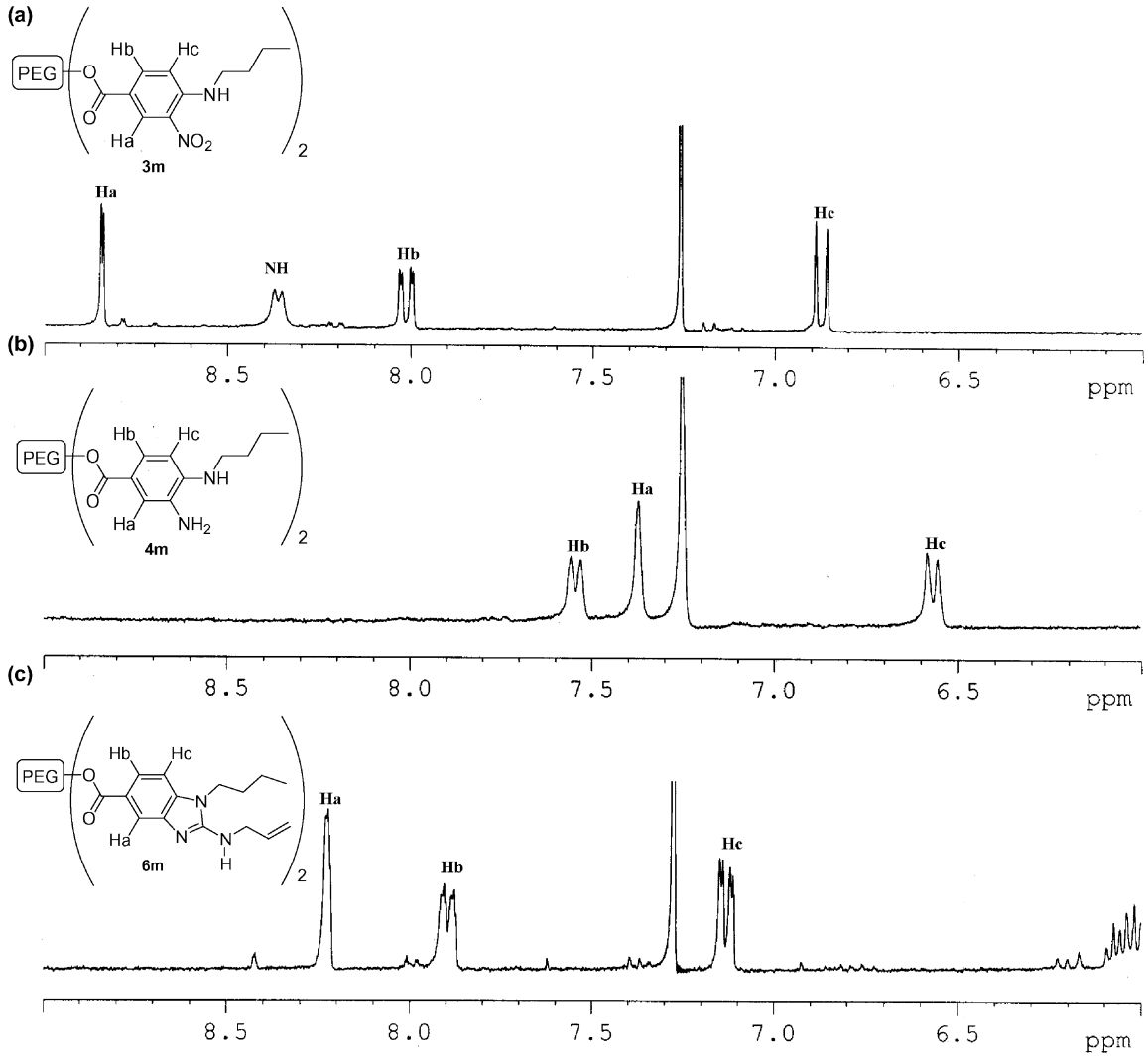


Scheme 1. Reagents and conditions: (a) 4-fluoro-3-nitrobenzoic acid, DCC, cat DMAP, CH_2Cl_2, MW (300 W), 5 min; (b) R_1NH_2, CH_2Cl_2, MW (300 W), 5 min; (c) Zn, NH_4Cl, CH_3OH, MW (100 W), 6 min; (d) R_2NCS, Et_3N, CH_3OH, MW (200 W), 15 min; (e) $HgCl_2$, Et_3N, $CHCl_3$, MW (200 W), 20 min; (f) R_2NCS, $HgCl_2$, Et_3N, $CHCl_3$, MW (200 W), 4 min; (g) CH_3ONa, CH_3OH, MW (100 W), 8 min.



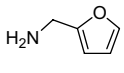
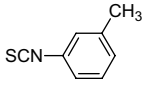
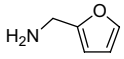
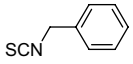
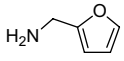
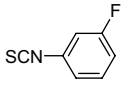
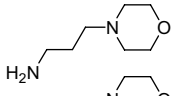
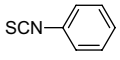
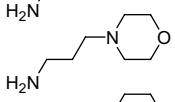
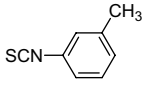
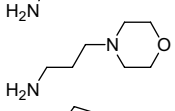
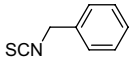
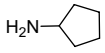
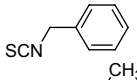
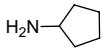
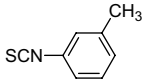
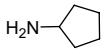
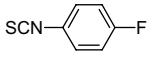
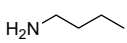
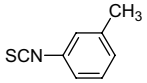
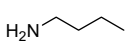
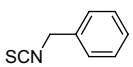
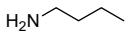
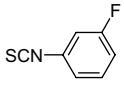
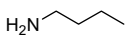
Scheme 2. ^1H NMR monitoring of a stepwise benzimidazole (**6m**) formation.

O—C═O bond at the polymer attached site was observed during the harsh MW irradiation. To verify the extent of reduction, small portion of polymer-supported products were cleaved and checked by ^{1}H NMR.

The next step is completing the synthetic sequence by key ring closure of PEG bound *o*-phenylenediamine **4**. The diamine moiety was then first converted to thiourea derivative followed by intramolecular cyclization to the benzimidazoles. Reaction of **4** with alkyl and aryl isothiocyanates gave *N*,*N*′-disubstituted thiourea **5** in 3 h by conventional thermo heating in methanol, whereas the same reactions were complete in 15 min under microwave irradiation. No undesired dithiourea formation was observed after cleavage of intermediates **5** under both reaction conditions. Subsequent treatment of thiourea **5** with mercury chloride and triethylamine delivered the desired compound **6** via intermolecular cyclization after 20 min microwave flash heating. By the use of regular heating, the reaction was done after 4 h. However, we found the cyclodesulfurization of polymer bound diamines **4** in one pot did occur with isothiocyanates and mercury chloride, which provided a more efficient route to the targeted compounds **6**. In Scheme 2, we demonstrated how the conventional ^{1}H NMR spectroscopy was used to monitor the preparation of compound **6m** without cleaving the compounds from the support. With this nondestructive monitoring method and experiences, each intermediate could be investigated thoroughly using standard ^{1}H NMR spectroscopy.

The intermolecular cyclization was then investigated using $HgCl_2$ and triethylamine in chloroform to form 1,2-disubstituted benzoimidazoles **6**. The insoluble mercuric sulfide formed is easily removed by using fluted filter paper before precipitation and washing of polymer bound intermediate. The same reaction was also carried out in single mode microwave irradiation and reaction time was reduced to 4 min without cleavage of polymer support.[9] Following ether and ethanol washes after precipitation, desired products **7** are liberated from the support by using sodium methoxide/methanol in order to confirm the structure. The transformation is successful in microwave cavity for 8 min judged by proton NMR to avoid resin imposed analytical limitations. By employing the desired reaction sequence, a validation

Table 1. Mercury chloride mediated cyclization toward benzimidazoles

Entry	R_1NH_2	R_2NCS	Crude yield[a] (%)	Crude yield[b] (%)	Mass
7a			98	87	361
7b			97	75	361
7c			85	73	365
7d			90	96	394
7e			99	89	408
7f			93	90	408
7g			99	77	349
7h			99	73	349
7i			99	88	335
7j			99	81	337
7k			99	77	337
7l			81	80	341
7m			97	90	287

[a] Determined based on weight of crude sample.
[b] Purity determined by HPLC analysis of crude products. Products show satisfactory ^{1}H NMR and MS data.

library containing compounds is synthesized. The structure, yield, and purity obtained for a diverse set of compounds are summarized in Table 1. Each crude product was analyzed by HPLC, which showed around 73–90% of purity.

In conclusion, we have successfully demonstrated a novel mercury(II)-catalyzed liquid phase synthesis of benzimidazoles. In each step of the reaction sequence, the immobilized intermediates were purified by simple precipitation and washing after microwave heating in open vessel system.[10] This synthetic design permits the introduction of a diverse array of substituents into the two positions of the benzimidazole skeleton. Crude products are usually obtained in high purity and high yields just by simple precipitation and washing after microwave irradiation, providing their direct use in biological assays without any purification. Synthesis and screening of focused combinatorial libraries based on pharmacophoric scaffold may lead to the discovery of interesting biological activities.

Acknowledgements

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9. The control reaction was also performed under normal thermal heating in refluxing chloroform (preheated oil bath) for 4 min, using identical stoichiometry. However, after cleavage we obtained only the un-reacted compound **4**. The same reaction was found completion in six hours by conventional heating. Similar enhancement through microwave irradiation has also been observed during the cleavage step. Compared to conventional thermal hearting, microwave irradiation decreased the reaction time on the support from several hours to several minutes.
10. All the microwave assisted polymer-supported reactions described here were performed in CEM Discover Microwave System at a frequency of 2450 MHz (0–300 W).