Microwave-Assisted Benzimidazole Cyclization by Bismuth Chloride

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Received 1 March 2005

Abstract: We have developed a multi-step, microwave-assisted method for the bismuth chloride catalyzed synthesis of 1,2-disubstituted benzimidazoles. Biologically interesting benzimidazoles were readily assembled using a S_NAr reaction, reduction, and finally a bismuth(III)-mediated cyclization under microwave irradiation. The desired products were then liberated from the soluble matrix in excellent yield and purity after cleavage. Each step of the synthetic sequence was performed under microwave conditions.

Key words: bismuth chloride, combinatorial chemistry, liquid-phase method, microwave assisted synthesis, scaffold

In recent years, design and synthesis of pharmacologically relevant heterocyclic molecules by combinatorial techniques has caught the imagination of medicinal chemists.[1] The application of microwave irradiation to combinatorial chemistry results in a powerful tool accelerating the pace of library synthesis.[2] A domestic microwave oven is most often 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. The major aim of this integrated technology is to exploit the high degree of molecular diversity and as well as utilize high-throughput organic synthesis to rapidly access the greatly expanded library of drug-like compounds without the need for tedious or time-consuming processes.[3] Convergent, polymer-supported microwave synthesis of discrete chemical entities provides an attractive lead optimization method for the refinement of biological activity. The use of soluble polymer support in combinatorial synthetic methodologies facilitates library synthesis and overcomes the difficulties associated with solid phase reactions.[4] Soluble polymer supported reactions are easily monitored by conventional analytical methods.[5]

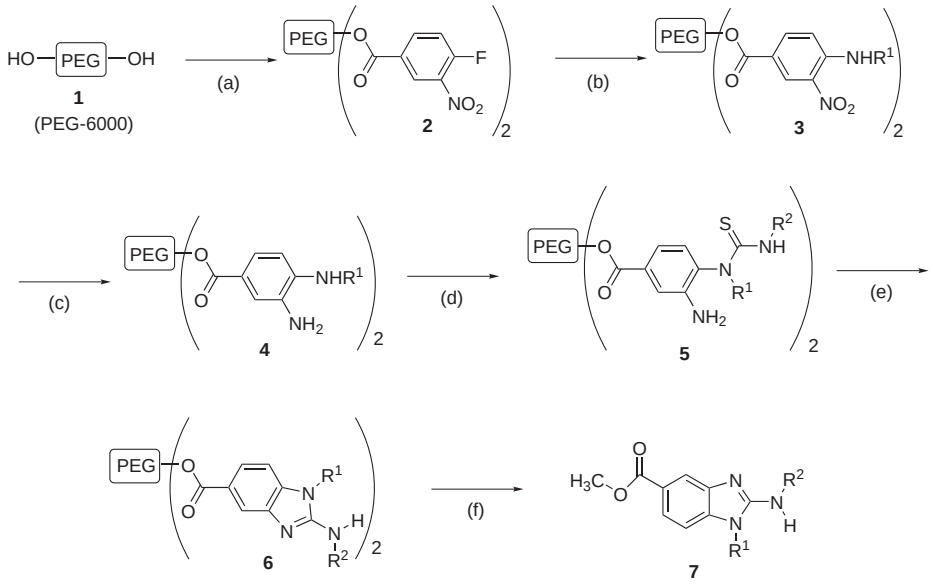
The benzimidazole moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including anti-ulcer, anti-tumor and anti-viral effects.[6] Therefore, a general method to rapidly synthesize benzimidazoles would be greatly advantageous and warrants further investigation. Although a number of solid-phase approaches for benzimidazole synthesis have been reported,[7] bismuth chloride catalyzed benzimidazole cyclization on soluble polymer support by microwave irradiation is unknown.[8]

SYNLETT 2005, No. 8, pp 1243–1246
Advanced online publication: 21.04.2005
DOI: 10.1055/s-2005-865240; Art ID: U05505ST

The first step of this convergent synthesis toward the targeted compounds involved the ligation of 4-fluoro-3-nitrobenzoic acid to the polymer 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 aromatic nucleophilic substitution with various primary amines, resulting in a diverse range of polymer-bound aryl amines. The ^1H NMR spectrum showed the conversion of **2** to **3** was complete in five minutes under microwave irradiation (Figure 1). Polymer immobilized *o*-nitrophenylamino ester **3** was treated with a suspension of Zn/NH_4Cl in methanol for six minutes under microwave irradiation to afford the corresponding immobilized diamine **4**.[9] All intermediates were synthesized successfully by multi-step microwave irradiation in an open vessel system. We did not find any cleavage of O–C=O bond during the harsh MW irradiation.

The next key step is the ring closure of PEG-bound *o*-phenylenediamine **4**. Recently, there have been many reports on the applications of a remarkable Lewis acid catalyst $BiCl_3$ in a range of organic transformations.[12–15] Most bismuth compounds are ecologically friendly, widely used in medicine, inexpensive, and easy to handle. Also, these compounds are crystalline and relatively non-toxic and non-carcinogenic.

To the best of our knowledge, there is no report to describe bismuth chloride promoted benzimidazole formation. In our preliminary study, the cyclization of polymer-bound diamines did not occur with isothiocyanates and bismuth chloride in a one-pot reaction. However, we realized that benzimidazoles were obtained when the diamine moiety was first converted to its thiourea derivative followed by intramolecular cyclization. Reaction of **4** with alkyl and aryl isothiocyanates gave *N*,*N*′-disubstituted thiourea **5** in three hours by conventional heating in methanol, but the same reactions were completed in 15 minutes under microwave irradiation. No undesired dithiourea formation was observed after cleavage of intermediates **5** under both types of reaction conditions. The conversion of diamines to the thiourea derivative by using isothiocyanates can be done in two ways (Scheme 2). Either it can be performed before the reduction of the nitro group or after reduction to the amine moiety, neither affected the formation of thiourea. The presence of a strong electron-withdrawing group on the benzene ring did not inhibit the reactivity of the secondary amine. Both of these products can be cleaved to deliver the same compound **9**.



Scheme 1 *Reagents and reaction 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) $BiCl_3$, Et_3N, $CHCl_3$, MW (200 W), 4 min; (f) CH_3ONa, CH_3OH, MW (100 W), 8 min.

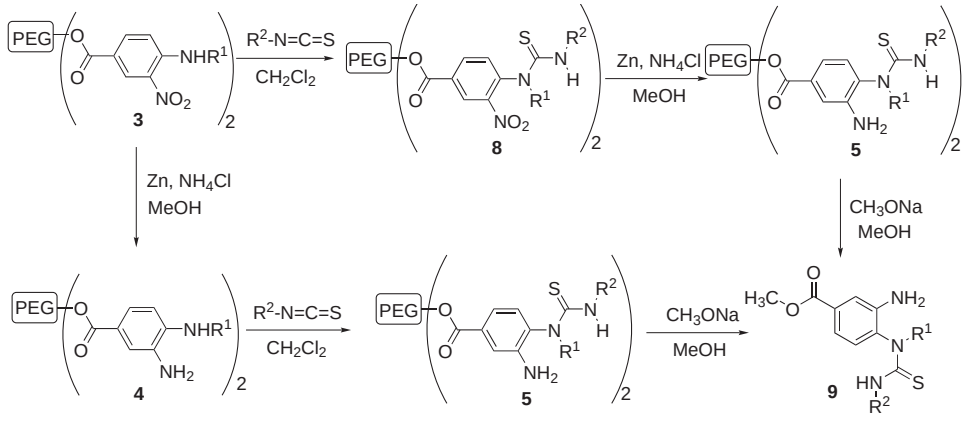
Figure 1 shows how conventional ^1H NMR spectroscopy was used to monitor the preparation of benzimidazoles on the soluble polymer support. With this non-destructive monitoring method, each intermediate could be investigated thoroughly using standard ^1H NMR spectroscopy.

The intramolecular cyclization was then performed using $BiCl_3$ and triethylamine in chloroform to form 1,2-disubstituted benzimidazoles **6**. The bismuth chloride can be easily removed by filtration using celite, before continuing with the work-up, precipitation, and washing of the polymer-bound intermediate. The same reaction was carried out under microwave irradiation and the reaction time was reduced to four minutes without cleaving the polymer support.[10] In the absence of microwave irradiation it took two hours to complete the reaction by conventional heating. After washing the precipitate with diethyl ether and ethanol, desired products **7** are liberated from the support by using sodium methoxide/methanol. This transformation, monitored by TLC, was complete in eight minutes under microwave irradiation. 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 70–94% purity.

In conclusion, we have successfully demonstrated a novel bismuth(III)-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 an open-vessel system.[11] Crude products are usually obtained in high purity and high yields just by simple work-up after microwave irradiation. Synthesis and screening of focused combinatorial libraries based on pharmacophoric scaffolds may lead to the discovery of interesting biological activities.

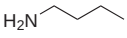
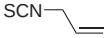
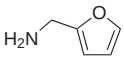
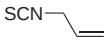
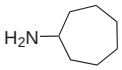
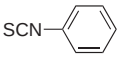
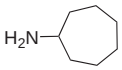
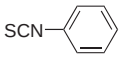
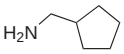
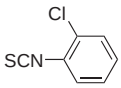
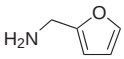
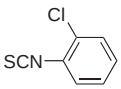
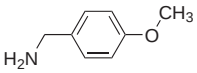
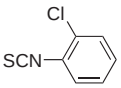
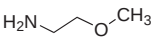
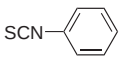
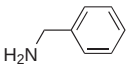
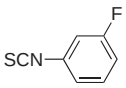
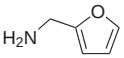
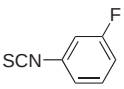
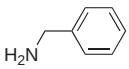
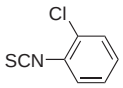
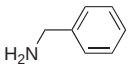
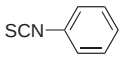
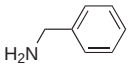
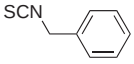
Acknowledgment

We thank the National Science Council of Taiwan for general financial support.



Scheme 2 Different routes used for the preparation of the thiourea derivative.

Table 1 Bismuth Chloride Catalyzed Cyclization toward Benzimidazoles **7**

Entry	R^1NH_2	R^2NCS	Crude yield[a] (%)	Crude purity[b] (%)	Mass
7a			92	85	287
7b			87	81	311
7c			95	84	390
7d			99	90	363
7e			99	90	369
7f			99	81	381
7g			99	85	421
7h			99	89	325
7i			99	86	375
7j			99	85	365
7k			99	74	391
7l			99	94	3576
7m			99	70	371

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

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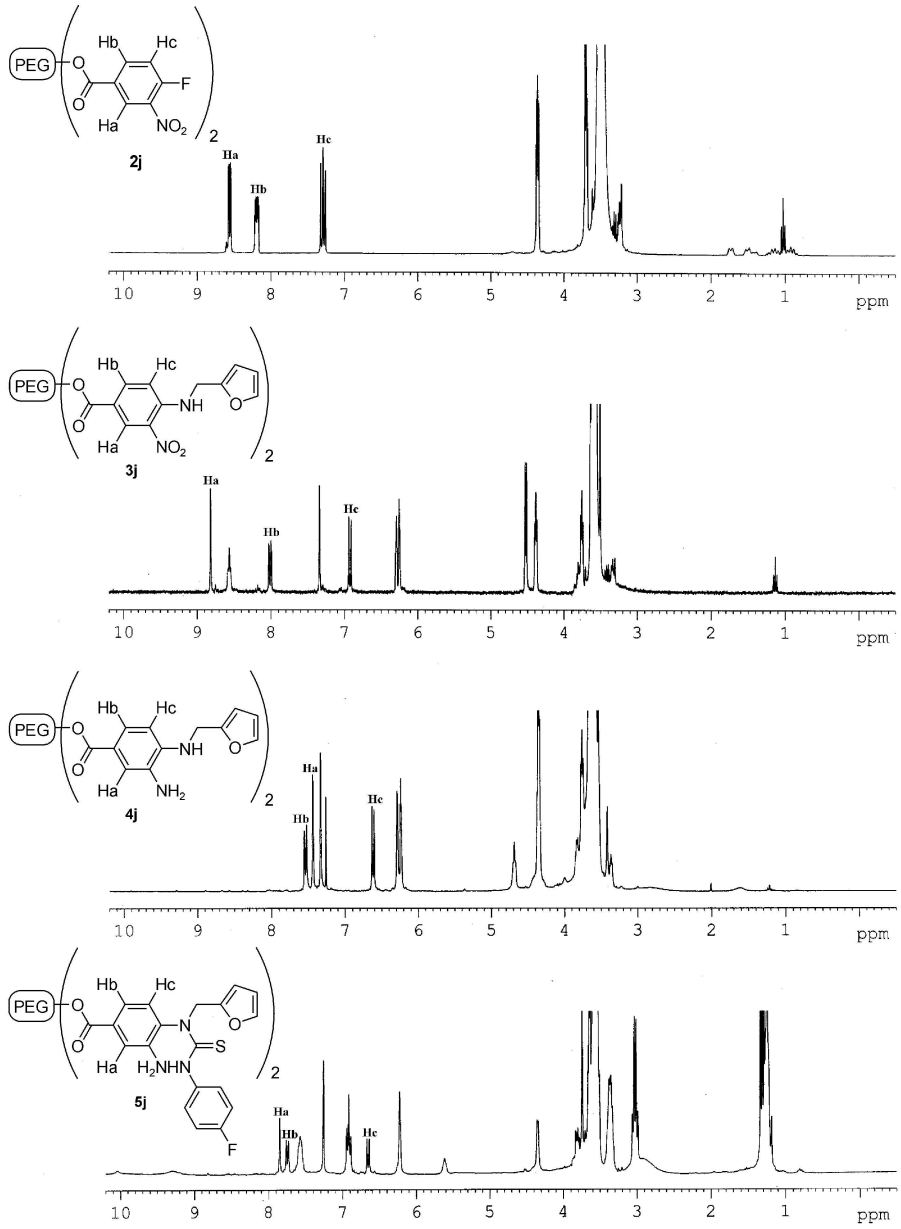

Figure 1 ^{1}H NMR monitoring of a stepwise benzimidazole formation.

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(10) The control reaction was also performed under normal thermal heating in refluxing chloroform (pre-heated oil bath) for four minutes, using identical stoichiometry. However, after cleavage we obtained only the unreacted compound **4**. The same reaction reached completion in two hours by conventional heating. Similar enhancement through microwave irradiation was also 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.

(11) All the microwave assisted polymer-supported reactions described here were performed in a CEM Discover Microwave System at a frequency of 2450 Hz (0–300 W).

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