Combinatorial Synthesis of Biheterocyclic Benzimidazoles by Microwave Irradiation

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Abstract: Liquid phasel synthesis of biheterocyclic benzimidazoles by controlled microwave irradiation was investigated. Polymer immobilized *o*-phenylenediamines was synthesized under microwave irradiation. The resulting PEG bound diamines was N-acylated with 4-fluoro-3-nitrobenzoic acid selectively in primary aromatic amino moiety. Nucleophilic aromatic substitution of amide was performed with various amines then cyclized to form the first benzimidazole scaffold in acidic condition. Successive reduction, cyclization with isothiocyanates yielded 5-(benzimidazol-2-yl)benzimidazoles. The desired products were released from the polymer support to afford the tri-substituted bis-benzimidazoles in good yields and purity.

Keywords: microwave irradiation, biheterocyclic benzimidazole, combinatorial synthesis.

In order to explore biological probes systematically by the use of small molecules, it will require preparing structurally diverse libraries in a wide population of chemical space [1]. Combinatorial chemistry provides a fast access to large quantities of compound collection to aim this need. In recent years, design and synthesis of pharmacologically relevant scaffolds by combinatorial techniques are the practical goals to the medicinal chemists [2]. The use of soluble polymer support in combinatorial synthesis facilitates the library preparation [3] and overcomes the experiencing difficulty of solid phase reactions [4]. 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. It is worthy to note that, in contrast to the various restrictions on the analysis of solid-phase reaction development, liquid-phase synthesis allows routine analytical instruments to monitor reaction progress without *cleave-&-analyze* follow-up [5].

Application of microwave irradiation to the combinatorial library synthesis is emerging as a powerful tool to enhance the effectiveness to deliver a large collection of drug-like molecules [6]. The rapid and thermal quench reactions by microwave irradiation often lead to decrease reaction time remarkably and fit into green chemistry protocols. 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.

Benzimidazole is an important heterocyclic scaffold in drug design since its derivatives are known for their diverse pharmacological significance [7]. In particular bisbenzimidazoles, containing benzimidazole repeating structural motif, are receiving considerable prominence due to their potential therapeutic applications [8] (Fig. (**1**)). For example, Telmisartan containing bisbenzimidazole core scaffold is a nonpeptidic angiotensin II receptor antagonist which plays an important role in the control of blood pressure [9]. Most notably Pibenzimol has two benzimidazoles linked in a head-to-tail manner which is capable to penetrate mammalian cells and exhibits anticancer activity through DNA minor groove binding at AT specific region [10-11]. To assess a broader population of chemical space of molecules associated with biological activities, the designing bisbenzimidazole libraries [12] could be developed with altered and extended sequence-selective preferences, some of which may be used as artificial gene regulation [13]. Most of reported procedures described synthesis of bisbenzimidazoles through the condensation of substituted benzaldehydes or imino ether hydrochloride with 1,2-diamino benzene [14]. In continuation with our research interest focusing on development of multifunctional benzimidazole library, we describe here the combinatorial microwave-assisted synthesis of bisbenzimidazoles on the soluble polymer support with three points of diversity [15].

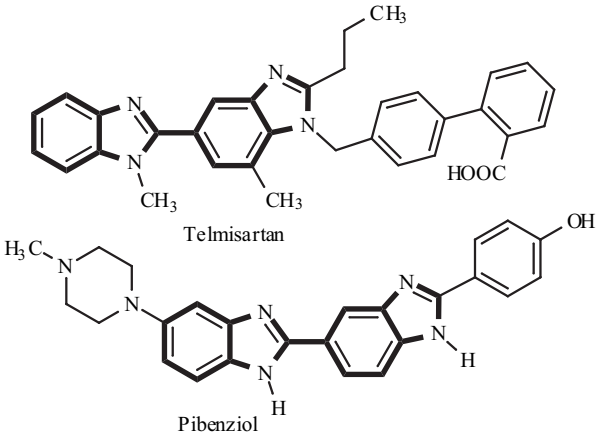

Fig. (1). Biological active biheterocyclic benzimidazoles.

Our convergent synthesis toward the targeted compounds was to couple 4-fluoro-3-nitrobenzoic acid to the polymer support **1** by dehydrative esterification. Rapid conversions were achieved by exposing substrate with DCC and DMAP in dichloromethane to open vessel microwave irradiation (Scheme 1). The resulting PEG bound *o*-fluoronitrobenzene **2** was subjected to *ipso*-fluoro displacement with various

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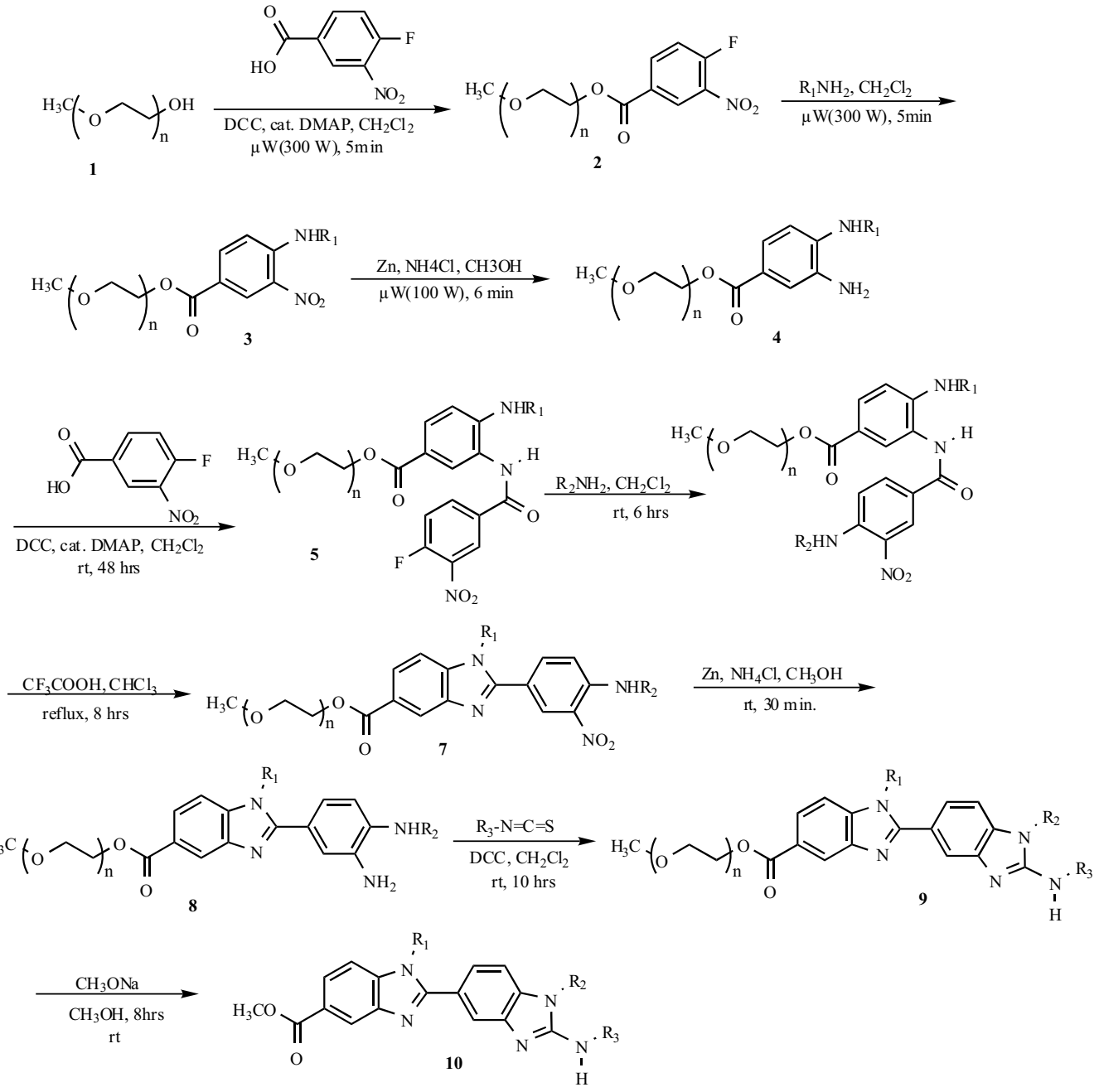
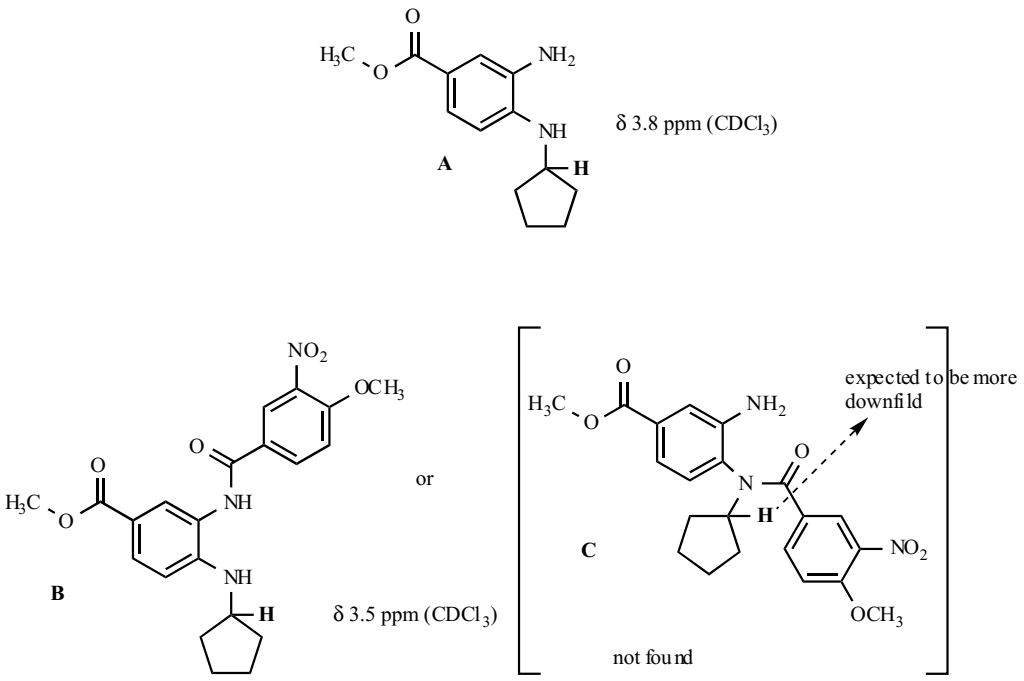
primary amines in 5 minutes under microwave irradiation. Polymer immobilized *o*-nitrophenylamino ester **3** was treated with Zn/NH_4Cl in methanol for 6 minutes in a microwave cavity. Synthesis of potential scaffold intermediates was performed successfully under microwave irradiation [16]. The PEG bound diamines **4** were then used as versatile templates for the synthesis of biheterocyclic analogs. In view to generate bisbenzimidazole libraries, polymer bound *o*-phenylenediamine was further extended by acylation with 4-fluoro-3-nitrobenzoic acid in the presence of DCC and catalytic amount of DMAP as described to prepare **5**. Completeness of the coupling was monitored by the conventional ^1H NMR.

In the case of the unsymmetrical 1,2-diaminobenzene **4**, two possible regioisomers may be obtained after acylation, depending on which of the ring nitrogen atom was reacted with the 4-fluoro-3-nitrobenzoic acid. During our mechanistic studies, it was found that only the primary amine reacted with 4-fluoro-3-nitrobenzoic acid to give substituted amides **5**. This was confirmed by proton NMR spectroscopy since the methine proton (CH) of the cyclopentyl substituent of released product was shifted upfield from 3.8 ppm (**A**) to 3.5 ppm (**B**). If 4-fluoro-3-nitrobenzoic acid was attached to more congested amine (like **C**), the methine proton (**C**) is expected to shift to more downfield position after cleavage from the support.

Therefore N-acylation most likely proceeded via the primary amine moiety due to the less relative steric congestion. Although secondary amine moiety of **4** is more nucleophilic, steric hindrance of DCC-DMAP-carboxylic



Scheme 1. Synthesis of bis-benzimidazoles **10** on the support.



Scheme 2. Two possible regioisomers obtained after acylation of polymer bound o- phenylenediamines.

acid complex may interfere the coupling with more bulky amine functional group. Furthermore, plausible fluorine replacement of 4-fluoro-3-nitrobenzoic acid at either amino group of compound **4** was not observed during the second coupling template (Fig. (**2**)). Thus obtained polymeric ester **5** served as a versatile template to condense with various primary amines via an *ipso*-fluoro displacement. The reaction proceeded smoothly at room temperature to yield >98% of products **6**. Trifluoroacetic acid (TFA) served the purpose of dehydrative cyclization to create the first benzimidazole moiety of the present scheme. Treatment of compound **6** with TFA at refluxing chloroform for overnight was sufficient to complete cyclodehydration to generate *o*-nitroaniline **7**.

Reduction of the nitro group on *o*-nitroaniline tethered at benzimidazole core was accomplished to afford polymer-supported *o*-phenylenediamine **8** by convenient Zn/NH_4Cl cocktail in methanol [17]. This reaction condition is particularly useful to prepare *o*-nitroaniline compared to that of well-established tin (II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) reagent if rapid, mild reduction is required on the support. Elaboration of compound **8** into the desired bis-benzimidazoles **9** was readily performed by the cyclization with various alkyl and aromatic isothiocyanate at room temperature. Progress of the cyclization reaction was easily monitored by regular proton NMR spectroscopy. No trace of the uncyclized compounds was observed after 10 hrs stirring. Upon completion of reaction, insoluble DCU (dicyclohexyl thiourea) was removed first by filtration, and PEG-bound bis-benzimidazoles **9** were precipitated selectively by adding diethyl ether to the reaction mixtures. To this end, polymer support was separated after sodium methoxide cleavage to isolate methyl ester of tri-substituted bisbenzimidazoles **10** in 71-93% yield and 73-92% HPLC purity (Table 1). 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 ppm to δ 3.6 ppm. In most cases, the cleavage reactions were done overnight. Their ^1H NMR, ^{13}C NMR and Mass spectral data confirmed structures of all the final products [18].

In summary, we have described here a rapid and convenient protocol for the construction of pharmacologically interesting biheterocyclic benzimidazoles through the use of commercially available building blocks. The coupling of microwave technology with liquid phase synthetic strategy constitutes a novel and attractive avenue

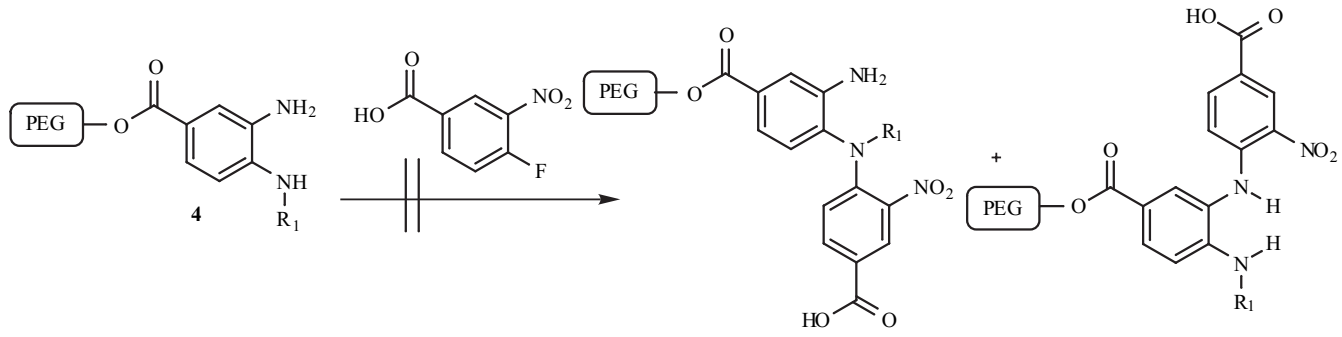
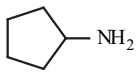
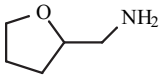
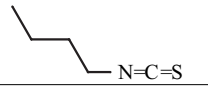
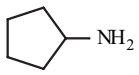
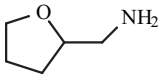
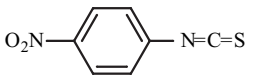
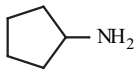
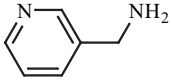
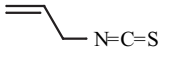
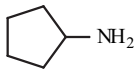
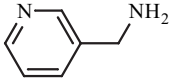
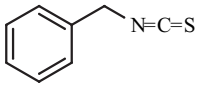
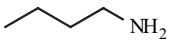
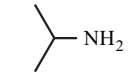
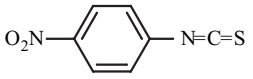
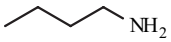
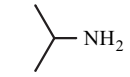
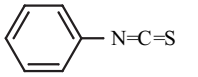
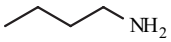
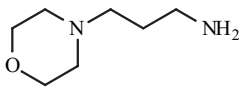
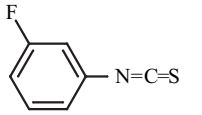
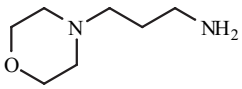
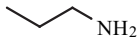
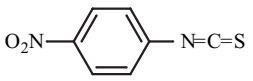
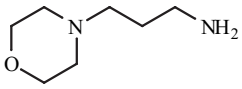
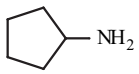
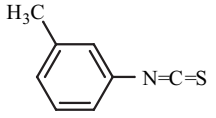
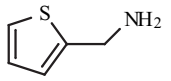
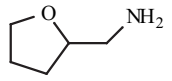
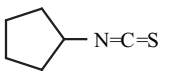
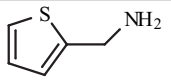
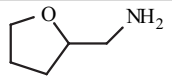
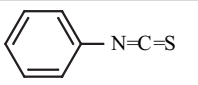
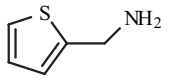
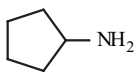
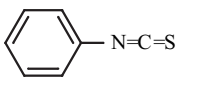
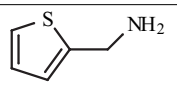
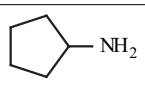
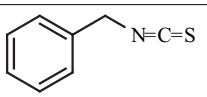


Fig. (2). Plausible fluorine repelacement is not found.

Table 1. Reperesetative Products and Results of Bis-Benzimidazoles

Entry	R_1NH_2	R_2NH_2	R_3-N=C=S	Mass	Yield[a]	Purity[b]
10a				515	82%	74%
10b				580	86%	93%
10c				506	71%	77%
10d				556	83%	86%
10e				526	74%	85%
10f				481	93%	85%
10g				584	80%	82%
10h				611	92%	92%
10i				592	80%	82%
10j				559	87%	93%
10k				563	90%	92%
10l				547	88%	86%
10m				561	88%	90%

a. Yield were determined on weight of crude sample

b. Purity determined by HPLC analysis of crude products, all products shows satisfactory ^{1}H NMR and Ms (MH^+, FAB) data.

for the rapid generation of structurally diverse libraries. Biological activities of synthetic libraries will be reported in due course.

ACKNOWLEDGEMENTS

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[18] Analytical data for cleaved compound **10f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.5 Hz, 1 H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.79 (s, 1 H), 7.51~7.42 (m, 5 H), 7.33~7.27 (m, 2 H), 7.25 (s, 1 H), 7.01 (m, 1 H), 4.67 (Sept, *J* = 6.9 Hz, 1 H), 4.30 (t, *J* = 7.5 Hz, 2 H), 3.94 (s, 3 H), 1.83~1.73 (m, 2 H), 1.58 (d, *J* = 6.9 Hz, 6 H) 1.28~1.21 (m, 2 H), 0.84 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 M Hz, $CDCl_3$) δ 167.8, 156.6, 150.6, 142.7, 140.7, 139.0, 133.7, 129.3, 124.4, 124.0, 123.0, 122.7, 122.5, 121.9, 118.7, 110.7, 109.8, 52.13, 47.4, 44.9, 31.9, 21.1, 20.0, 14.1; IR (cm^{-1}, neat): 2965, 2929, 1713, 1614, 1461, 1299; Mass spectrum (EI) m/z 481 (M^+). Exact mass calculated for $C_{29}H_{31}N_5O_2$: m/z 481.2478. Found 481.2467.

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