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High-throughput combinatorial synthesis of substituted benzimidazolones

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Abstract

An efficient liquid-phase synthesis of substituted benzimidazolones **7** is described. Resin bound *o*-fluoronitrobenzene **1** is reacted with various primary amines to afford *o*-nitroaniline derivatives **2**. Subsequent reduction of the aromatic nitro group followed by cyclization gives a PEG bound benzimidazole-2-one **4**. *N*-Alkylation of this resin bound scaffold **4** with several electrophiles gives the resulting library in excellent yield and purity after cleavage.

Combinatorial chemistry[1–3] has emerged as an increasingly powerful tool for accelerating a drug discovery program. Solid-phase organic synthesis, which is the core technology of combinatorial chemistry, offers the opportunity for rapidly synthesizing drug-like molecules without tedious and time-consuming purification. However, such an approach requires a great deal of research time and effort to work up synthetic conditions on solid support. As part of our program toward development of library synthesis, we investigated possible routes for generating heterocyclic libraries by the use of soluble polymer support.[4–7] This macromolecular carrier, in contrast to an insoluble matrix, is soluble in most organic solvents and has a strong tendency for precipitation in particular solvents. After a reaction is complete, the product remains covalently bound to the support, and purification is generally carried out after precipitation simply by filtering and washing away the unwanted material. Furthermore, this method allows routine analytical methods (e.g. ^{1}H, ^{13}C NMR, IR, TLC) to monitor reaction progress and characterization without following the cleave-&-analyze technique.

Substituted benzimidazolones **7** have proven to be crucial as drug leads which have elicited considerable pharmacological interest.[8,9] In addition, 2-substituted benzimidazoles cover a broad range of biological activities, including anti-ulcer, antitumor and antiviral effects.[10,11] Therefore, a general method of rapidly synthesizing analogues of benzimidazolone would be greatly advantageous and warrants further investigation for drug discovery.[12–15] In our continuing research efforts to adapt heterocyclic methods to a high-throughput synthesis format, we report the first liquid phase synthesis of this important class of compounds by the use of soluble polymer support.[16]

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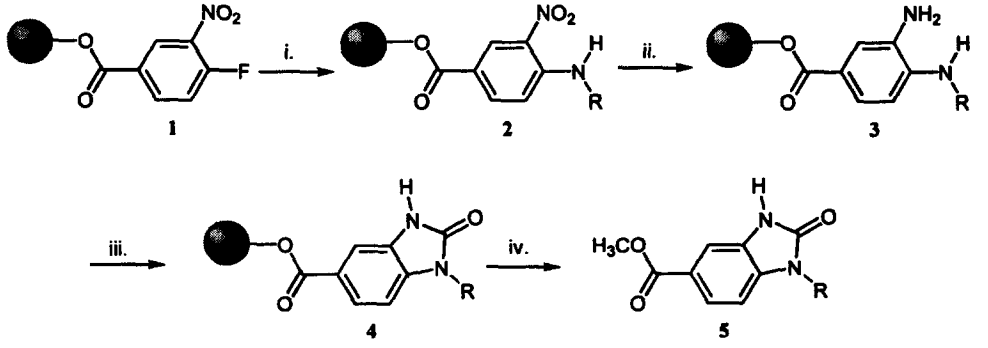
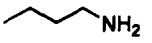
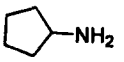
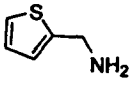
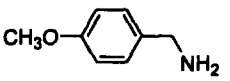
The synthetic route described in Scheme 1 is utilized for the synthesis of a representative library. PEG resin is coupled with the commercially available 4-fluoro-3-nitrobenzoic acid through the DCC/DMAP activation to give the resin-bound fluoro-nitro aryl intermediate **1** in quantitative yield.[7] This intermediate has previously been shown to undergo nucleophilic aromatic substitution of the fluorine group with secondary piperazine on the solid support.[17] The first point of diversity of **1** is then incorporated by several primary amines via an *ipso*-fluoro displacement to give polymer bound nitroanilines **2**. The reaction proceeds well with various amines without cleavage of the O–*C*=O bond at the polymer attached site. After attempting several methods to reduce the aryl nitro group of **2**,[18] we have concluded that Zn/NH_4Cl-mediated reduction of the nitro group in methanol to polymer bound diamine **3** is the most efficient method.[19] The heterogeneous catalyst is removed first by filtration and the polymer-bound diamine **3** is purified by precipitation. The remaining step for completing the synthetic sequence involves key cyclization of **3** with triphosgene. This transformation is performed smoothly in the presence of triethylamine to give compound **4** at room temperature. Benzimidazolone formation with DSC (disuccinimidocarbonate) does not give satisfactory results because of poor solubility of DSC in methylene chloride.[20] In order to assess the efficiency of cyclization, compounds (**5a–5e**) are liberated from the support to confirm the desired structures in good yield and good purity (Table 1). To further expand the scale and introduce an additional diversity element into the library of the targeted molecules, polymer bound benzimidazoles **4** are deprotonated by NaH followed by quenching with various alkyl and benzylic halides to give the fully functionalized benzimidazolones **6** (Scheme 2). *N*-Alkylation proceeds smoothly after standing overnight at room temperature. This transformation is successful as judged by ^1H NMR analysis to avoid resin-imposed analytical limitations. Following ether and ethanol washes after precipitation, polymer-supported alkylated products **6** are subjected to a very efficient cleavage from the support with sodium methanolate in methanol to provide the targeted compounds in 81–98% overall yield for six steps (Table 2). By employing the desired reaction sequence, a validated library containing a diverse set of compounds is synthesized. The structures, yields and purities obtained for representative sets of compounds are summarized in Table 2.[21] Each crude product is then analyzed by HPLC, which shows around 84–96% purity. Because compound libraries are usually not purified before biological screening, crude products of high purity obtained from our liquid-phase protocol is especially valuable.



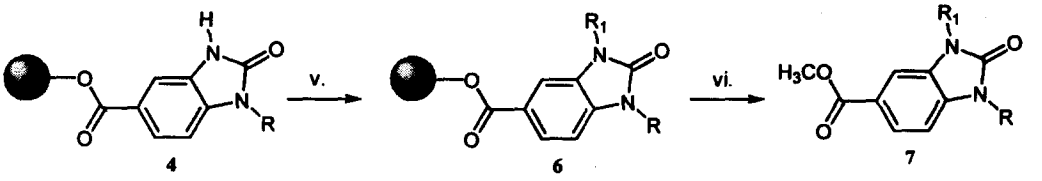
Scheme 1. Reagents and conditions: (i) RNH_2 (1.2 equiv.), CH_2Cl_2, rt, 1 h. (ii) Zn (20 equiv.), NH_4Cl (6 equiv.), CH_3OH, rt, 3 h. (iii) triphosgene (3 equiv.), Et_3N (5 equiv.), CH_2Cl_2, rt, 8 h. (iv) 1% KCN, CH_3OH, rt, 10 h

To the best of our knowledge, this is the first example for the synthesis of a benzimidazolone library by the liquid phase methodology using soluble polymer support. Crude products are usually obtained in high purity and high yield just by simple precipitation and washings, providing their direct use in biological assays without any purification. This method should decrease the difficulties of adapting established solution-phase precedents to polymer-supported reactions since reactions can be carried out

Table 1
Liquid phase synthesis of benzimidazole-2-ones

Entry	RNH_2	Observed MS	Crude yield[a] (%)	Crude purity[b] (%)
5a		248	88	85
5b		248	79	81
5c		260	75	89
5d		288	96	86
5e		308	90	77

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



Scheme 2. Reagents and conditions: (v) NaH (10 equiv.), R_1CH_2X (2 equiv.), rt, 10 h. (vi) NaOMe (2 equiv.), MeOH, rt, 8 h

in homogeneous solution. All reactions involved are highly efficient in giving the desired compounds at room temperature. This method of synthesis is versatile and produces compounds with known pharmacophoric scaffolds, and which are thus ideally suited for combinatorial library generation.

Acknowledgements

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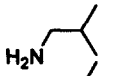
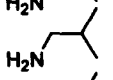
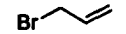
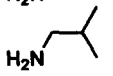
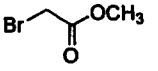
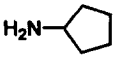
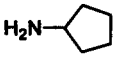
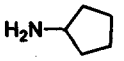
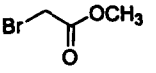
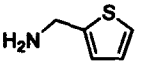
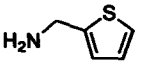
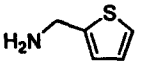
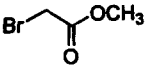
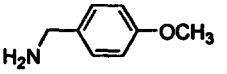
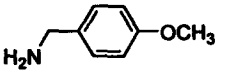
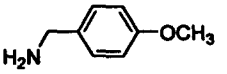
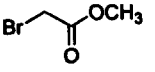
Table 2
Liquid phase synthesis of 1-alkyl-2-alkylthio-5-carbamoylbenzimidazoles

Entry	R_1NH_2	R_2X	Crude yield[a] (%)	Crude purity[b] (%)
7a		CH_3CH_2I	89	85
7b			98	92
7c			90	93
7d		CH_3CH_2I	89	91
7e			85	90
7f			91	92
7g		CH_3CH_2I	90	88
7h			81	84
7i			87	86
7j		CH_3CH_2I	86	86
7k			95	96
7l			92	92

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

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21. All the compounds listed in Table 2 give satisfactory ^1H NMR, ^{13}C NMR and mass data. The data for **7a** is as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J*=8.1, 1.2 Hz, 1H), 7.69 (d, *J*=1.2 Hz, 1H), 7.01 (d, *J*=8.1 Hz, 1H), 3.99 (q, *J*=7.2 Hz, 2H), 3.94 (s, 3H), 3.71 (d, *J*=7.5 Hz, 2H), 2.21 (m, 1H), 1.37 (t, *J*=7.2 Hz, 3H), 0.94 (d, *J*=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 154.6, 134.0, 129.0, 123.8, 123.1, 108.8, 107.4, 52.3, 49.0, 36.3, 31.2, 28.2, 20.3. IR (KBr) 1698, 1648, 1354. MS (EI): *m/z* 276.95 (M+). HRMS calcd for $C_{15}H_{20}O_3N_2$: 276.1474; found: 276.1472.