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Liquid-phase synthesis of 2-(alkylthio) benzimidazoles

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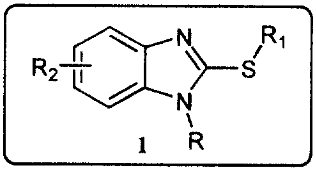
Abstract

An efficient liquid-phase synthesis of 2-alkylthio-5-carbamoylbenzimidazoles **1** is described. Immobilized *o*-fluoronitrobenzene **2** undergoes nucleophilic addition of primary amine to afford *o*-nitroaniline derivatives **3**. Subsequent reduction of the aromatic nitro group followed by cyclization gives a PEG-bound benzimidazole-2-thione **5**. *S*-Alkylation of polymer-supported scaffold **5** followed by cleavage gives the resulting library in high yield and high purity. © 1999 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry[1–3] has been widely regarded as a potentially powerful tool of the accelerating drug discovery progress. Solid-phase synthesis of drug-like molecules offers significant advantages over many conventional solution phase routes to such compounds. However, such an approach requires a great deal of development time and effort to work up synthetic conditions on solid support. In our continuing research effort toward the liquid-phase combinatorial synthesis (LPCS), we are interested in the versatile synthetic methodology to generate libraries by the use of soluble polymer support.[4–6] This macromolecular carrier, in contrast to an insoluble matrix, is soluble in many organic solvents and has a strong tendency to precipitate in ether. After reactions are complete, the products remain covalently bound to the support, and purification is generally carried out after precipitation simply by filtering and washing away the unwanted material. Furthermore, this non-destructive method allows routine analytical methodologies (e.g. ^1H, ^{13}C NMR, IR, TLC) to monitor success of the reaction transformations and to determine structures of compounds directly attached to polymer support.



1

Substituted 2-alkylthiobenzimidazoles **1** have proven to be crucial drug leads which have elicited considerable pharmacological interest. In addition, 2-substituted benzimidazoles cover a broad range of biological activities, including antiulcer, antitumor and antiviral effects.[7–11] Therefore, a general method

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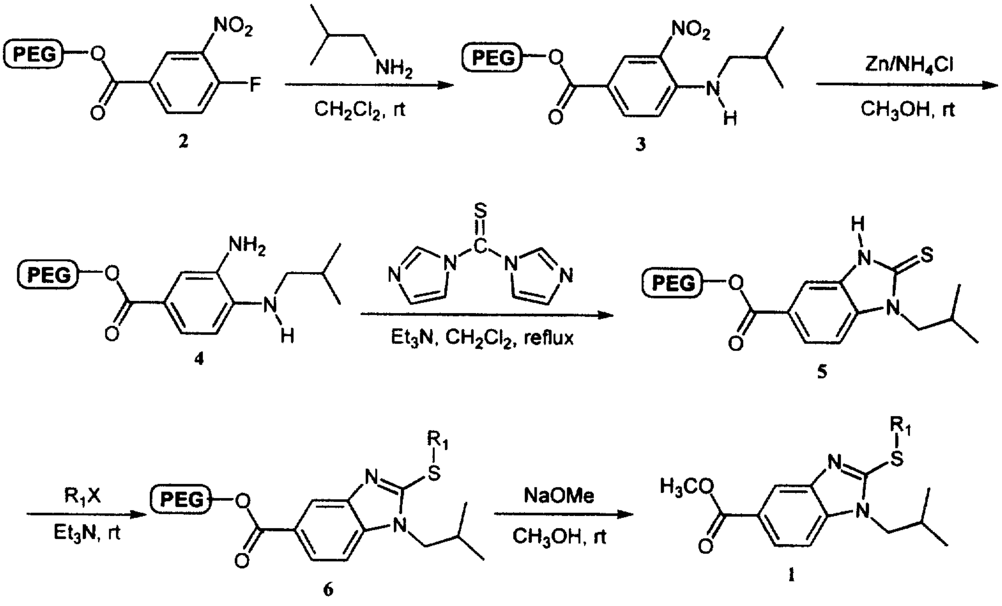
of rapidly preparing analogues of benzimidazoles would be advantageous and merits investigation for drug discovery.[12–14,17] As part of our continuing effort to adapt heterocyclic methods to a high-throughput synthesis format, we report here the first soluble polymer-supported synthesis of 1-alkyl-2-alkylthio-5-carbamoylbenzimidazoles.[15]

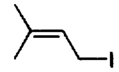
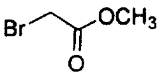
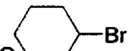
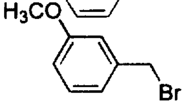
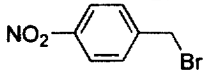
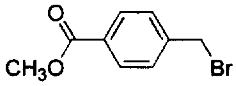
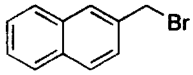
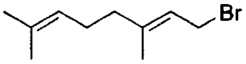
The synthetic route described in Scheme 1 is utilized for the synthesis of a representative library. MeO-PEG-OH is modified with the commercially available 4-fluoro-3-nitrobenzoic acid through the DCC/DMAP activation[6,16] to afford the immobilized *o*-fluoronitrobenzene **2** in quantitative yield. This reaction intermediate has previously been shown to undergo facile S_NAr type reaction with secondary nitrogen-nucleophiles.[6] The first point of diversity is then introduced by nucleophilic aromatic substitution of isobutyl amine with **2** via an *ipso*-fluoro displacement to give polymer-bound nitroanilines **3**. Reactions proceed efficiently with various primary amines without cleavage of the O–C=O bond at the polymer attached site. Reduction of the aryl nitro group in the resulting nitro derivative **3** is successfully accomplished with a suspensible solution of Zn/NH_4Cl in methanol to afford immobilized diamine **4** at ambient temperature.[18] The heterogeneous catalyst is removed by filtration during the work-up and the polymer-bound diamine **4** is purified by precipitation. It should be mentioned that with another system, such as tin(II) chloride mediated nitro reduction does not give satisfactory results.[19] The remaining step to complete the synthetic sequence involves key cyclization of **4** with TCD (1,1′-thiocarbonyldiimidazole). This transformation is performed smoothly in the presence of triethylamine to give compound **5** in the refluxing methylene chloride.



Scheme 1.

In order to increase the diversity of the molecules, polymer-bound benzimidazole **5** is treated with various alkyl and benzylic halides with Et_3N in CH_2Cl_2 (Table 1). *S*-Alkylation proceeded well leading to the expected products after leaving overnight at room temperature. The course of the reactions is easily followed by TLC analysis (observation of disappearing R_1X) and is conveniently estimated by ^1H NMR without detaching material from the support. 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 desired compounds in 72–99% crude yield (Table 1).[20] By

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

Entry	R_1X	Observed MS	Crude yield[a] (%)	Crude purity[b] (%)
1a	CH_3CH_2I	292.94	99	90
1b	$CH_3CH_2CH_2I$	307.77[c]	76	80
1c	$HC\equiv C-CH_2Br$	302.93	80	81
1d	$N\equiv C-CH_2Br$	289.35	84	60
1e		332.46	76	85
1f		336.40	82	72
1g		344.47	72	87
1h		385.16[c]	86	90
1i		399.84	78	87
1j		412.83	81	81
1k		405.09[c]	84	86
1l		400.58	85	74

a. based on loading of original MeO-PEG-OH

b. Purity determined by HPLC analysis (UV detection at λ = 254 nm) of crude products. Products show satisfactory ^1H NMR and MS data. c. M+1 peak (FAB)

varying the positions and functionalization of substituents around the benzimidazole scaffold, libraries composed of a diverse set of compounds could be possibly produced. Each crude product is then analyzed by HPLC and gives around 60–90% purity. Because libraries are usually not purified before screening, crude products of high purity obtained from liquid-phase protocol are especially valuable.

In summary, we have shown liquid-phase methodology for the controlled stepwise synthesis of substituted benzimidazoles. This method should decrease the difficulties of adapting established solution-phase precedents to polymer-supported reactions since reactions can be carried out in homogeneous solution. Although the final products contain a methyl ester group, it can be further transformed to other useful functional groups and is a possible site for another point of diversity. Reactions involved here are highly efficient in giving the desired compounds in high yields and high purity just by simple precipitation and washings. This method of synthesis is versatile and produces compounds with known pharmacophoric scaffolds, and which are thus adaptable for the parallel synthesis of the targeted structures on the soluble polymer support.

Acknowledgements

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20. In a typical procedure for the synthesis of **1k** is as follows: PEG supported benzimidazole-2-thione **5** (506 mg, 0.1 mmol), 2-(bromomethyl)-napthalene (32.1 mg, 0.145 mmol) and triethylamine (0.054 ml, 0.39 mmol) were stirred in 5 mL CH_2Cl_2 for 8 h. After completion, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by addition of *t*-butyl methyl ether. Polymer bound product was then filtered under aspirator pressure using a fritted funnel and washed several times with ether. The crude PEG product was redissolved, precipitated twice and dried in vacuo for the next sequence. The transesterification of alkylated product in NaOMe/methanol was representative for the cleavage procedure: 425.4 mg of polymer-bound *S*-alkylated benzimidazole **6k** is dissolved in 5 mL CH_3OH and NaOMe (15.7 mg, 0.29 mmol) and stirred at room temperature for overnight. The solution was evaporated under vacuum to remove methanol and PEG product was dissolved in 4 mL methylene chloride, precipitated into icy-cold ether. The polymer was filtered and the combined filtrate was dried to give crude product **1k** as a bright yellow solid (32.8 mg, 84%). The crude purity of this compound was determined to be 86% by the HPLC analysis (250×4.6 mm Sphereclone 5μ Si, gradient elution 50% ethyl acetate/hexane, 1mL/min; UV detection at λ=254 nm); ^1H NMR (300 MHz, $CDCl_3$) 8.45 (d, *J*=1.2 Hz, 1H), 7.95 (dd, *J*=8.7, 1.2 Hz, 1H), 7.89 (brs, 1H), 7.79 (m, 3H), 7.55 (dd, *J*=8.4, 1.6 Hz, 1H), 7.46 (m, 2H), 7.24 (d, *J*=8.7 Hz, 1H), 4.83 (s, 2H), 3.95 (s, 3H), 3.84 (d, *J*=7.8 Hz, 2H), 2.19 (m, 1H), 0.91 (d, *J*=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 167.6, 154.0, 142.7, 139.7, 133.7, 133.2, 132.8, 128.5, 128.0, 127.8, 127.6, 126.9, 126.3, 126.1, 124.0, 123.6, 120.3, 108.8, 52.1, 51.7, 37.5, 29.0, 20.1; MS(FAB): *m/z* 405.09 (MH^+).