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Use of polymer supported thiophenol for the synthesis and purification of a benzimidazol-2-one library

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Abstract

An efficient solution phase synthesis of substituted benzimidazol-2-ones is described. Polymer-supported thiophenol is used to remove excess alkylating agents. A library of 24 mono- and di-substituted benzimidazol-2-ones has been prepared in 60–99% yield and 65–99% purity.

Keywords: molecular recognition; alkylation; supported reagents/reactions.

Recent trends in the search for novel pharmacological agents have focused on the preparation of chemical libraries as potential sources of new lead compounds for drug discovery. Combinatorial chemistry and parallel synthesis are the main strategies in creating a wide array of various pharmacophores and optimising molecular diversity. The methodology in this area has utilised the advantages of solid phase organic synthesis, such as separation of reagents from the product by filtration and the use of excess starting materials to drive reactions to completion. Recently several purification strategies for solution-phase combinatorial library synthesis have been reported.[1–3] The method, described by Flynn,[4] and Parlow et al.,[5] relies on the principles of complementary molecular reactivity and recognition (CMR/R) using polystyrene beads bearing reactive groups complementary to those of reagents or byproducts requiring resin sequestration. This approach is characterised by the following attributes: (1) library members are synthesised in solution; (2) reactants, catalysts and reagents have inherent or artificially imparted functional groups which enable their post-reaction sequestration; (3) removal of reactants, catalysts and reagents is accomplished by incubation and filtration of the reaction mixture through resins containing complementary molecular-reactivity or molecular-recognition functionalities; (4) purified products are obtained by simple filtration.

Benzimidazol-2-ones and related urea derivatives exhibit a wide variety of interesting biochemical and pharmacological properties.[6,7] Several solution based[8–10] and recently solid phase[11,12] syntheses have been reported.

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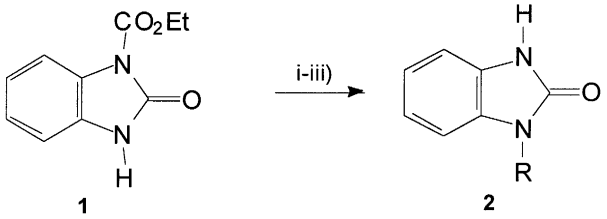
We report herein a significant improvement in the synthesis of 1,3-dihydro-benzimidazol-2-ones compared to that originally described by Meanwell et al.[13] In the latter work the heterocycle was alkylated using a variety of alkyl halides. A deprotection step was necessary in order to give the desired product. Using polymer-supported (PS) thiophenol[14] we were able to bypass these additional purification and isolation procedures by selective removal of excess alkylating agents. Subsequent hydrolysis of the ethoxycarbonyl protecting group yielded the monofunctionalised urea derivatives in high yields and purities (Scheme 1).



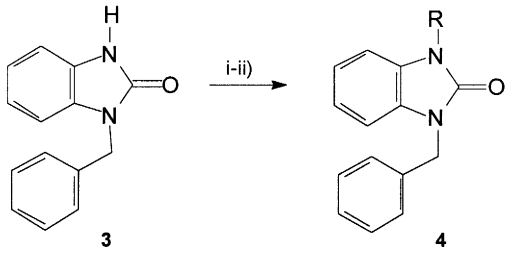
Scheme 1. Reagents and conditions. (i) R–X, K_2CO_3, KI, DMF, rt, 16 h; (ii) PS-thiophenol, DMF, rt, 6 h; (iii) K_2CO_3, EtOH, rt, 6 h

Thus ethyl 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (**1**) was reacted with a range of alkyl halides (1.1 equiv.) in dry DMF in the presence of powdered K_2CO_3 (1.2 equiv.) and a catalytic amount of KI. PS-Thiophenol (3 equiv. to excess halide) was added to the reaction to remove any excess electrophile. In situ hydrolysis of the carboxylic ester moiety using the same base (1 equiv.) in ethanol followed by a simple work-up[15] yielded the products **2a**–**p** in high overall yields. Purities were assessed by HPLC-MS (Table 1) and yields were corrected.

Table 1
Synthesis of 1-substituted 1,3-dihydro-benzimidazol-2-ones

Entry	R-	Yield [%]	Purity [%]
2-a	2-chlorobenzyl-	70	90
-b	3-chlorobenzyl-	89	92
-c	4-chlorobenzyl-	87	92
-d	2,6-dichlorobenzyl-	81	98
-e	2-methylbenzyl-	87	93
-f	4-methylbenzyl-	89	92
-g	hexyl-	83	99
-h	cinnamyl-	86	83
-i	2´-naphthylacyl-	98	95
-j	2-[(phenylsulfonyl)methyl]benzyl-	86	85
-k	2-naphthylmethyl-	78	76
-l	*tert*. -butylacyl-	81	96
-m	3,4-dichlorophenacyl-	64	65
-n	1,4-benzodioxan-6-ylacyl-	99	90
-o	3-methylbenzo[b]thiophene-2-ylacyl-	99	93
-p	4-(difluoromethoxy)phenacyl-	99	96

In order to further explore the versatility of this methodology and increase the diversity of molecules in the library the second, now unprotected urea nitrogen, was alkylated; the strategy is exemplified using the *N*-benzyl compound **3** (Scheme 2). After quenching with polymer supported thiophenol, again the key operation in the process, and an extractive work-up[16] the bisfunctionalised heterocycles **4a**–**h** were obtained in good yields and excellent purities (Table 2).



Scheme 2. Reagents and conditions. (i) R–X, K_2CO_3, KI, DMF, rt, 16 h; (ii) PS-thiophenol, DMF, rt, 6 h

Table 2
Synthesis of 1,3-disubstituted 1,3-dihydro-benzimidazol-2-ones

Entry	R-	Yield [%]	Purity [%]
4-a	2-chlorobenzyl-	80	94
-b	3-chlorobenzyl-	70	87
-c	4-chlorobenzyl-	80	98
-d	4-methylbenzyl-	68	79
-e	4-*tert.* -butylbenzyl-	77	91
-f	2-naphthylmethyl-	66	80
-g	3,4-dichlorophenacyl-	60	80
-h	*tert.*- butylacyl-	79	98

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14. Supplied by Argonaut Technologies, San Carlos, CA 94070.
15. The resins were filtered off and the solvent evaporated. The residue was acidified with 1N HCl and the resulting precipitate filtered off and dried in vacuo.
16. The resins were removed by filtration. The filtrate was diluted with water and extracted with Et_2O:hexane (1:1). This solvent switch was necessary to avoid DMF impurities. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent yielded the bisalkylated heterocycles.