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# Solid-Phase Synthesis of Bis-2-imidazolidinethiones from Resin-Bound Tripeptides

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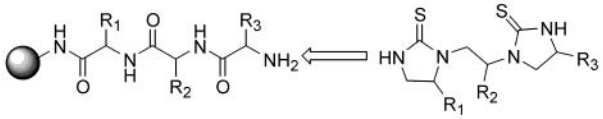
## ABSTRACT



**The exhaustive reduction of resin-bound tripeptides with borane afforded three secondary amines and one primary amine. The treatment of the solid-support polyamines with thiocarbonyldiimidazole afforded, following cleavage of the solid support, the corresponding bis-cyclic thiourea in good purity and yield.**

Solid-phase organic synthesis (SPOS) is a powerful approach for the design and the parallel rapid synthesis of acyclic and heterocyclic compounds.[1] Combinatorial chemistry techniques have been adopted by major pharmaceutical companies and were rated lately by the journal *Science* as one of nine breakthroughs in scientific research.[2] Herein, we describe an efficient method for the solid-phase synthesis of individual bis-cyclic thioureas from resin-bound tripeptides **1**. Substituted thioureas possess a wide variety of known biological activities, including non-nucleoside inhibition of HIV-1 and HIV-2 reverse transcriptases, [3] potent orally active antagonism of the bradykinin B (**2**) receptor,[4] and antioxidant active compounds with potent anti-HIV activity. [5]

In the current study, starting from *p*-methylbenzhydrilamine (MBHA) resin, tripeptides were synthesized using conventional Boc chemistry.[6] Following coupling of the third amino acid and Boc deprotection, the resin-bound tripeptide was treated with borane in THF, resulting in the exhaustive reduction of the amides to yield resin-bound polyamines containing three secondary amines and one terminal primary amine (Scheme 1).[7]

The resin-bound polyamine **2** is then treated with thiocarbonyldiimidazole to afford following HF cleavage the bis-cyclic thiourea **4**. Kinetically, the primary amine reacts first with thiocabonyldiimidazole which favors interaction with the adjacent secondary amine in an intermolecular cyclization to yield the energetically favorable five-membered ring cyclic thiourea. The two remaining secondary amines further react with thiocarbonyldiimidazole to yield the second heterocycle. Following a number of attempts at different concentrations of thiocarbonyldiimidazole, we observed that working at low concentration and using a small excess of the reagents led to the desired bis-heterocyclic compounds with purities greater than 80%. High concentrations and/or large excesses of the reagent increase the probability that the different amines will react with thiocarbonyldiimidazole and prevent the cyclization step. In support of our kinetic hypothesis, we found that the treatment of a resin-bound polyamine containing four secondary amines led to the formation of multiple products. We have previously used the combination of resin-bound amines and thiocarbonyldiimidazole for the synthesis of cyclic thiourea[8] and bicyclic guanidine libraries.[7a]

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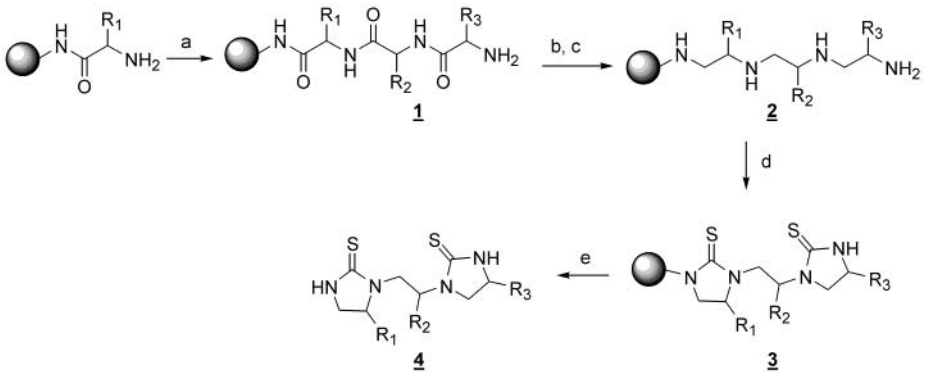
**Scheme 1**[a]




[a](a) BocNH-($R_2$)-COOH, DICDI, HOBT; 55% TFA in DCM; BocNH-($R_3$)-COOH, DICDI, HOBT; 55% TFA in DCM; (b) $BH_3$−THF, 65 °C; (c) pipeidine, 65 °C; (d) TCDI in DCM; (e) HF/anisole.

We have optimized the reactions conditions of this synthetic route by the parallel synthesis of eight different bis-imidazolidinethiones. Phenylalanine and leucine were chosen for the $R_1$ and $R_2$ positions and alanine and leucine for the $R_3$ position. As shown in Table 1, all compounds were obtained in good purity (>80%) with yields greater than 85% relative to the initial loading of the resin. We are in the course of expanding this approach for the parallel synthesis of a large number of individual compounds which will serve as controls for the selection of building blocks for the synthesis of a bis-imidazolidinethione library.

**Table 1.** Products Were Run on a Vydac Column, Gradient 5−95% of 0.05% TFA in ACN in 7 min. The Purity Was Estimated on Analytical Traces at $\lambda = 214$ nm

| Entry | $R_1$ | $R_2$ | $R_3$ | HPLC purity | MW found |
|---|---|---|---|---|---|
| 4a |  |  |  | 90 % | 433.1 ($MH^+$) |
| 4b |  |  |  | 93 % | 391.3 ($MH^+$) |
| 4c |  |  |  | 91 % | 399.6 ($MH^+$) |
| 4d |  |  |  | 89 % | 357.2 ($MH^+$) |
| 4e |  |  |  | 92 % | 467.3 ($MH^+$) |
| 4f |  |  |  | 87 % | 425.1 ($MH^+$) |
| 4g |  |  |  | 82 % | 433.1 ($MH^+$) |
| 4h |  |  |  | 88 % | 391.1 ($MH^+$) |

This approach is a continuation of our efforts directed toward the synthesis of acyclic and heterocyclic compounds from short peptides.[9] Using the concept of "libraries from libraries",[10] we are thus able to generate bis-heterocyclic cyclic thioureas from the amines resulting from the exhaustive reduction of resin-bound tripeptides. We are in the course of expanding this approach for the solid-phase synthesis of other bis-heterocyclic compounds using a variety of different bifunctional reagents.

**Supporting Information Available:** Experimental procedures and LC-MS data for all compounds. LC-MS data for the treatment of four resin-bound secondary amines with thiocarbonyldiimidazole.This material is available free of charge via Internet at http://pubs.acs.org.

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