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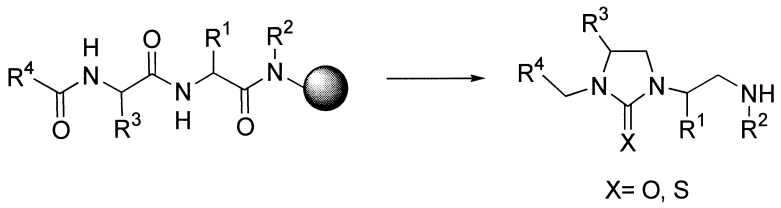

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Solid-Phase Synthesis of Trisubstituted 2-Imidazolidones and 2-Imidazolidinethiones

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An efficient method for the solid-phase synthesis of 1,3,4-trisubstituted-2-imidazolidones and 1,3,4-trisubstituted-2-imidazolidinethiones from reduced N-acylated dipeptides is described. The complete reduction of the amide bonds of an N-acylated dipeptide with borane in THF results in two secondary and one tertiary amine. Reaction of the resulting resin-bound polyamine **4** with carbonyldiimidazole or thiocarbonyldiimidazole affords, respectively, cyclic ureas **6** and cyclic thioureas **7** in high yield and purity. Details on the selection of the building blocks and characterization of the controls for the libraries' synthesis will be presented. These procedures have also been used to generate parallel arrays and mixture-based combinatorial libraries of cyclic ureas and thioureas.

Combinatorial chemistry initially involved the synthesis of very large libraries of biological oligomers such as peptides, peptidomimetics, and oligonucleotides.[1−5] Such oligomers, while valuable in their own right, have limitations as pharmaceutical agents and are susceptible to rapid enzymatic degradation. The focus of combinatorial chemistry has shifted in recent years to libraries of small acyclic and heterocyclic molecules having molecular weights of 500 Da or less, due to their extensive utility as therapeutic agents.[6−9]

An efficient, practical solid-phase synthesis of 1,3,4-trisubstituted-2-imidazolidones and 1,3,4-trisubstituted-2-imidazolidinethiones from a common intermediate, a resin-bound reduced N-acylated dipeptide **4** (Scheme 1), is described. Cyclic ureas and cyclic thioureas have recently been found to be active as protease inhibitors of human immunodeficiency virus (HIV) and HIV replication.[10] The synthesis of oligomeric cyclic ureas has also been reported as nonnatural biopolymers.[11] Recently, Goff reported the synthesis of 2-imidazolidones on solid support by tandem aminoacylation/Michael addition.[12]

Herein we report the solid-phase synthesis of these two related heterocyclic pharmacophores through the application of the "libraries from libraries" concept.[13] This is a continuation of our ongoing efforts to identify highly active compounds from synthetic combinatorial libraries.[14−19]

Starting from a protected *p*-methylbenzhydrylamine (MBHA) resin-bound amino acid and following deprotection of the N-terminal protecting group (Boc or Fmoc), the free amine is reprotected with a trityl (Trt) group. The amide bond is then selectively alkylated in the presence of lithium *tert*-butoxide in THF and an alkylating reagent (methyl iodide or benzyl bromide) in DMSO.[16]

Following Trt deprotection (**1**), a second amino acid is coupled to the resin-bound *N*-alkyl amino acid. It was found that the alkylation of the amide resin linkage dramatically increases the acid sensitivity of the MBHA resin-bound peptide.[17] Cleavage can be avoided through the subsequent use of Fmoc amino acid chemistry. Following Fmoc removal, the resulting primary amine of the dipeptide **2** was acylated with one of a wide range of available carboxylic acids. Using diborane in THF, the amide groups were fully reduced to generate a single tertiary and two secondary amines.[18−20] The reaction of the resulting resin-bound polyamine **4** with carbonyldiimidazole ($COIm_2$) or thiocarbonyldiimidazole ($CSIm_2$) afforded only the desired resin-bound cyclic ureas or cyclic thioureas **5**, respectively, and avoided problems of polymerization expected in solution-based chemistries. The cyclization step has also been successfully carried out using triphosgene and thiophosgene.

The N-alkylation of the amides and their reduction were carried out under an anhydrous nitrogen atmosphere.[19,21] Potential racemization during tritylation, amide nitrogen alkylation, and/or reduction was studied using analytical reverse-phase high-performance liquid chromatography (RP-HPLC). Different dipeptides were used as controls for the chemical reactions involved, and all possible diastereomers were synthesized. The diastereomers did not coelute. Three different reactions were studied: (1) tritylation of a simple N-acylated dipeptide (R_2 = H) in which the first amino acid undergoes tritylation (without alkylation) to determine if racemization occurs during overnight excess base treatment; (2) LiOtBu treatment of alkylated N-acylated dipeptides; and (3) reduction of the N-acylated dipeptides **3** (R^2 = H). It was found that 0−5% racemization occurred during the N-alkylation step depending on the amino acid involved. During the reduction step, both the reduction and piperidine treatment were studied. Initially, we optimized the conditions by individually testing five different amino acids (Phe, Ala, Tyr, Ser, Lys) at R^1, three amino acids (Val, Phe, Ala) at R^2, and two carboxylic acids (phenylacetic acid, cyclohexane

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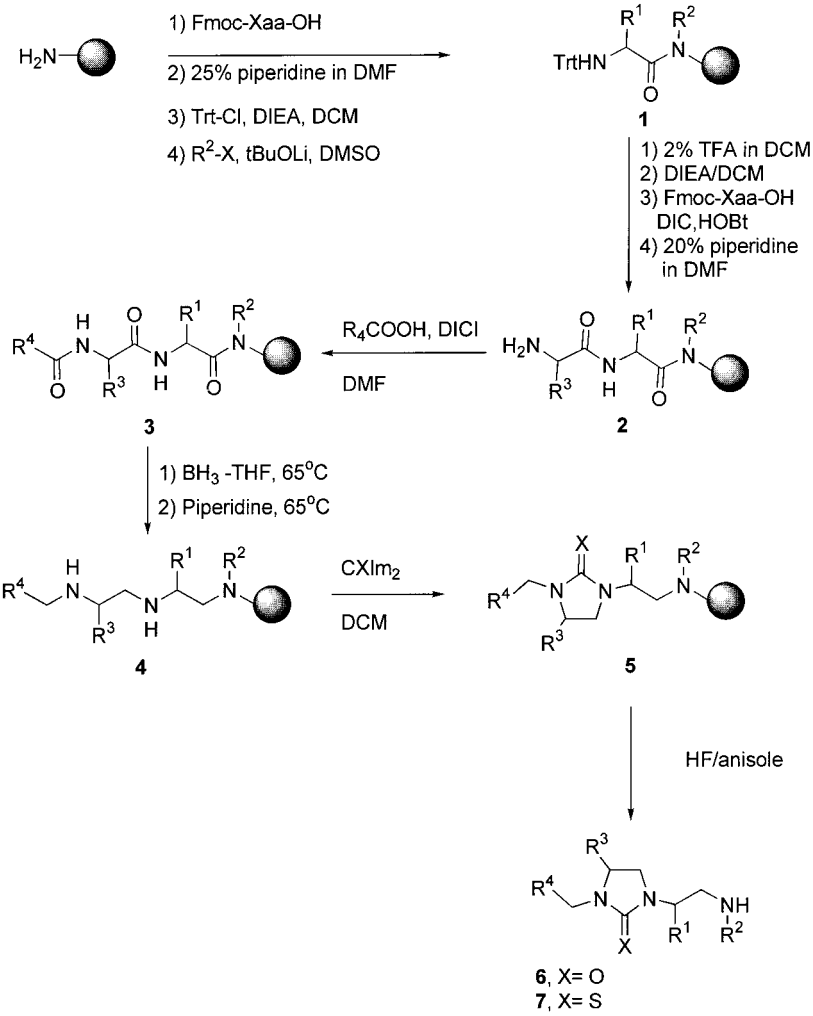
Scheme 1. General Polymer-Supported Synthesis of Trisubstituted 2-Imidazolidones and 2-Imidazolidinethiones



acetic acid) at R^3. Thus, 30 individual cyclic ureas and 30 cyclic thioureas were synthesized as controls and were found to be obtained in good yield and purity with little or no racemization.[22] Next, we expanded our controls by the synthesis of a large number of individual controls by separately varying each of the three positions. More than 40 different amino acids for the first and second position of diversities and more than 80 carboxylic acids for the third position of diversity were prepared.[23] Again, little or no racemization was found.

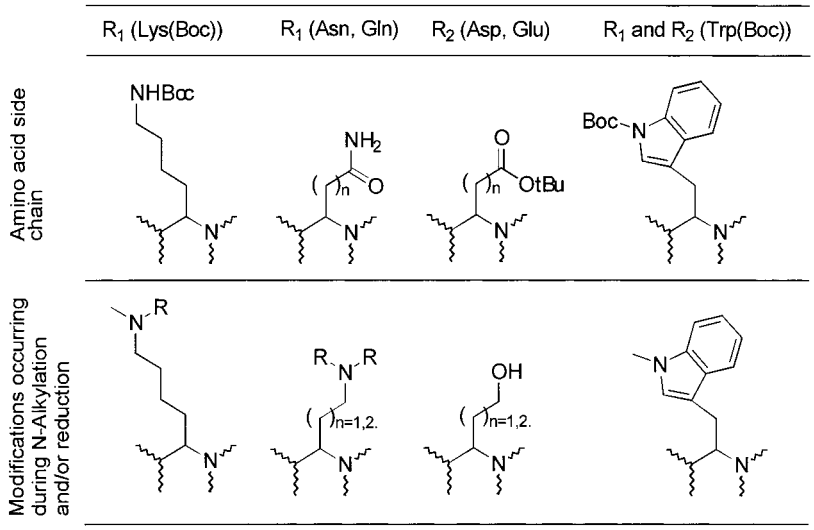
Modifications occurring in the amino acid side chains during the N-alkylation and reduction steps have been carefully studied; amino acids that were incompatible with our strategy were excluded.[24] The side chain modifications of some functionalized amino acids are shown in Table 1. Such modifications are typically complete and lead to final products having good yield and purity.

The compounds containing Arg(Pmc), Trp(Boc), and His-(Trt), which yielded aggregated and/or polymerized products, were excluded since these amino acids led to the desired product in less than 50% yield. Excellent yields were obtained for the remaining amino acids with average HPLC purities higher than 80%.

A wide range of carboxylic acids have been tested, from acetic acid to substituted benzoic acids to complex carboxylic acids. We observed that following amide reduction, electron rich substituted benzoic acids (such as *p*-methoxy-benzoic acid), which after reduction yield *N*-benzyl derivatives, are completely cleaved during exposure to HF for 6 h under the cleavage conditions used. These carboxylic acids were therefore excluded from our libraries as well as the nitro aromatic carboxylic acids due to the partial reduction of the nitro group during borane treatment. The majority of the aromatic carboxylic acids chosen for the library synthesis are derivatives of phenylacetic acid. With a number of carboxylic acids, such as 2-phenylbutyric acid, incomplete cyclization was obtained, which is most likely due to steric hindrance and leads to the reduced dipeptide **4** as a secondary product.

Using the data from the control experiments described above, we have prepared four separate positional scanning combinatorial libraries (SCLs) [*N*-methyl amino cyclic urea **6** (R^2 = Me) and thiourea **7** (R^2 = Me), and *N*-benzyl amino cyclic urea **6** (R^2 = Bzl) and thiourea **7** (R^2 = Bzl)], each containing 118 400 (37 R^1 × 40 R^3 × 80 R^4) different cyclic ureas or thioureas. These single position defined SCLs were then screened to identify the most important functionalities at each position of diversity within a library.[6,25−26] The preparation of these libraries and the identification of highly active individual cyclic ureas and thioureas effective for the

Table 1. Side Chain Modification of Amino Acids during Reduction[a]



[a] R is derived from the alkylating reagent (RX).

inhibition of *Candida albicans* growth, a common opportunistic fungi and the fungal infection most frequently associated with HIV-positive patients, have been presented.[27]

Summary

Amino acids and short peptides are versatile precursors for the solid-phase synthesis of individual heterocyclic compounds and combinatorial libraries. Through the application of the "libraries from libraries" approach, modified dipeptides have been successfully used for the generation of positional scanning cyclic urea and cyclic thiourea libraries.

A wide range of other heterocyclic pharmacophores and their corresponding SCLs are being prepared. Their synthesis and use for the discovery of novel active compounds will be reported elsewhere.

Experimental Section

Fmoc-amino acid derivatives and HOBt were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA), Bachem Bioscience Inc. (Philadelphia, PA), and Bachem California (Torrance, CA). MBHA resin, 1% divinylbenzene, 100−200 mesh, 0.81 mmol/g substitution, was purchased from Chem Impex Intl. (Wood Dale, IL). *N*,*N*′-Diisopropylcarbodiimide (DIC) was purchased from Chem Impex Intl., trifluoroacetic acid (TFA) from Halocarbon (River Edge, NJ), and hydrogen fluoride from Air Products (San Marcos, CA). All other reagents and anhydrous solvents (DMSO and THF) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman System Gold instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C_{18} column (0.46 × 25 cm).

Typical Procedure for the Individual Synthesis of Cyclic Urea and Cyclic Thiourea. (1) Selective Amide Nitrogen Alkylation. A 100 mg sample of *p*-methylbenzydrylamine (MBHA) resin (0.81 mequiv/g, 100−200 mesh) was contained within a sealed polypropylene mesh packet.[28] Reactions were carried out in 10 mL polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. The first amino acid (Fmoc-Xaa-OH, 6 equiv) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 6 equiv) and diisopropylcarbodiimide (DIC, 6 equiv) in anhydrous DMF for 60 min. Following removal of the protecting group with 25% piperidine in DMF (2 times, 2 × 10 min) and washing with DMF (8 times), the mesh packet was shaken overnight in a solution of trityl chloride (10 equiv) in DCM/DMF (9:1) in the presence of DIEA (10 equiv). Completeness of the trityl coupling was verified using the bromophenol blue color test.[29] N-alkylation was performed by treatment of the resin packet with 1 M lithium *tert*-butoxide in THF (20 equiv) during 10 min at room temperature. Excess base was removed by cannulation, followed by addition of the individual alkylating agent (20 equiv) in anhydrous DMSO. The solution was vigorously shaken for 2 h at room temperature.

(2) N-Acylated Dipeptide. Upon removal of the trityl from the α-amino group with 2% TFA in DCM (2 × 10 min), the resin packet was washed and neutralized with a solution of 5% DIEA in DCM, and the second amino acid (Fmoc-Xaa-OH) was coupled in the same conditions as described before. Following removal of the Fmoc group, the dipeptide was N-acylated with a carboxylic acid (10 equiv) in the presence of DIC (10 equiv) and HOBt (10 equiv) in anhydrous DMF.

(3) Exhaustive Reduction of the Amide Groups. The reduction was performed in 50 mL kimax tubes under nitrogen. Boric acid (40×) and trimethyl borate (40×) were added, followed by 1 M BH_3-THF (40×). The tubes were heated at 65 °C for 72 h, followed by quenching with MeOH. The resin was then washed with methanol (2 times) and the borane disproportionated by treatment with piperidine at 65 °C overnight. The resin was then washed with methanol (2 times) and DMF (6 times) and dried.

(4) Cyclic Urea and Cyclic Thiourea Formation. The cyclization occurred following treatment of the reduced acylated dipeptide overnight with carbonyldiimidazole (20×) in anhydrous DCM for cyclic urea formation and with thiocarbonyldiimidazole (20×) in anhydrous DCM for

thiourea formation. Following cleavage from the resin with anhydrous HF[30] in the presence of anisole at 0 °C for 6 h, the desired product was extracted with acetonitrile/water (50:50) and lyophilized.

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Supporting Information Available. LC−MS of individual cyclic ureas and cyclic thioureas, NMR spectra of individual cyclic ureas and cyclic thioureas, and HPLC spectra showing the partial reduction of the nitro group during the reduction of the amide bonds with borane. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The products were run on a Vydac C_{18} column, using a 5−95% gradient of 0.05% TFA in ACN in 7 min. The purity was estimated using analytical traces at 214 nm. The yields obtained in all cases were higher then 75% relative to the initial loading of the resin.

(23) The R^1 and R^2 groups were derived from the D- and L- forms of the following amino acids: Ala, Phe, Gly, Ile, His(Trt), Leu, Ser(tBu), Thr(tBu), Val, Tyr(tBu), Nva, Nle, Cha, Nal. In addition R^1 included the D- and L- forms of Lys(Boc), Asn, and Gln. R^2 included also β-Ala (leading to the six-member rings of cyclic ureas and cyclic thioureas) and the D- and L- forms of Glu(tBu).

(24) Functionalized amino acids such as Lys, Gln, and Asn were excluded in the second position. Following the reduction of the amide bonds, the generated secondary amine (resulting from the side chain of Lys) or primary amines (resulting from the side chains of Gln and Asn) compete during the cyclization step with the two other secondary amines, leading to the generation of multiple compounds.

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