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SOLID PHASE SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM LINEAR PEPTIDES: CYCLIC UREAS AND THIOUREAS

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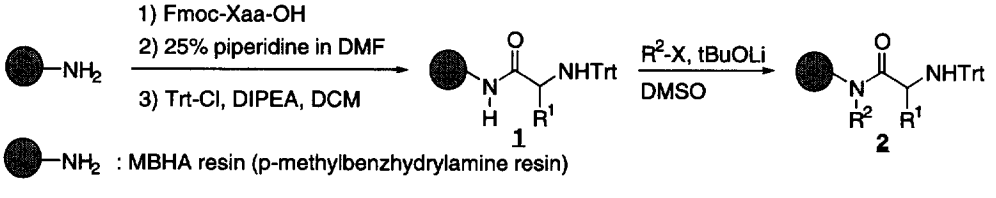
Abstract: The solid phase synthesis of cyclic ureas and thioureas is described. The reduction of acylated dipeptides followed by treatment with carbonyldiimidazole or thiocarbonyldiimidazole affords the corresponding cyclic urea or thiourea in good yield and high purity. This is an example of a broader approach to the solid phase synthesis of individual heterocyclic compounds and combinatorial libraries using peptides as starting materials. © 1997, Elsevier Science Ltd. All rights reserved.

We report here the design and solid phase synthesis of cyclic ureas and thioureas **6** (Scheme 2) derived from acylated dipeptides. The general approach for synthesis on a solid support of a variety of heterocyclic and small linear molecules having molecular weights less than 600 daltons is described.

Many biologically active compounds contain cyclic ureas, including inhibitors of human immunodeficiency virus (HIV) protease and HIV replication.[1] Recently, Kim et al. presented an illustration of the synthesis of oligomeric cyclic ureas as non-natural biopolymers.[2]

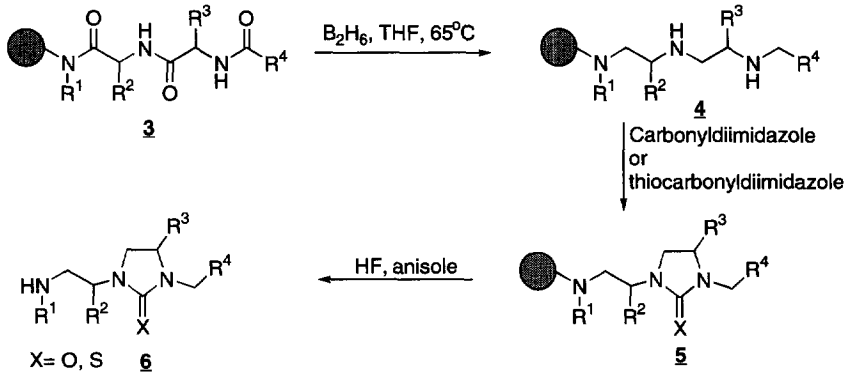
The first step of our strategy is the selective N-alkylation of the amide linked to the solid support as illustrated in Scheme 1. The N-alkylation is performed using lithium t-butoxide in THF, followed by addition of the alkylating agent (methyl iodide, benzyl bromide) in DMSO. This method of N-alkylation has been extensively used in our laboratory for the synthesis of soluble peptidomimetic combinatorial libraries through successive or exhaustive amide alkylation using traditional solid phase synthesis resins.[3] Following removal of the Trt protecting group with 2% TFA in DCM, the second amino acid is added, and the resulting dipeptide is then acylated with one of a wide range of available carboxylic acids to obtain the acylated dipeptide.



Scheme 1: Selective N-alkylation of N-α-protected amides linked to the resin
(R^1= amino acid side chain; R^2= Me, Bzl).

The second step in the synthetic process is the reduction of the amide groups of the acylated dipeptide using diborane in THF at 65°C to generate a tertiary and two secondary amines. We have successfully employed this

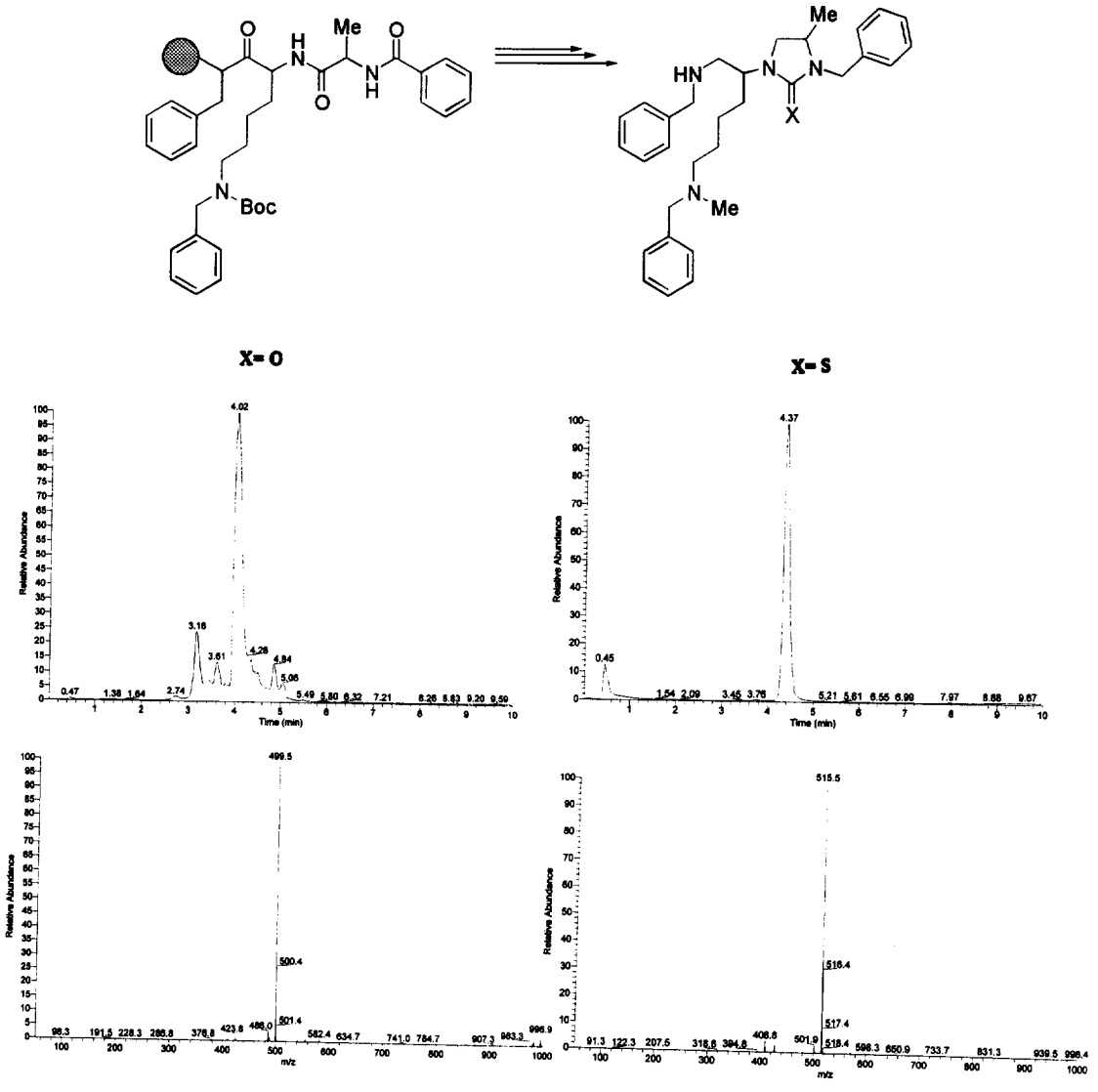
strategy to generate diverse chemical libraries using the "libraries from libraries" concept.[3b,4] The cyclizations to obtain the five-member ring cyclic ureas and cyclic thioureas were performed using carbonyldiimidazole and thiocarbonyldiimidazole. The desired products were obtained in good yields and high purity (>90% by HPLC) following cleavage from the resin with anhydrous HF. The cyclization step has also been successfully carried out using triphosgene and thiophosgene.



Scheme 2: Solid phase synthesis of cyclic ureas and thioureas using acylated dipeptides as starting material (R^3= amino acid; R^4= carboxylic acid).

In Scheme 3, we show the RP-HPLC and LCQ-Mass spectra of the cyclic urea **6a** (expected mass: 498) and cyclic thiourea **6b** (expected mass: 514), with R^1= side chain of lysine, R^2= Bzl, R^3= side chain of alanine, and R^4= benzyl (from reduction of benzoyl), which are representative of the purities obtained in each case. During the N-alkylation with benzyl bromide, the Boc-protected N^{ϵ}-amine of lysine was N-benzylated. The Boc protecting group was then cleanly reduced to form an N-methyl during the reduction. Modifications occurring in the amino acid side chains following alkylation and reduction were reported earlier by this laboratory.[4] Less than 1% racemization was found during these steps.[3-4] The lack of diastereomers in the ^{1}H-NMR suggest little or no racemization occurred during the cyclization step. Amino acids selected from the 20 naturally occurring L-amino acids and their D counterparts, excluding those which are incompatible with the reduction and alkylation steps,[4] were used to create the diversity at the R^1 and R^3 positions.[5] The carboxylic acids included in the acylation step range from acetic acid to substituted benzoic acids to more complex alkyl carboxylic acids such as abietic acid.

This laboratory has previously reported a range of soluble combinatorial libraries,[3-4,6-8] prepared using solid phase approaches, but cleaved and used in solution. Such libraries have incorporated a wide range of functionalities, including hydrogen bonding donors and acceptors, positive and negative charges, functionalities of differing chiralities, hydrophobic and hydrophilic substituents, etc. In a positional scanning format,[7-8] we have prepared four combinatorial libraries (R^2 = Me, Bzl; X = O, S), each containing 118,400 cyclic ureas and cyclic thioureas (37 R^1 x 40 R^3 x 80 R^4), using the chemistry described above.[9] The preparation of these libraries and their use in a range of assays for the identification of highly active, individual cyclic ureas and thioureas will be described elsewhere.



Scheme 3: RP-HPLC and LCQ-Mass spectra of 6a and 6b

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5. The R^1 and R^3 groups were derived from the D- and L- forms of the following Fmoc-amino acids: Ala, Phe, Gly, Ile, His(Trt), Leu, Arg(Pmc), Ser(tBu), Thr(tBu), Val, Tyr(tBu), Nve, Nle, Cha, Nal. In addition, R^1 included the D- and L- forms of Lys(Boc), Asn, Gln, and Trp. R^3 also included β-Ala, and the D- and L-forms of Glu(tBu) and Trp(Boc).
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9. Typical procedure for the synthesis of individual cyclic ureas and cyclic thioureas: 180 mg p-methylbenzhydrylamine resin was contained within a sealed polypropylene mesh packet. Following neutralization with 5% DIEA in dichloromethane (DCM), the resin was washed with DCM. The first Fmoc amino acid was coupled using hydroxybenzotriazole (HOBt) and diisopropylcarbodiimide (DICI). Following removal of the FMOC group with 25% piperidine in DMF, the mesh packet was shaken overnight in a solution of trityl chloride in DCM/DMF (9:1) in the presence of DIEA. N-alkylation was performed by treatment of the resin packet with 1 M lithium t-butoxide in THF. Excess base was removed, followed by addition of the alkylating agent in DMSO. The solution was vigorously shaken for 2 h at room temperature. Upon removal of the trityl group with 2%TFA in DCM (2 x 10 min), the packet was washed, neutralized and the second Fmoc amino acid coupled. Following removal of the Fmoc group, the dipeptide was individually acylated with a carboxylic acid in the presence of DICI and HOBt. The reductions were performed in 50 ml kimax tubes under nitrogen. Boric acid (40x) and trimethyl borate (40x) were added, followed by 1M BH_3-THF (40x). The tubes were heated at 65°C for 72 h, followed by quenching with MeOH. The resin was then washed with methanol. The borane-complex could be hydrolyzed by overnight treatment with 1M HCl/MeOH at 65°C. The cyclization occurred following treatment of the reduced acylated dipeptide overnight with carbonyldiimidazole for cyclic urea formation and thiocarbonyldiimidazole for thiourea formation. Following cleavage from the resin with anhydrous HF in the presence of anisole,[10] the desired product was extracted and lyophilized.
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