JOURNAL OF combinatorial CHEMISTRY

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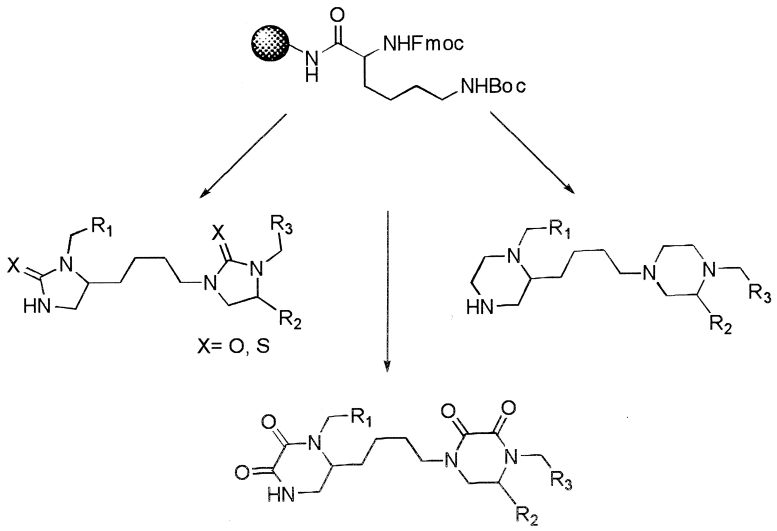
J. Comb. Chem., **2001**, 3 (1), 68-70• DOI: 10.1021/cc000061t • Publication Date (Web): 21 October 2000



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Solid-Phase Synthesis of Bis-Heterocyclic Compounds from Resin-Bound Orthogonally Protected Lysine

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Received July 10, 2000

An efficient method for the solid-phase synthesis of bis-heterocyclic compounds from resin-bound orthogonally protected lysine is presented. The initial reaction step involves the exhaustive reduction of resin-bound tetra-amides using borane-THF, followed by cyclization of the resulting tetra-amine with either carbonyldiimidazole, thiocarbonyldiimidaziole, or oxalyldiimidazole to generate resin-bound bis-cyclic ureas, bis-cyclic thioureas, and bis-cyclic diketopiperazines, respectively. Cleavage from the solid support using hydrogen fluoride, followed by extraction and lyophilization, yields the desired bis-heterocyclic compounds in excellent yield and high purity.

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.[1] Polyamines are highly versatile starting materials for the generation of a wide variety of heterocyclic compounds and their respective combinatorial libraries.[2] We have previously reported the synthesis of 2-imidazolidones, 2-imidazolidinethiones, and bicyclic guanidines libraries from resin-bound reduced N-acylated dipeptides.[3,4] We describe herein efficient, practical solid-phase syntheses of a variety of bis-heterocyclic compounds from resin-bound tetra-amines (Scheme 1).

Starting from resin-bound Fmoc-Lys(Boc)-OH **1**, the Fmoc group is cleaved in the presence of a solution of piperidine in dimethylformamide (DMF), and the resulting free amine is *N*-acylated with a variety of carboxylic acids. Following cleavage of the Boc group on the ξ-amine of the lysine in the presence of trifluoroacetic acid (TFA) and subsequent neutralization, a Boc-amino acid is coupled to the resulting free amine using standard SPPS chemistry.[5] The Boc group is cleaved, and the resulting amine is neutralized and then *N*-acylated with different carboxylic acids. The exhaustive reduction of amide bonds (**2)** on the solid support is performed in the presence of borane in THF to generate four secondary amines.[4,6] Treatment of the resin-bound tetra-amines **3** with carbonyldiimidazole, thiocarbonyldiimidazole, or oxalyldiimidazole at low concentrations resulted in the formation of the energetically favorable five- and six-membered rings, which correspond to the bis-cyclic ureas **4**, bis-cyclic thioureas **5**, and bis-cyclic diketopiperazines **6**.

Structural characterization of compounds demonstrates the success of the major transformations described. Following HF cleavage at 0 °C for 90 min, LC-MS of crude tetra-amines showed >95% purity, and the desired bis-heterocyclic compounds were obtained with purities ranging from 85% to 95%. Yields in all cases were greater than 85%.

Prior to HF cleavage, and using the "libraries from libraries" approach,[7] an extra set of the resin-bound bis-diketopiperazines were treated with borane in THF to reduce the resin-bound oxamide moieties to their corresponding amines. Following HF cleavage, the resulting bis-piperazines **7** were obtained in purities higher than 85%. We have previously reported the successful solid-phase synthesis of 2,3-diketopiperazines and their corresponding piperazines.[8]

This synthetic approach has been expanded to include a wide range of different amino acids and carboxylic acids. More than 100 individual controls were synthesized for each bis-heterocyclic compound type. For each potential building block tested, only those yielding individual control tetra-amines having crude purities higher than 90% and corresponding controls of bis-heterocyclic compounds higher than 80% were considered for further inclusion in the synthesis of combinatorial libraries.

In summary, an efficient and general solid-phase synthesis of bis-heterocyclic compounds from resin-bound orthogonally protected lysine is presented here. This synthetic approach extends the previously described "libraries from libraries" concept.[7] These transformations enable both individual compounds and mixture-based combinatorial libraries to be prepared with excellent yield and purity.

Experimental Section

Solid-phase syntheses were carried out using the "teabag" method, in which the resin is contained within sealed polypropylene mesh packets.[9] The completeness of amino acid coupling and *N*-acylation were verified using the ninhydrin test.[10]

(1) Amino Acid Coupling and N^{α}-Acylation: A total of 100 mg of *p*-methylbenzydrylamine (MBHA) resin (0.1 mequiv/g, 100−200 mesh) was contained within a sealed polypropylene mesh packet. Reactions were carried out in 10 mL polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIPEA) in dichloromethane (DCM), the resin was washed with DCM. The Fmoc-Lys(ξ-Boc) (6equiv) was coupled in the presence of hydroxybenzotriazole (HOBt, 6e quiv) and diisopropylcarbodiimide (DIPCDI, 6equiv) in anhydrous DMF for 60 min. Following

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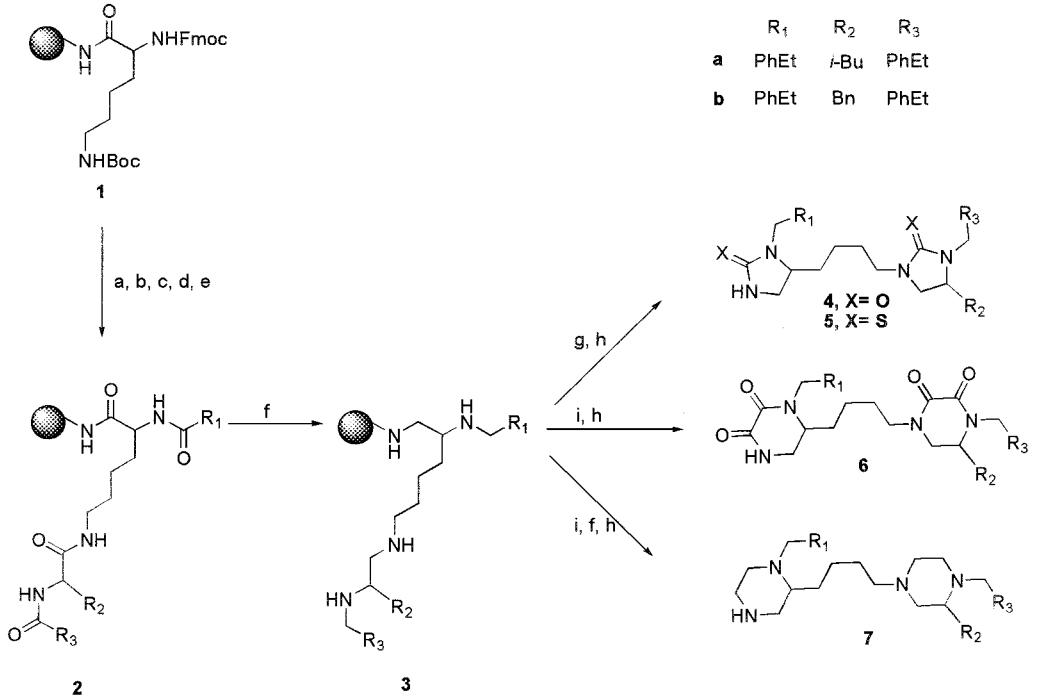
10.1021/cc000061t CCC: $20.00
Published on Web 10/21/2000

Scheme 1[a]



[a] Reagents and conditions: (a) 25 % piperidine in DMF; (b) R_1COOH, DIPCDI, HOBt, DMF; (c) 50% TFA in DCM; (d) Boc-Xaa-OH, DIPCDI, HOBT, DMF; (e) c, R_3COOH, DIPCDI, HOBt, DMF; (f) BH_3-THF, 65 °C; (g) CXIm2 (X= O, S), DCM; (h) HF/anisole; (i) $C_2O_2Im_2$, DMF.

removal of the Fmoc group with 25% piperidine in DMF (2 × 10 min) and washing with DMF (8×), the amino acid was N-acylated with a carboxylic acid (10 equiv) in the presence of DIPCDI (10 equiv) and HOBt (10 equiv) overnight in anhydrous DMF.

(2) Amino Acid Coupling and Acylation: Following removal of the Boc group from the ξ-amino group of the lysine with 50% TFA in DCM for 30 min, neutralization with a solution of 5% DIPEA in DCM and washing with DMF (8×), a Boc amino acid was coupled (6 equiv) in the presence of DIPCDI (6 equiv) for 60 min. The Boc group was then cleaved with 50% TFA in DCM. Following neutralization and washing, the amine was N-acylated with a carboxylic acid (10 equiv) in the presence of DIPCDI (10 equiv) and HOBt (10 equiv) overnight in anhydrous DMF.

(3) Exhaustive Reduction of the Amide Groups: The reduction was performed in 50 mL Kimax tubes under nitrogen. The resin packet (1 mequiv of resin, 100 mg of starting resin, 0.2 mequiv of carbonyl) and boric acid (15-fold excess over each amide bond) were added to each tube. Trimethyl borate (15-fold excess over each amide bond) was added, followed by 1 M BH_3-THF (40-fold excess over each amide bond). The tubes were heated at 65 °C for 72 h, decanted, washed with HF, and any remaining borane quenched with MeOH. The borane was disproportionated by treatment with piperidine at 65 °C overnight. The resin was then washed with methanol (2×) and DMF (6×) and dried. The completeness of the reaction was verified by cleavage and analysis following reduction.

(4) Cyclization: Cyclization occurred following treatment of the resin-bound tetra-amine overnight with a 5-fold excess of carbonyldiimidazole (0.05 M) in anhydrous DCM, thiocarbonyldiimidazole (0.05 M) in anhydrous DCM, or oxalyldiimidazole (0.05 M) in anhydrous DMF. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0 °C for 90 min, the desired product was extracted with acetonitrile/water (50:50) and lyophilized. The identity of all compounds were determined by LC-MS, ^{1}H NMR, and ^{13}C NMR.

***N*^{6}-{4-Methyl-2-[(2-phenylethyl)amino]pentyl}-*N*^{2}-(2-phenylethyl)-1,2,6-hexanetriamine (3a)** (following cleavage of the solid support): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31−7.17 (m, 10H), 3.22 (m, 6H), 3.12 (m, 6H), 2.94 (m, 7H), 1.70 (m, 2H), 1.65 (m, 2H), 1.55 (m, 2H), 1.39 (m, 2H), 0.90 (2d, J = 7.1, J = 6.8 Hz, 6H). ES-MS calcd for $C_{28}H_{46}N_4$: 438.7, found: 439.3 (MH^+).

***N*^{2}-(2-Phenylethyl)-*N*^{6}-{3-phenyl-2-[(2-phenylethyl)amino]propyl}-1,2,6-hexanetriamine (3b)** (following cleavage of the solid support): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38−7.23 (m, 15H), 3.68 (m, 2H), 3.22 (m, 4H), 3.10 (m, 1H), 2.97 (m, 1H), 2.93 (m, 8H), 1.67 (m, 2H), 1.54 (m, 2H), 1.33 (m, J = 2H). ES-MS calcd for $C_{31}H_{44}N_4$: 472.7, found: 473.4 (MH^+).

4-Isopropyl-1-{4-[2-oxo-3-(2-phenylethyl)-4-imidazolidinyl]butyl}-3-(2-phenylethyl)-2-imidazolidone (4a): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29−7.17 (m, 10H), 6.22 (s, 1H), 3.50 (m, 1H), 3.44 (m, 2H), 3.11 (m, 3H), 2.97 (m, 2H), 2.84 (m, 2H), 2.78 (m, 2H), 2.62 (m, 2H), 1.69 (m, 2H), 1.51 (m, 2H), 1.41 (m, 2H), 1.23 (m, 1H), 1.15 (m, 3H), 0.86 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 5.8 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): 161.6, 160.0, 139.4, 128.6, 128.3, 126.0, 54.6, 51.1, 48.3, 43.1, 42.6, 42.0, 41.2, 33.6, 33.5, 31.2, 26.6, 24.0, 23.7, 21.6. ES-MS calcd for $C_{30}H_{42}N_4O_2$: 490.6, found: 491.4 (MH^+).

4-Isopropyl-3-(2-phenylethyl)-1-{4-[3-(2-phenylethyl)-2-thioxo-4-imidazolidinyl]butyl}-2-imidazolidinethione (5a): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.31−7.18 (m, 10H), 3.95 (m, 1H), 3.78 (m, 1H), 3.59 (m, 2H), 3.56

(m, 2H), 3.39 (m, 2H), 3.10 (m, 2H), 2.89 (m, 2H), 2.72 (m, 2H), 1.78 (m, 1H), 1.53 (m, 5H), 1.46 (m, 1H), 1.23 (m, 2H), 1.16 (m, 2H), 0.88 (d, $J = 6.2$ Hz, 3H), 0.82 (d, $J = 5.9$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): 181.9, 181.1, 139.1, 139.0, 128.6, 128.3, 128.3, 126.1, 58.7, 55.4, 51.3, 46.2, 45.9, 45.8, 44.8, 40.0, 33.0, 33.0, 30.9, 25.8, 24.2, 23.6, 21.4, 20.6. ES-MS calcd for $C_{30}H_{42}N_4S_2$: 522.2, found: 523.3 (MH^+).

1-{4-[5,6-Dioxo-1-(2-phenylethyl)-2-piperazinyl]butyl}-5-isopropyl-4-(2-phenylehtyl)-2,3-piperazinedione (6a): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (d, $J = 5.2$ Hz, 1H), 7.32−7.19 (m, 10H), 3.50 (dd, $J = 3.56$, $J = 13.4$ Hz, 1H), 3.32 (m, 2H), 3.22 (m, 2H), 3.12 (m, 1H), 3.06 (m, 2H), 2.84 (m, 4H), 1.54 (m, 3H), 1.43 (m, 3H), 1.24 (m, 2H), 1.20 (m, 2H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.3$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): 157.5, 157.0, 156.6, 156.3, 138.9, 138.8, 128.7, 128.4, 128.3, 126.4, 126.3, 55.2, 52.3, 47.4, 47.4, 46.1, 46.0, 40.2, 33.4, 33.3, 30.1, 26.3, 24.3, 23.2, 22.9, 21.2. ES-MS calcd for $C_{32}H_{42}N_4O_4$: 546.7, found: 547.8 (MH^+).

2-Isopropyl-1-(2-phenylethyl)-4-{4-[1-(2-phenylethyl)-2-piperazinyl]butyl}piperazine (7a): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29−7.16 (m, 10H), 3.50 (m, 2H), 3.37 (m, 2H), 3.22 (m, 2H), 3.12 (m, 1H), 3.06 (m, 2H), 2.89 (m, 3H), 1.52 (m, 4H), 1.24 (m, 2H), 1.12 (m, 2H), 0.89 (d, $J = 5.9$ Hz, 3H), 0.86 (d, $J = 6.0$ Hz). ES-MS calcd for $C_{32}H_{50}N_4$: 490.7, found: 491.5 (MH^+).

4-Benzyl-1-{4-[2-oxo-3-(2-phenylethyl)-4-imidazolidinyl]-butyl}-3-(2-phenylethyl)-2-imidazolidone (4b): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31−7.16 (m, 15H), 3.71 (m, 1H), 3.23 (m, 2H), 3.15 (m, 1H), 3.07 (m, 2H), 3.00 (m, 4H), 2.88 (m, 2H), 2.82 (m, 2H), 2.62 (m, 2H), 2.55 (m, 1H), 1.63 (m, 1H), 1.30 (m, 4H), 1.09 (m, 2H). ES-MS calcd for $C_{33}H_{40}N_4O_2$: 524.7, found: 525.4 (MH^+).

4-Benzyl-3-(2-phenylethyl)-1-{4-[3-(2-phenylethyl)-2-thioxo-4-imidazolidinyl]butyl}-2-imidazolidinethione (5b): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.31−7.20 (m, 15H), 4.07 (m, 1H), 3.96 (m, 2H), 3.75 (m, 1H), 3.44 (m, 4H), 3.37 (m, 2H), 3.18 (dd, $J = 6.8$, $J = 9.9$ Hz, 1H), 3.07 (m, 2H), 2.73 (m, 2H), 2.64 (dd, $J = 8.6$, $J = 13.5$ Hz, 1H), 1.71 (m, 1H), 1.39 (m, 3H), 1.06 (m, 2H). ES-MS calcd for $C_{33}H_{40}N_4S_2$: 556.2, found: 557.3 (MH^+).

1-{4-[5,6-Dioxo-1-(2-phenylethyl)-2-piperazinyl]butyl}-5-benzyl-4-(2-phenylehtyl)-2,3-piperazinedione (6b): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (d, $J = 5.2$ Hz, 1H), 7.31−7.16 (m, 15H), 3.92 (m, 2H), 3.80 (m, 2H), 3.39 (m, 2H), 3.29 (dd, $J = 3.9$, $J = 13.1$ Hz, 1H), 3.25 (m, 1H), 3.12 (m, 2H), 3.07 (m, 1H), 2.97 (d, $J = 12.9$ Hz, 1H), 2.90 (m, 2H), 2.84 (m, 2H), 2.77 (m, 2H), 1.53 (m, 2H), 1.40 (m, 2H), 1.19 (m, 2H). ES-MS calcd for $C_{35}H_{40}N_4O_4$: 580.7, found: 581.6 (MH^+).

2-Benzyl-1-(2-phenylethyl)-4-{4-[1-(2-phenylethyl)-2-piperazinyl]butyl}piperazine (7b): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32−7.19 (m, 15H), 3.95 (m, 2H), 3.85 (m, 2H), 3.53 (m, 2H), 3.21 (m, 2H), 3.12 (m, 2H), 3.10 (m, 1H), 2.99 (m, 1H), 2.93 (m, 2H), 2.88 (m, 2H), 2.76 (m, 2H), 1.49 (m, 2H), 1.37 (m, 2H), 1.22 (m, 2H). ES-MS calcd for $C_{35}H_{48}N_4$: 524.7, found: 525.5 (MH^+).

Acknowledgment. This work was funded by National Cancer Institute Grant 1P01CA78040 (Houghten).

Supporting Information Available. ^{1}H NMR spectra of (**4a**−**b**, **5a**−**b**, **6a**−**b**), ^{13}C NMR spectra of (**4a**, **5a**, **6a**), and LC-MS of all compounds; list of the amino acids and carboxylic acids selected for the synthesis of all libraries; LC-MS spectra of randomly chosen individual compounds from the bis-heterocyclic compounds **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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