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The Synthesis of 2-Oxopiperazines by Intramolecular Michael Addition On Solid Support

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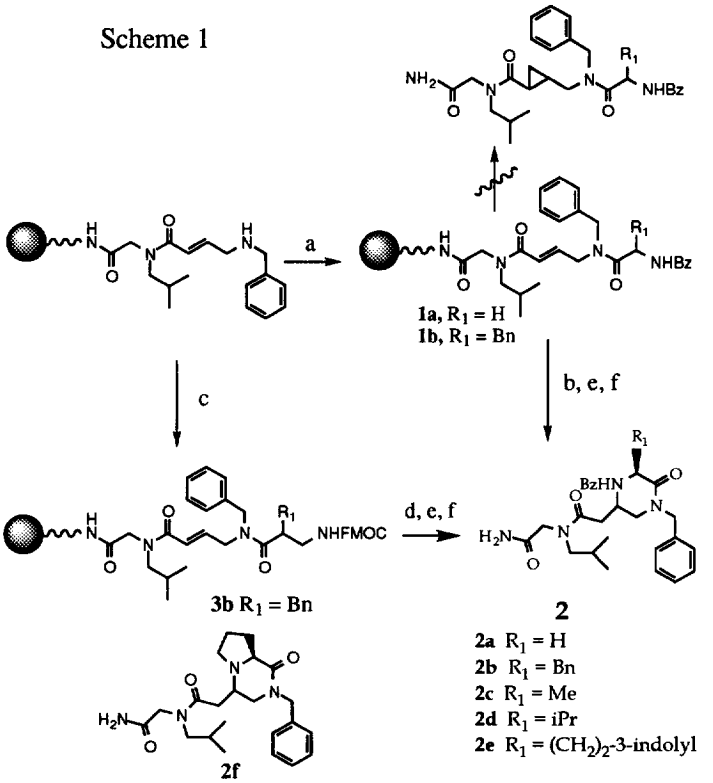
Abstract: Attempted cyclopropanation of unsaturated peptoids on solid support led to the discovery of a facile method for generating libraries of constrained cyclic peptoids.

We have recently described the use of *trans*-4-bromo-2-butenoic acid as a building block for the solid phase construction of unsaturated peptoids.[1] Functionalization of the double bond while the peptoid oligomer is still bound to the solid support could lead to a variety of peptidomimetic structures without the need to synthesize the monomeric units individually. Since structurally constrained peptides containing cyclopropyl amino acids have been of considerable interest[2] we decided to treat unsaturated resin bound dipeptoid **1a** with dimethyloxosulfonium methylide (Corey cyclopopanation reagent) in DMSO. We isolated a single product **2a** having a slightly shorter retention time on C-18 reversed phase HPLC than starting material **1a** (24.0 vs. 24.9 min) but with an identical parent ion (MH^+ = 465.4) by electrospray mass spectrometry. ^1H NMR of **2a** showed complete loss of the vinylic resonances of **1a** thus leading to the conclusion that **2a** is a cyclic 2-oxopiperazine (monoketopiperazine). Presumably deprotonation of the amide NH of resin bound **1a** leads to a rapid 6-exo trig cyclization precluding any cyclopropanation. Similarly, when the same dipeptoid capped with N-benzoyl-L-phenylalanine (**1b**) was treated with the Corey reagent a clean cyclization occurred to give, after cleavage from the resin with 95/5TFA/H_2O, a 1:1 ratio of two products (HPLC retention times of 29.1 and 30 min) which both gave the same electrospray protonated parent ion at 555.3. The two compounds were separated by semipreparative HPLC. ^1H NMR showed no vinylic resonances in either fraction. Since starting material **1b** also has a molecular weight of 554 but a different HPLC retention time (30.4 min) and does show the expected vinylic resonances in the ^1H NMR, we conclude that these two products are the diastereomeric monoketopiperazines **2b**. Unfortunately the NMR resonances of **2b** are quite broad, presumably due to hindered rotation about the N-benzoyl group. The possibility of cis-trans amide bond conformers around the isobutyl amide bond also exits. Thus we were unable to assign the stereochemistry.

To simplify the synthesis we decided to attempt the cyclization of **3b**, prepared by acylation of the dipeptoid with FMOC-L-phenylalanine and DIC/HOBt in DMF. Treatment of **3b** with 20% piperidine in DMF (1 x 10 min, 1 x 30 min), followed by treatment with benzoyl chloride/Et_3N in 1,2-dichloroethane (2 x 30 min) again gave two compounds with retention times of 29.1 and 29.9 min, this time in a 3:1 ratio. Both peaks gave a protonated parent ion at 555.3. Thus the diastereomeric monoketopiperazines **2b** could be prepared

Scheme 1

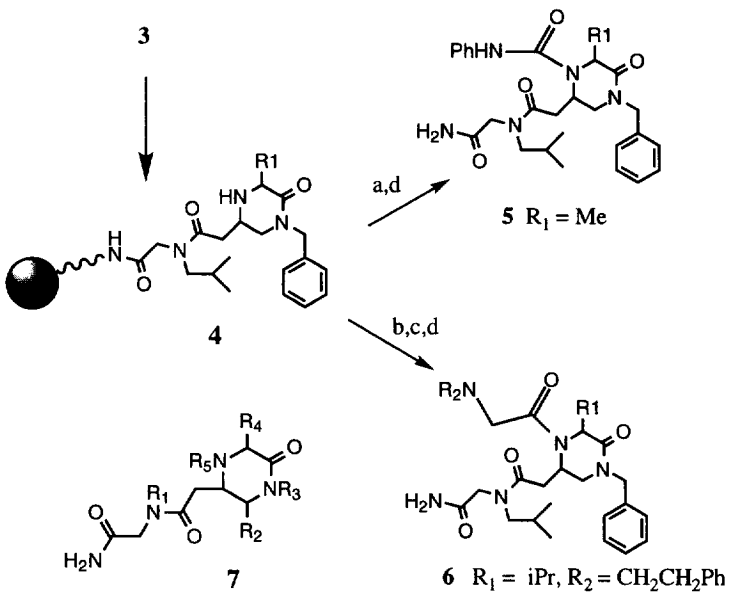


Conditions: a) N-benzoylglycine/HOBt/DIC, RT, 2x30 min; b) trimethylsulfoxonium iodide, NaH, DMSO, RT, 1h; c) FMOC amino acid/ HOBt/ DIC, 1h, RT; d) 20% piperidine/DMF, 1x10 min, 1x30 min, RT; e) benzoyl chloride, triethylamine (1 equiv.), 1,2-dichloroethane, 2x30 min, RT; f) 95/5 TFA/H_20, 20 min, RT.

simply by standard deprotection of the FMOC group of **3b**. The different ratio of diastereomers produced from **3b** versus **1b** is doubtless due to the presence of the benzoyl group on the nitrogen of **1b** during the cyclization. Using this mild procedure a variety of FMOC-L-amino acids was used to produce monoketopiperazines **2a-f.** Aromatic amino acids (tryptophan and phenylalanine) as well as a hindered aliphatic amino acid (valine) all gave products of greater than 80% purity as judged by HPLC. FMOC-L-proline gave the interesting bicyclic compound **2f**. Except in the case of **2b** (R_1 = Bn) all of these N-benzoylated compounds showed only a single peak under our HPLC conditions. Undoubtedly, however, **2a-f** are mixtures of diastereomers, and efforts are underway to synthesize simpler compounds where the diastereomeric ratio can be determined directly by NMR of the crude product. In fact, when **3c** was deprotected with 20% piperidine in DMF, followed by treatment with phenyl isocyanate (rather than benzoyl chloride) in the presence of Et_3N (RT, 2 x 30 min in 1,2-

dichloroethane) two diastereomeric ureas **5** were obtained (retention times of 26.1 and 27.4 min in a 3:1 ratio, both with electrospray $MH^+ = 494.3$). Similarly, when **3d** was treated with 20% piperidine in DMF as before, followed by acylation with 0.6M bromoacetic acid and 0.6M DIC in DMF (2 x 30 min), followed by treatment with 2M phenethylamine (2h, RT), the cyclic tripeptoid **6** was obtained as an approximately 1:2 ratio of diastereomers with retention times of 25.6 and 25.8 min, both with the expected $MH^+ = 564.3$ (Scheme 2).

Scheme 2



Conditions: a) PhNCO, Et_3N, RT, 2x30 min b) bromoacetic acid, DIC, DMF, 2x30 min, RT c) 2M phenethylamine in DMSO, 2h, RT d) 95/5 TFA/H_2O, 20 min, RT.

These examples show that the chemistry described here, while leading to only modest 1,3 asymmetric induction, neverthless has excellent possibilities for the development of combinatorial libraries. Hence one can readily envision libraries of compounds such as **6** which contain four diverse elements arranged around the monoketopiperazine ring. Three of the elements come from the large supply of commercially available amines while the fourth comes from FMOC amino acids. Similarly the free secondary amine of intermediate **4** can be reacted with a variety of acylating agents (isocyanates, acid chlorides, sulfonyl halides etc) to produce other interesting types of highly diverse, heavily functionalized libraries. Finally, a 3-substituted bromocrotonic acid can be used to introduce a further substituent as R_2 in **7.** The simplicity of the synthesis makes it readily adaptable to robotics. One limitation should be noted: anilines or hindered amines such as benzhydryl amine do not work as NR_3 as the synthesis is currently performed. The problem with anilines is probably due to the low

reactivity of the aniline nitrogen in the acylation step and could perhaps be overcome by the use of FMOC amino acid fluorides.[3] The failure to acylate hindered amines may be due to steric interaction with the bulky FMOC protecting group.

Although our original goal of cyclopropanating the unsaturated peptoid backbone was thwarted, an interesting family of constrained cyclic peptoids was obtained instead. Further applications of this chemistry as well as the construction of a full scale library of monoketopiperazines are underway. [4]

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4. Typical experimental procedure (Compound **2b**): Rink amide resin (5.7 gm, 0.51 mmol/gm substitution, Advanced Chemtech) was swollen in DMF, then drained and treated 1x 5 min and 1x 30 min with 50 mL of 20% piperidine in DMF. The resin was washed well with DMF, then treated 2 x 30 min with a solution of bromoacetic acid (30 mmoL) and diisopropyl carbodiimide (DIC) (30 mmoL) in DMF (50 mL). The resin was washed well with DMF, then treated for 2h at RT with a 2.0 M solution of isobutyl amine in DMSO (50 mL). The resin was again washed with DMF and treated 2 x 30 min with 4-bromo-2-butenoic acid (30 mmoL) and DIC (30 mmoL) in DMF (50 mL). The resin was washed with DMF, then treated for 2h with a 2M solution of benzylamine in DMSO (50 mL). The resin was then washed with DMF and dichloromethane and dried overnight *in vacuo* at RT. All the synthesis operations above were performed under Ar in a 250 mL fritted reaction vessel with agitation on an orbital shaker at 200 rpm. A 1.5gm portion of this unsaturated dipeptoid was then swollen with DMF and drained. The resin was then treated with a solution of FMOC-L-phenylalanine (15 mmoL), HOBt (15 mmoL) and DIC (15 mmoL) in DMF (25 mL) for 1h. The resin was then washed and dried as before. A 190 mg portion of the capped dipeptoid was transferred to a Symphony Multiple Peptide Synthesizer (Rainin Instruments) and swollen in DMF for 5 min followed by treatment with 20% piperidine in DMF (1 x 5 min, 1 x 30 mim, 5 mL). The resin was washed well with DMF and then 1,2-dichloroethane (1,2-DCE).Then the resin was treated 2 x 30 min with 2 mL of 1.0 M benzoyl chloride in 1,2-DCE and 2 mL of 1.0M Et_3N in 1,2-DCE. The resin was then washed well with DMF and dichloromethane and cleaved with 95/5 TFA/H_2O, 20 min, RT to give crude **2b.** The crude products were characterized by hplc (C-18 RP, Vydac, gradient 0-80% acetonitrile with water containing 0.1% TFA over 40 min., 1.0 mL/ min. flow rate. Detection at 214 nm) and electrospray ms. Proton nmr spectra were obtained for all compounds.

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