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SOLUTION AND SOLID PHASE COMBINATORIAL SYNTHESIS OF PEPTIDOMIMETIC LIBRARY CONTAINING DIVERSIFIED α-METHYLATED AMINO ACIDS

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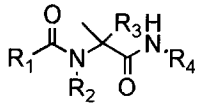
Abstract: A combinatorial peptidomimetic library containing diversified α-methylated amino acids was generated by the Ugi four component condensation (4cc) reaction from acids, amines, isocyanides and ketones in both solution and solid phase synthetic procedures. This one-pot methodology overall gave fair to good yields, which compare well with multi-step syntheses.

Peptidomimetics have become immensely important for new drug discovery since peptides are essential to virtually every biochemical process. Most processes are initiated by the binding of a peptide to a protein. During such binding, peptides adopt a specific conformation (bioactive conformation). Thus, in drug discovery studies to obtain highly active and selective compounds, conformational constraints that mimic the bioactive conformation as closely as possible have been adopted. Many of the resulting constrained peptidomimetics have demonstrated higher bioactivity and selectivity than their parent peptides. Moreover, in many cases, these peptidomimetic compounds have shown pharmacodynamic properties superior to natural peptides, including good oral bioavailability and long duration of action.[1]

Various constrained amino acids have been incorporated into many peptides as constraints to stabilize desired conformations. Among them, the α-methylated amino acid[2] is well known to stabilize β-turn or 3_{10}-helix in tripeptides and longer peptides. Such secondary structures are very often found in the bioactive conformations of various peptides. Thus, peptidomimetic libraries containing α-methylated amino acids such as **1** are useful in accelerating drug lead generation.[1]



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However, several difficulties can be anticipated in the construction of peptidomimetic libraries from α-methylated amino acids using conventional peptide coupling methods. For example, only a limited number of α-methylated amino acids are commercially available and the synthesis of α-methylated amino acids requires several steps reducing the ease of diversification of the sidechain.[3]

Thus, this paper describes the preparation of a peptidomimetic library containing diversified α-methylated amino acid using the Ugi 4-component condensation (4CC) reaction in solution and solid phase

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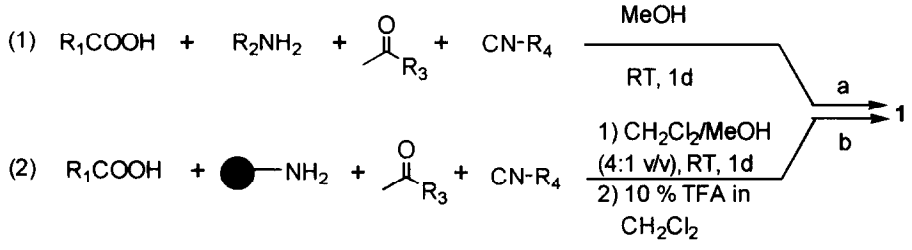
(Scheme 1).[4] Up to now, this reaction with ketones was difficult compared to that of aldehyde on solid phase and solution phase synthesis.[4a,4b] From this method, the desired peptidomimetics were obtained in a one-pot synthesis. Using various methyl ketone derivatives (R_3), diverse α-methylated amino acid moieties were produced. In addition, the resulting petidomimetics can be elongated by the introduction of appropriately protected amino acids in the R_1 component and protected carboxylic acids in the isocyanide R_4 component.



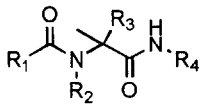
Scheme 1. Synthesis of peptidomimetic library containing α-methylated amino acids in solution (a) and on solid phase (b)

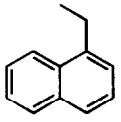
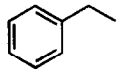
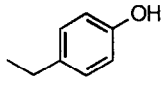
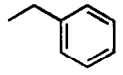
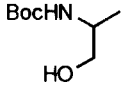
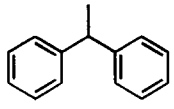
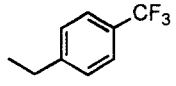
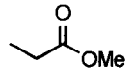
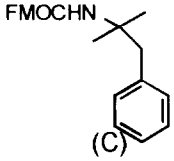
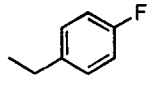
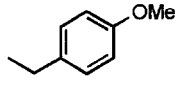
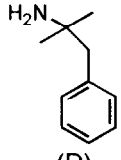
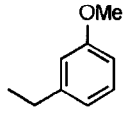
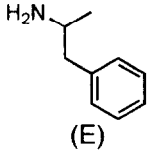
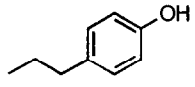
The general experimental procedure is as follows: i) in solution phase; carboxylic acid (1.0 eq), amine (1.0 eq), ketone (1.0 eq) and isocyanide (1.0 eq)[5] in methanol were stirred for 1 day at room temperature. The solvent was then removed under vacuum followed by acid workup to remove unreacted amine and base workup to remove the unreacted acid which was performed in an ependorf tube. Generally, good purity (average 92%) and 60-70% yields were obtained. ii) on solid phase; commercially available Rink amide resin[6] was treated with 20% piperidine in DMF for 1 hour to remove the Fmoc protecting group. Excess DMF was removed by filteration and the resin was rinsed with CH_2Cl_2 and methanol several times. The treated resin (1.0 eq), acid (3.5 eq), ketone (3.5 eq) and isocyanide (3.5 eq) were added in CH_2Cl_2 and methanol (4:1 v/v) at room temperature in a 96 well plate. The reaction mixture was stirred for 1 day at room temperature then excess solvent and reagents were removed by filtering and rinsing with CH_2Cl_2 and methanol several times. The dried resin was treated with 10% TFA in CH_2Cl_2 to deblock the resin. After evaporation of solvent, the desired product was given in 30-40% yield.

In the solid phase method, the products were cleaved from the resin by treatment with 10% TFA in DCM, concentrated and then analyzed by LC and MS. The chromatographed products were analyzed again by LC and ^1H NMR to confirm structure and purity (average 51%). In the solution method, the desired products were treated using the above mentioned general procedure and obtained in 60 % to 70 % yields. Although the yields were a little low on solid (average 40%) and fair in solution (average 66%), these yields are good when compared to the overall yields of multi-step syntheses.[2] The isolated yields of the members of the peptidomimetic library are shown in Table 1. Even with bulky acid and amine residues for R_1 and R_2 the procedure worked satisfactorily.

In conclusion, an efficient and general method has been demonstrated for the synthesis of 150 peptidomimetic libraries containing diversified α-methylated amino acids using a Rink amide linker through a one-step Ugi 4- component condensation reaction on solid and in solution. Although the construction of α-methylated peptidomimetics is difficult, this methodology resulted in good to fair yields.

Table 1. Representative members of the peptidomimetic library prepared using the Ugi 4-component condensation reaction



R_1	R_2	R_3	R_4	Combination	Method	Yield[a]
 (A)	 (I)	 (1)	 (α)	AxIx1xα	a	70
				AxIIx1xα	a	71
				AxIIIx1xα	a	67[b]
 (B)	 (II)	 (2)	 (β)	BxIIx1xα	a	63
				AxIIIx1xα	b	42
 (C)	H (III)	 (3)		CxIIx1xα	a	70
				DxIIIx1xα	b	41
				DxIIIx1xβ	b	43
		 (4)		ExIIIx1xβ	b	37
				ExIIIx2xβ	b	35
 (D)		 (5)		ExIIIx1xβ	b	41
				ExIIIx5xβ	b	37
 (E)		 (6)		ExIIIx3xβ	b	31
				ExIIIx6xβ	b	39

Method; a: solution phase synthesis. b: solid phase synthesis. [a]isolated yields were based on the support-bound. [b]obtained from AxIIx1xα combination in solution phase and then removing the diphenylmethyl protecting group by treatment with TFA.

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4. i) in sloution phase: a) Weber, L.; Wallbaum, S.; Broger, C.; Gubernator, K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2280. b) Keating, T.A.; Armstrong, R.W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. c) McAlpine, I.J.; Armstrong, R.W. *J. Org. Chem.* **1996**, *61*, 5674. d) Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810. ii) on solid phase: a) Armstrong, R.W.; Combs, A.P.; Tempest, P.A.; Brown, S.D.; Keating, T.A. *Acc. Chem. Res.* **1996**, *29*, 123. b) Armstrong, R.W.; Brown, S.D.; Keating, T.A.; Tempest, P.A. *Combinatorial Chemistry, Synthesis and Application*, Ed by S.R. Wilson and A.W. Czarnil, Wiley-Interscience, New York **1997**, 153. c) Ugi, I.; Domling, A,; Horl, W. *Endeavour* **1994**, *18*, 1152. d) Kiselyov, A.S. and Armstrong, R.W. *Tetrahedron Lett.* **1997**, *38*, 6163.

5. Commercially unavailable isocyanide was prepared as follows: to a solution of amine in ethyl formate was added dropwise triethylamine (1.1 eq) while refluxing in a round bottomed flask. The reaction mixture was refluxed overnight while protected with a drying tube, cooled to room temp, filtered, to remove triethylamine hydrochloride removed by washing with ether, the ether evaporated and then purified by then chromatography. $POCl_3$ was added dropwise to a CH_2Cl_2 solution at 0 °C of the previously formed N-formylaldehyde and triethylamine. The solution was allowed to stir at 0 °C for 30 minutes after which the reaction was quenched with cold Na_2CO_3 (2.0 eq.), the aqueous layer was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and then chromatographed.

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