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Synthesis of Nitrogen-containing Cyclopeptides from N-Terminal Lysine Precursor on Solid Supports

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Abstract: Three synthetic routes for the preparation of nitrogen containing cyclic compounds have been developed, in which the assembling of Fomc-Lys(Boc) residue at N-terminal of resin-bound intermediates is a key prerequisite. Six peptides with nitrogen containing local cyclic structure were efficiently synthesized in good yield starting from chloromethyl resin.

Keywords: Local-cyclic peptides, intramolecular cyclization, solid-phase synthesis, *pseudo*-dilution effect.

The nitrogen containing ring system has usually attracted considerable interest in the search for novel pharmaceuticals. Especially in the case of small peptides, introducing a local constrained nitrogen containing ring as the surrogate for Arg, Lys and His residues would be a reasonable way to enhance the resistance of leading molecules to enzymatic hydrolysis.

In connection with our research program on structure modification of RGD[1], reversal YIGSR[2] and other basic oligopeptides, we were interested in synthesizing N-terminal cyclized analogues. Three different synthetic routes were implemented, and therefore the N-terminal structure in targeting compounds were dissimilar each other. In order to ensure intramolecular cyclization, the synthesis was performed on solid supports (**Scheme 1**-**3**)[3].

It is worthy of noting for the synthesis of compound **8**, besides the synthetic route presented in **Scheme 2**, there would be another way to construct 12-membered ring. In that case, Boc-Ida (iminodiacetic acid) would be coupled first with the α-amino group of lysine residue from **5**, but the following coupling efficiency between the ε-NH_2 and the second carboxylic group of Ida would be very poor, because the free imino group of Ida liberated simultaneously with ε-amino group and would increase the polarity, decrease the swelling ability of the resin in organic solvents. Based on this consideration, more reasonable route showed in **Scheme 2** has been adopted and finally the targeting compound **8a** and **8b** were obtained in good yield (**Table 1**).

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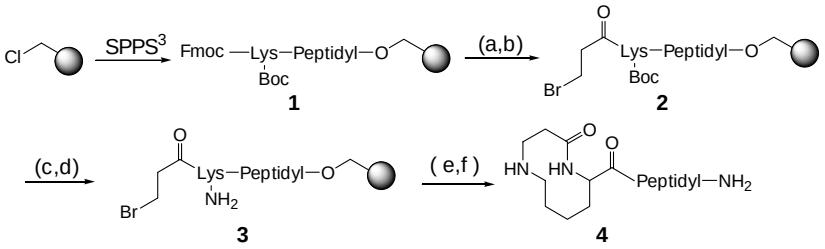
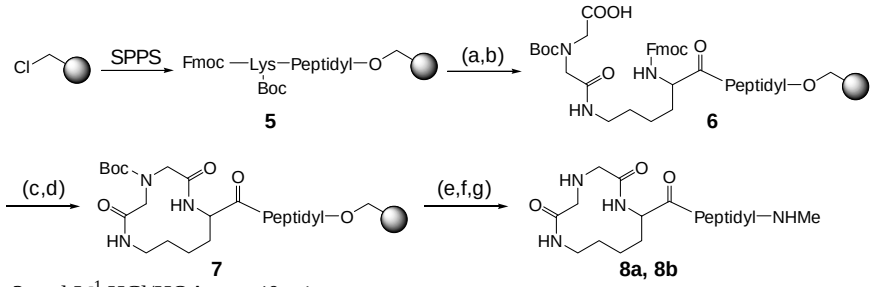
Scheme 1



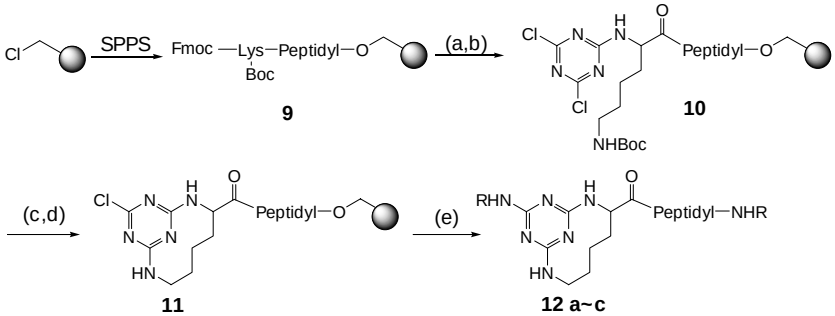
(a) 20% piperidine/DMF, rt, 0.5 h
(b) $BrCH_2CH_2COOH$, DCC/CH_2Cl_2, rt, 3 h
(c) 3 mol·L^{-1} HCl/ HOAc, rt, 40 min
(d) 5%TEA/DMF
(e) Cs_2CO_3/DMSO, 60℃, 48 h
(f) 27% NH_3/MeOH-THF(2:1) , rt, 24 h

Scheme 2



(a) 3 mol·L^{-1} HCl/HOAc, rt, 40 min
(b) Boc-iminodiacetic acid, DCC/THF, TEA, rt, 8 h
(c) 20% piperidine/DMF, rt, 0.5 h
(d) HBTU, NMM/DMF, rt, 5h;
(e) 3 mol·L^{-1} HCl/HOAc, rt, 40 min
(f) TEA/DMF
(g) 27% H_2NMe/H_2O-THF(1:1), rt, 24 h

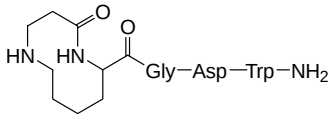
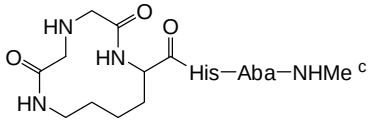
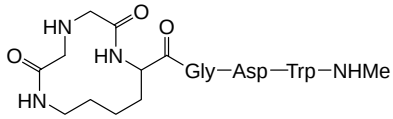
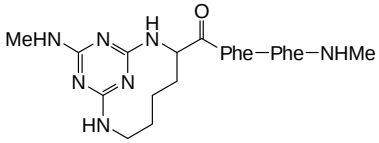
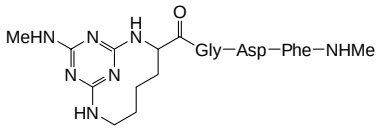
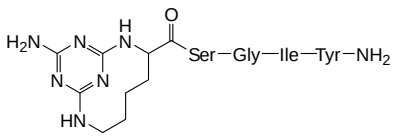
Scheme 3



(a) 20% piperidine/DMF, rt, 0.5 h
(b) Cyanuric chloride/CH_2Cl_2, DIEA, rt, 2 h
(c) 3 mol·L^{-1} HCl/HOAc, rt, 40 min
(d) DIEA/THF(1:5), rt, 48 h
(e) 27% H_2N-R/EtOH-THF, 40℃, 24 h

In the preparation of triazine involved N-terminal cyclic peptides (**12a~c**), a notable merit of *pseudo*-dilution effect (PDE) on resin supports was shown. Compared with conventional solution-phase synthesis, in which a great attention should be paid to deal with different amination at three reaction sites in cyanuric chloride (Cya) molecule, only one site of Cya was bound to resin component giving **10**. Also based on PDE, the intramolecular cyclization was easy achieved following the second amination between the next reactive site of Cya and ε-amino group of lysine residue, forming 10-membered ring structure **11**.

Table 1 Yields and selected analytic data of *N*-terminal cyclic peptides

Product	Structure	Yield (%)[a]	AA ratio[b]	MS [M+H]$^+$ Found	MS [M+H]$^+$ Calculated
4		81	Gly 1.01, Asp 1.00, Trp 0.98	558.2	558.3
8a		78	Lys 1.02, His 0.99, Aba 1.00	479.5	479.3
8b		72	Lys 1.01, Gly 1.00, Asp 0.99, Trp 0.98	615.7	615.3
12a		76	___	560.6	560.3
12b		77	Gly 1.00, Asp 0.99, Phe 1.01	585.7	585.3
12c		71	Ser 0.98, Gly 1.00, Ile 1.00, Tyr 0.99	658.4	658.3

a. Overall yield based on the substitution of chloromethyl resin
b. From amino acid analysis (AAA)
c. Aba: 4-aminobutyric acid

In summary, we have accomplished the synthesis of nitrogen containing local-cyclo peptide derived from lysine residue on solid support. All the products (**4**, **8a**,**b** and **12a~c**) were obtained in 71~86% overall yields, and characterized by AAA and ESI-MS (**Table 1**.)

The results from present study indicated that solid-phase synthesis would be an efficient way for the preparation of cyclic compounds due to the PDE elicited from solid supports.

Acknowledgments

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References and Notes

1. M. D. Pierschbacher, E. Ruoslahti, *Nature*, **1984**, *309*, 30.
2. J. Graf., R. C. Ogle, F. A. Robey, *et al.*, *Biochemistry*, **1987**, *26*, 6896.
3. General procedure of SPPS (Solid-Phase peptide synthesis), (i) Attachment of C-terminal residue: three equivalents of Boc-AA-OH (the precursor of *C*-terminal residue), Cs_2CO_3 and 0.1 equivalent of NaI were mixed with chloromethyl resin in DMF. The suspension was rotated at 60℃ for 24 h. After washing with DMF (×5) and EtOH (×5) and CH_2Cl_2(×2), the Boc-AA-resin was mixed with 3 mol·L^{-1} HCl/HOAc (10 mL/g resin, 2 min+40 min), and then washed with CH_2Cl_2 (×5), EtOH (×5) and Et_2O (×2). (ii) Sequence assembly: In each coupling cycle, five equivalents of Fmoc-AA-OH were activated by HBTU/NMM/DMF, and shaked with amino component on resin at room temperature for 3h. Fmoc group was removed by 20% piperidine in DMF. The washing after coupling reaction and de-Fmoc treatment were performed by use of DMF(×5), EtOH(×5) and Et_2O(×2).
4. G. R. Gustafson, C. M. Baldino, *et al.*, *Tetrahedron*, **1998**, *54*, 4051.

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