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An Efficient Synthesis of Cyclopeptides Bridged with Aliphatic-aryl Ether Bond

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Abstract: Based on the pseudo-dilution effect (PDE) on solid support, three cyclopeptides with an aliphatic-aryl ether bond as the bridge were synthesized *via* S_N2 reaction between bromoacetylated at N-terminal and the phenol –OH group in C-terminal Tyr residue. All the products were obtained in good overall yields and characterized by related analytic data.

Keywords: Intramolecular S_N^2 reaction, cyclopeptide, solid-phase organic synthesis, *pseudo*-dilution effect.

In the most cases, the conformational flexibility of peptide often results in low selective protein binding and poor oral bioavailability. Therefore, many efforts have been made to design and prepare comformational constrained peptide analogues. Some routes for the synthesis of cyclopeptide mimetics have been reported in literatures. However most of them required introducing a special building block[1-3] as the bridging structure and usually need some orthogonal protecting strategy[4,5]. Keeping this in view, we wish to report an efficient way to synthesizing cyclic ether containing peptides **A**, **B** and **C** *via* minimum steps, aimed at getting modified OGP fragment[6].

In the present approach, the key precursor was a peptide fragment jointed with bromoacyl at the N-terminal and a tyrosine residue at the C-terminal. For the synthesis of products **A** and **B**, the chloromethyl resin was used as solid supports. After the C-terminal Tyr residue attached on the resin, different sequences were assembled by standard SPPS procedure[7]. Finally, using different kinds of aminolysis, the desired products **A** and **B** were liberated from the resin (**Scheme 1**).

It is worthy of noting that there are two modified residues in the main chain of product **C**: (*p*-HO-Ph-N-)Gly mimic-Tyr, (Bn-N-)Gly mimic-Phe and Aca (ω-amino-caproic acid) mimic -GlyGly- of OGP fragment. For the synthesis of NSG (N-substituted glycine)[8] peptide, excess amount of primary amines were used to substitute bromide from bromoacetyl on the resin **(Schem 3)**. In current conditions, the benzyl ester linkage between the peptide and the resin would be cleaved simultaneously *via* aminolysis with RNH_2. In order to avoid the premature cleavage from solid supports,

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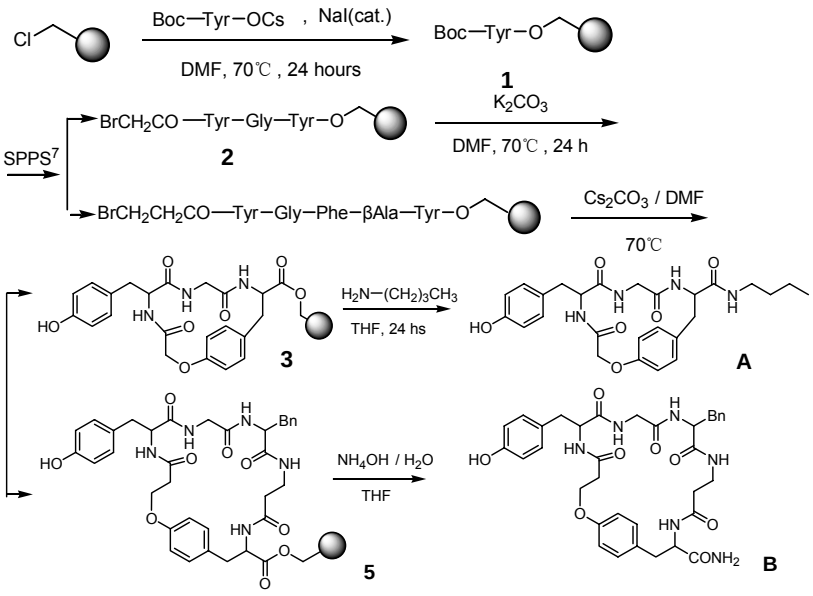
Scheme 1



(trifluoromethanesulfonic acid) [9] was used to release the final product from MBHA resin (**Scheme 2**).

General procedure for the formation of the intramolecular ether bonding

MBHA resin was used in the synthesis of compound **C**, and TFMSA bromoacyl peptidyl-resin, K_2CO_3 (for **A**, **C**) or Cs_2CO_3 (for **B**) were mixed in DMF with the ratio of 1 mmol : 2 mmol : 15~20 mL. The mixture was stirred at 70℃ for 24 hours, and then filtrated. The resin was washed with following solvents: DMF×3, 95% EtOH×2, H_2O×3, EtOH×3 and Et_2O×2.

*General procedure for the aminolysis to release **A** and **B***

0.5 g peptidyl-resin was mixed with 6 mL of butylamine (for **A**) or 6 mL of NH_4OH (for **B**) and 6 mL of THF in a sealed vessel. After 24 hours (with occasional shaking), the supernatent was collected and concentrated at 50℃ in vacuum to dryness. To the residue was added 30 mL of anhydrous ether. After trituration and filtration, powdered products **A** (165 mg) and **B** (131 mg) were obtained.

*General procedure for TFMSA cleavage to release **C***

1.0 g peptidyl-MBHA resin was mixed with 1.5 mL of thioanisole 10 mL of TFA and 1.2 mL of TFMSA at 0℃. After stiring for 2 hours, the supernatent was filtered into 200 mL cold anhydrous ether and the crude product was precipitate out.

Scheme 2

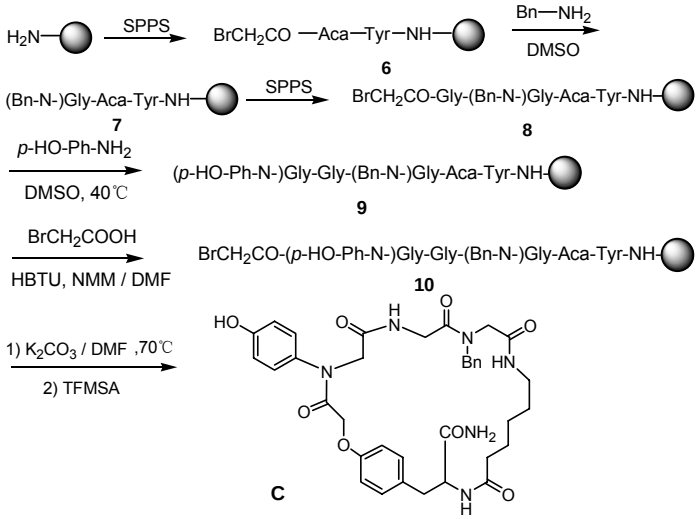
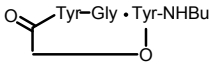
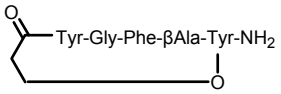
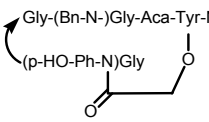


Table 1 Yields and selected analytic data of final products

	Products	Yield[a] (%)	AA ratio[b]	ESI-MS Found	ESI-MS Calculated	Purity[10] (HPLC)
A		82.5	Gly 1.00, Tyr 1.91	497.2 (M+H)	496.6	58.6%
B		80.6	Gly 1.00, Phe 1.01 β-Ala 1.10, Tyr 1.92	673.6 (M+H)	672.7	61.1%
C		58.9		725.3 (M+K)	686.8	62.9%

a: Overall yield from resin ; b: From amino acid analysis (AAA); c: Aca: ω -amino capronic acid

General procedure for the purification of product ***C***

The viscous precipitate was separated from ether and dissolved in 50 mL water. The aqueous solution was washed with ether three times, then neutralized with 10% NH_4OH and passed through a C-18 filtering layer, which was drained with plenty of water until the filtrate showed negative result from ninhydrin test, and then eluted with 150 mL EtOH-HOAc (2:1,V/V). The collected eluate was concentrated at 50℃ in vacuum to dryness. The residue was triturated with 30 mL anhydrous ether and filtered giving powdered product **C** (297 mg).

In summary, we have achieved the synthesis of cyclic ether-linked peptides on solid supports with minimum steps. All final products (**A**, **B** and **C**) were obtained in good overall yields (58.9~87.1%), and characterized by AAA (except **C**) and ESI-MS **(Table 1)**. The results of the present study indicated that the solid-phase synthesis would be an

efficient way for the preparation of cyclic compounds benefited from the *pseudo*-dilution effect on solid support.

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References and Notes

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10. The Conditions for HPLC analysis: Instrument type: Alltech 426, Column: Alltima C18, 5u (10×250 mm), Mobile phase: buffer A: 0.05% TFA/H_2O; buffer B: 0.05% TFA/acetonitrile is from 0% to 100% in 15 minutes at a flow rate of 1.0 mL/min , Wave length: 278 nm.

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