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Improvement of Thioester Method by Using Pac Ester for Synthesis of Cyclopentapeptides

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Abstract: Thioester method was improved by using Pac (phenacyl group) ester as protecting group of 3-mercaptopropionic acid. Two cyclopentapeptides c(Ala-Tyr-Leu-Ala-Gly) and c(Pro-Tyr-Leu-Ala-Gly) were synthesized successfully by this method.

Keywords: Thioester method, Pac ester, cyclopentapeptide.

Thioester method was developed by Aimoto[1] and Tam[2] for peptides synthesis. In this method, the protected thioester was linked to a resin by solid-phase method. After elongation of the peptide chain, the peptide thioester was cyclized successfully on or off resin[3]. We extended the thioester method by using Pac (Pac=-$CH_2COC_6H_5$) ester as a protecting group of 3-mercaptopropionic acid. Two cyclopentapeptides, c(Ala-Tyr-Leu-Ala-Gly) and c(Pro-Tyr-Leu-Ala-Gly) were synthe-sized successfully by this method.

3-mercaptopropionic acid was used as a thioester group of Boc-Gly-OH. Boc-Gly-S-CH_2CH_2COOH[1] was reacted with 2-bromoacetophenone (PacBr) easily. The resulting thioester Boc-Gly-$SCH_2CH_2COOPac$ was then elongated using DEPBT[4] as a coupling reagent by solution method. The synthetic route was shown in **Scheme 1**. All of the compounds synthesized were identified by FAB-MS, ^{1}H NMR , elemental analysis *etc*..

Physical constants of some linear peptides and their derivatives were shown in **Table 1**. The phenacyl group was removed with great facility at room temperature with zinc in 90% acetic acid[5]. After removal of Boc protecting group from N-terminal, two pentapeptide thioesters, H-Ala-Tyr-Leu-Ala-Gly-SCH_2CH_2COOH and H-Pro-Tyr-Leu-Ala-Gly-SCH_2CH_2COOH were obtained. Cyclization was carried out in 0.2 mol/L sodium acetate buffer from pH 4.6 to 5.8. Effects of different buffer pH, different concentration of silver ions on the cyclization yields were studied.

In summary, the protected amino acid thioester and peptide derivatives synthesized by the improved method, were easy to be purified, so the final linear peptides were pure enough for cyclization. The Pac group was easy to be removed from C-terminal.

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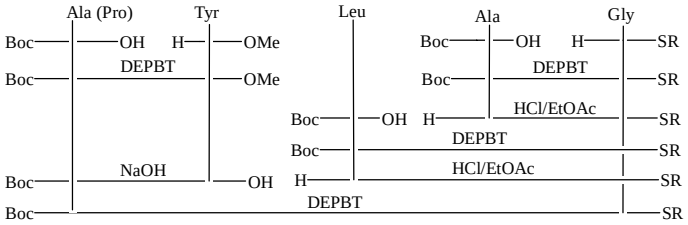
Scheme 1 Synthetic route of Boc-Ala (Pro)-Tyr-Leu-Ala-Gly-$SCH_2CH_2COOPac$



R= $-CH_2CH_2COOPac$; Pac= $-CH_2COC_6H_5$

DEPBT: 3-(diethoxyphosphoryloxy)-1, 2, 3 - benzotriazin - 4 (3*H*)-one

Table 1 Physical constants of some linear peptides and their derivatives[6]

No.	Compounds	Yield (%)	m.p.(°C)	FAB-MS*	$[\alpha]_D^{20}$
a	Boc-Gly-SCH_2CH_2COOH**	85	103-106	264	
b	Boc-Gly-$SCH_2CH_2COOPac$	85.3	73-73.5	382	
c	Boc-Ala-Gly-SR***	75.2	97.5-98.5	453	-12.3 (c 1, AcOEt)
d	Boc-Leu-Ala-Gly-SR	56.5	108.5-109	566	-20.8 (c 1, AcOEt)
e	Boc-Pro-Tyr-Leu-Ala-Gly-SR	50.8	132-135	826	-37.5 (c 1, MeOH)
f	Boc-Ala-Tyr-Leu-Ala-Gly-SR	44.6	127-130	800	-32.8 (c 1, MeOH)

* $[M+H]^+$, ** Total yield from Boc-Gly-ONp, *** R=-$CH_2CH_2COOPac$, the following is the same.

Furthermore, this method is flexible for peptide chain elongation, either from C-terminal or N-terminal. It is also an efficient and practical method for synthesis of bioactive peptides, including cyclic peptides.

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References and Notes

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6. **a**. Lit[1]: 104-106°C. **b**. Anal calcd for $C_{18}H_{23}NO_6S$: C 56.69, H 6.04, N 3.68. found: C 56.91, H 6.10, N 3.52. **c**. Anal calcd for $C_{21}H_{28}N_2O_7S$: C 55.75, H 6.19, N 6.19. found C 55.65, H 5.83, N 6.06. **d**. Anal calcd for $C_{27}H_{39}N_3O_8S$: C 57.34, H 6.90, N 7.43. found: C 57.32, H 6.88, N 7.28. **e**. Anal calcd for $C_{41}H_{55}N_5O_{11}S$: C 59.61, H 6.72, N 8.48. found: C 59.45, H 6.60, N 8.40. **f**. HRMS calcd for $C_{39}H_{53}N_5O_{11}S$ 800.3540 $(M+H)^+$, found 800.3522.

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