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Good Coupling Performance of PyBOP in the Solid-phase Synthesis of Tetrapeptide, OH-Pro-Leu-Ala-Ileu-NH_2

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Abstract. PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) was found as a good coupling reagent in the solid-phase synthesis of a tetrapeptide, OH-Pro-Leu-Ala-Ile-NH_2**1**. The peptide was chosen as the target of synthesis due to its bioactivity as an antibacterial agent. The synthesis was carried out on solid support, 2-chlorotrityl chloride resin with Fmoc strategy. Proline was selected as the first amino acid to be attached on the resin that was followed by the attachment of leucine, alanine and isoleucine. In the synthesis, Fmoc deprotection step was undertaken by taking advantage of 20% piperidine in DMF and coupling reaction was done by the addition of amino acid and PyBOP in a mixture of dichloromethane and DMF (1:1) and in the presence of basic DIPEA. The analytical RP-HPLC of the final product showed a single peak at 22.0 minutes (20-90% of acetonitrile in water with 0.1% of TFA during 30 minutes), indicating that each coupling could give a good coupling performance that resulted in a pure product. The desired product showed the correct molecular weight with *m/z* 413.3 $[M+H]^+$ and 435.3 [M+Na].

INTRODUCTION

Peptides have been found to play a crucial role in the fundamental physiological and biochemical functions of life. They have for decades now attracted much attention for their potential therapeutic use. Fosgerau and Hoffman (2016) mentioned that peptides can act as hormons, neurotransmitter, growth factors, ion-channel ligands, or anti-infectives [1].

Due to the interesting bioactivities of the peptides, studies on peptides is still of our interest, particularly on the exploration of synthetic method of the peptides. Total synthesis of peptides can be undertaken in two methods. The first method is peptide synthesis in solution phase that has been clearly shown to be challenging and time consuming [2-4].Most of the time, purification between steps is also required which also impacts the yield. The second method is solid-phase peptide synthesis, pioneered by Merrifield [5].This method is useful to overcome some of the problems inherent in solution chemistry and has been applied to successfully synthesise several peptides [6-8]. The later method was employed and described in thepresent paper.

One of peptides of interest is a cyclic tetrapeptide, OH-Pro-Leu-Ala-Ile-NH_2**1** (Figure 1), that has antibacterial properties. This peptide was isolated from marine bacteria, *Pseudomonas* sp. and *Pseudoalteromonas* sp [9].This peptide showed a moderate antibacterial activity towards Gram-negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and antifungal activity against pathogenic *Candida albicans* with minimum inhibitory concentration (MIC) values of 6 μg/mL. Dahiya & Gautam (2011) hadsuccessfully synthesised the peptides through the solution-phase method [9]. The linear peptide was synthesised in solution phase that was followed by the cyclisation.

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