An approach to the Synthesis of Oxytocin from cystine

ABSTRACT

Oxytocin is a single chain oligopeptide containing nine amino acid residues with one disulfide bridge. The amino acid sequence of oxytocin is as follows: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH2 │ │ └─────────┘

A synthetic approach to cystine-containing peptide Using cystine as a starting material is disclosed in the thesis. Emphasis is placed on enzymatic catalyzed condensation and liquid phase method to study the synthesis of oxytocin. Enzyme catalyzed peptide synthesis was explored first. Ficin was able to catalyzed the condensation of (Boc-Cys)2 with amino acid ester and triethylamine to form asymmetric cystine peptide. The reactions were performed at pH 5.7 and shaken at 24 ℃ for 4 hours. Mono coupled cystine peptide was afforded in the yield of 73.7%. However, the coupling of (Boc-Cys)2-TyrOMe and Pro-Leu-GlyNH2 was not successful. Therefore, condensation of (Boc-Cys)2 with Pro-Leu-GlyNH2 was studied as an alternative pathway. Boc-Pro and LeuOBn were condensed with DCC to form Boc-Pro-LeuOBn, which was hydrogenated to obtain Boc-Pro-Leu. Pro-Leu-GlyNH2 was synthesized by coupling of Boc-Pro-Leu with GlyNH2 using DCC and DMAP. Removal of the Boc group by TFA generated Pro-Leu-GlyNH2. (Boc-Cys)2-Pro-Leu-GlyNH2 was synthesized smoothly by using DCC as condensing agent. The other segment, Tyr-Ile-Gln-AsnOMe, was also synthesized by a stepwise method using DCC. Cbz-Asn was reacted with dimethyl sulfate to form Cbz-AsnOMe, which was hydrogenated to remove Cbz group. The resulting compound was then coupled with Cbz-Gln to form Cbz-Gln-AsnOMe, which was hydrogenated to remove Cbz group and obtain Gln-AsnOMe. Boc-Tyr was reacted with IleOBn to form Boc-Tyr-IleOBn, which was hydrogenated to obtain Boc-Tyr-Ile. Coupling of Boc-Tyr-Ile with Gln-AsnOMe and removal of the Boc group by TFA afforded Tyr-Ile-Gln-AsnOMe. Unfortunately, the tetrapeptide and the pentapeptide were unable to form a protected nonapeptide with various coupling reagents.

Keywords: oxytocin; cystine; liquid phase synthesis; enzymatic catalyst

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