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(R, S) 2-Fluoro (Chloro) -4'-Carboxy-Triphenyl Methanol. Novel Acid Labile Trityl Type Handles For Solid Phase Peptide Synthesis

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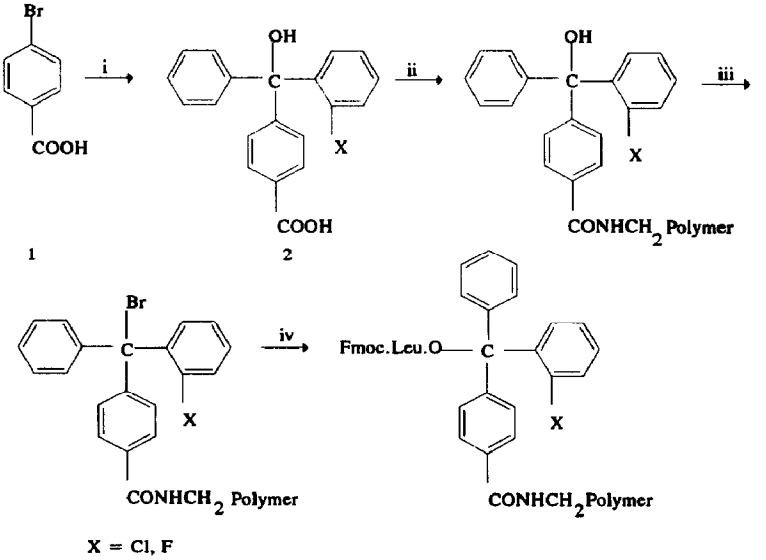
Abstract: Novel trityl type handles have been prepared and applied to solid phase synthesis using 9 - fluorenylmethyloxycarbonyl (Fmoc) for N^a - amino protection and acid labile protecting groups for side chain protection. The cleavage of the resultant ester can be carried out by using appropriate mild acidic cocktails 0.1 % (v/v) trifluoroacetic acid, and TFE : CH_2Cl_2 : CH_3COOH 1 : 8 : 1 (v/v).

In recent years, a strategy employing the orthogonal[1] combination of base labile 9 - fluorenylmethyloxy carbonyl (Fmoc) for N^a - amino protection has gained considerable popularity[2]. With this technique the removal of fully protected peptides from the solid support can be achieved by using mild acidic conditions[3]. Several other studies [4,5,6] have been made to this end in an effort to achieve the optimum conditions for selective removal of the peptides in high purity and yields.

The target molecule (R,S) 2-fluoro(chloro)-4'-carboxy-triphenyl methanol (2) was synthesized in 50% yield by the route shown in scheme 1 according to the procedure described by W.E. Parham et. al.[7] The



Scheme 1. (i) BuLi, 2-fluoro(chloro)benzophenone; (ii) HOBT, DIPCDI; DMF, aminomethylpolystyrene; (iii) CH_3COBr, CH_2Cl_2; (iv) FMOC-Leu-OH, DIEA, CH_2Cl_2.

overall yield of II to IV stages is 75-80%.

These easily prepared handles can be used with any aminomethyl-resin. The ester bond which is achieved between the Fmoc amino acid and the resin is quite stable (especially the fluoro-derivative, as demonstrated later in this paper) toward to free C^{α} - carboxy group of an incoming protected amino acid during coupling . This stability results to better yields of the target peptide.

In addition, the stability of the ester bond toward to nucleophiles allows the use of 40% piperidine / DMF for the removal of the Fmoc protecting group.

In order to assess the stability of the esteric linkage between amino acid and handle - resin, Fmoc- Val Trt (Cl, F) - R was treated with 0.2 M Boc-Gly-OH in DMF solution and 0.2 M HOBT in DMF solution for 24h. The Fmoc substitution level was measured by U.V. analysis using the fluorene chromophore at the dibenzofulvene - piperidine adduct at 301 nm (ε = 7800 M^{-1} cm^{-1})[8]. Under these conditions, it was found that the loss of the Fmoc-Val-OH for the chloro- and the fluoro-derivative was 1% and 0.25% respectively.

Demonstration of the usefulness of these handles was provided by the synthesis of a protected segment with the sequence : Fmoc-Tyr (But)-Met-Gly-Glu (But)-Ile-Ala-Ser (But)-Phe-Asp (But)-Lys (Boc) Ala-Lys (BOC)-OH. Amino methyl - polystyrene resin, Fmoc amino acids and HOBT / DIPCDI were used for the synthesis, while 20% piperidine in DMF was employed for the deprotection. Also a protected Leu^5 - enkephalin (Fmoc-Tyr (But)-Gly-Gly-Phe-Leu-OH) was prepared either as described above or by using 40% instead of 20% piperidine in DMF solution for the removal of the Fmoc group. In both cases the yield of the Leu^5 - enkephalin was 95% and the purity of the crude peptides was >99% by HPLC. The fully protected peptides have been removed from the solid support by twenty minutes treatment with either a cocktail of AcOH : TFE : CH_2Cl_2 (1 : 1 : 8)[5] or 0.1% (v/v) TFA in CH_2Cl_2.

Synthesis of Trp-Leu-OH posed no problem. The peptide was obtained quantitatively, indicating that no back-addition of the peptide to support has occured.

The purity and yields of the protected fragments were the same using either the chloro- or fluoro-handles.

In conclusion the two new handles have the desirable stability during the peptide synthesis and the appropriate sensitivity towards acids and can be used with any amino - functionalized support.

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