CHAPTER IV

CONCLUSION

Aryl 4-nitrobenzenesulfonates were proved to be useful for peptide synthesis. Aryl esters of a variety of Boc- and Fmoc- protected amino acids, which are the important intermediates for peptide coupling, were prepared in good yield from the reaction between carboxylic acids and aryl 4-nitrobenzenesulfonate in the presence of a tertiary organic base and a catalytic amount of 1-hydroxybenzotriazole (HOBt). In most cases the reaction proceeded as expected under similar conditions except that diisopropylethylamine (DIEA) was used in place of triethylamine when Fmoc-protected amino acids were employed. Furthermore, it was found that these aryl sulfonates could directly be used as efficient coupling reagents for preparing dipeptide esters without prior isolation of the active esters in excellent yield.

The role of HOBt in catalysing the reaction is likely that the HOBt reacted with the aryl sulfonate first to form the benzotriazolyl sulfonate as a reactive intermediate. Further, reaction with the carboxylate ion gave the mixed carboxylic-sulfonic acid anhydride which then reacted with the phenoxide ion generated in the first step to form the aryl ester. Although the existence of the mixed carboxylic-sulfonic acid anhydride could not be proven by direct isolation, direct S_NAr mechanism is unlikely since 2,4,5-trichlorophenyl 4-nitrobenzenesulfonate (**4b**) reacted with morpholine in the presence of HOBt under similar conditions to give exclusively 4-nitrobenzenesulfonylmorpholine and not 2,4,5-trichlorophenyl morpholine which would be the S_NAr product. 4-Dimethylaminopyridine (DMAP) which is normally used as acylation catalyst of hindered alcohol is totally ineffective in catalysing this reaction.

Racemization during peptide coupling by reagent (**4c**) was also studied. It was found that no racemization was observed during the reaction with urethane-protected amino acid, but in the case of *N*-acyl amino acid, the resulting product was completely

racemized. Therefore, the application of this method must be limited to the urethane-protected amino acids.

The aryl 4-nitrobenzenesulfonates as coupling reagents are stable crystalline solids and have some advantages over the most widely utilized reagent, dicyclohexylcarbodiimide (DCC), because of the following facts : (1) no problem of insoluble by-product; (2) excellent synthetic yield and high coupling speed; (3) simplicity of the coupling procedure; (4) simple preparation of the reagents.