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AN IMPROVED PROCEDURE FOR THE CHLOROMETHYLATION OF POLYSTYRENE-DIVINYLBENZENE

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To obtain a solid support for peptide synthesis, Merrifield (1,2) used stannic chloride/chloromethyl methyl ether in order to chloromethylate polystyrene-divinylbenzene beads prior to esterification with salts of tert-butyloxycarbonyl amino acids. Using this procedure, the level of substitution has been difficult to control, particularly at the lower levels suggested as being the best for peptide synthesis. More recently, Feinberg and Merrifield (3) have published a procedure using anhydrous zinc chloride/chloromethyl methyl ether which reportedly is easily controlled to give active chloride contents of 0.1-0.2 meq/g.

We wish to report another procedure for chloromethylation utilizing boron trifluoride-etherate and chloromethyl ethyl ether which offers the following advantages over the procedures previously used: 1) using commercially available chloromethyl ethyl ether while probably carcinogenic obviates preparing and using the highly carcinogenic chloromethyl methyl ether, 2) $BF_3 \cdot Et_2O$ catalysis eliminates preparing anhydrous zinc chloride, 3) chloride incorporation is easily controlled in the range of 0.1 to 0.6 meq/g by the addition of increasing amounts of $BF_3 \cdot Et_2O$ catalyst, and 4) most important, the resins prepared by the $BF_3 \cdot Et_2O$ method swell to a greater extent in methylene chloride than those prepared in our hands using $SnCl_4$ or $ZnCl_2$ as catalyst.

Experimental

Chloromethylation Procedure. To 100 ml of hexane was added 10 g of polystyrene - 1% divinylbenzene beads (Bio-Rad SX1) and 25 ml of chloromethyl ethyl ether (Aldrich). After stirring 5 minutes, 1.25 ml of $BF_3 \cdot Et_2O$ (Eastman Kodak) was added and the temperature

raised to 35°. Stirring was continued for 3 hours at this temperature and then the resin was removed by filtration and washed three times with 100 ml portions of the following solvents: hexane, methanol, water, methanol, and methylene chloride. The resin was dried in vacuo and the active chloride content determined (4) with the following results: using 1.25 ml $BF_3 \cdot Et_2O$, 0.10-0.20 meq Cl/g; 2.50 ml $BF_3 \cdot Et_2O$, 0.3-0.4 meq Cl^-/g; 5 ml $BF_3 \cdot Et_2O$; 0.5-0.6 meq Cl^-/g.

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