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POLYMERIC NITROPHENYLSULFENYL CHLORIDE, AN INSOLUBLE AMINO PROTECTING REAGENT IN PEPTIDE SYNTHESIS

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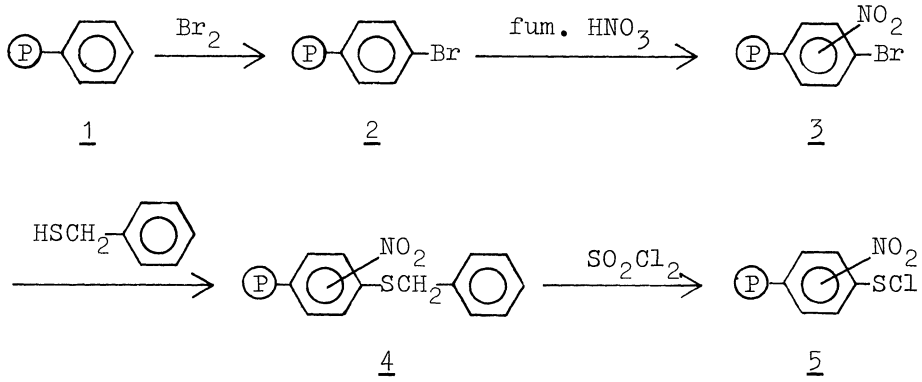
A polymeric nitrophenylsulfenyl chloride(5) was synthesized and used for amino protection during peptide synthesis. The insoluble protecting group can be selectively removed from the amino derivative with mild acid treatment similarly to o-nitrophenylsulfenyl(Nps) group, and the separation is quite easy due to its insolubility. When the protected derivative is treated with hydrogen chloride for deprotection, the polymeric reagent(5) is regenerated so that it can be used for amino protection repeatedly.

When Nps peptide[1,2] is treated with hydrogen chloride for deprotection, regenerated Nps chloride partly attaches to the resulting peptide, and this is reflected in a lower yield and purity of products. If polymeric Nps chloride is available, the disadvantage above mentioned will be not only removed but also the insoluble reagent regenerated can be used repeatedly. Thus an insoluble sulfenyl chloride(5) was synthesized in the following way:



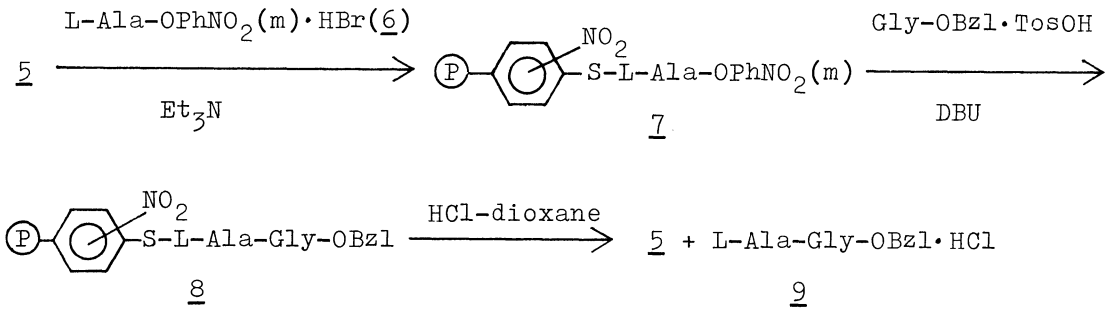
1 2 3 4 5

The brominated and nitrated polymer(IR 820, 880, 1345 cm^{-1})(3) was prepared by bromination of polystyrene(divinylbenzene content, 2 %)(1) followed by nitration according to the method of Merrifield.[3] The polymer(3) was smoothly converted to benzylthio derivatives(IR 690, 750, 3020 cm^{-1})(4) with benzyl mercaptan in dimethylsulfoxide containing sodium ethoxide at a room-temperature substantially according to the method of Kharasch and Langford.[4]

Treatment of 4 with sulfuryl chloride for 10 min at a room-temperature afforded 5, of which the chlorine content(0.57 meq/g) was determined by estimating chlorine in diethyl ammonium chloride produced by treatment of 5 with an excess of diethyl amine.

Since 5 hardly swells in water, it is very difficult to bind an amino acid to 5 in aqueous solution; therefore, amino acid was bound to 5 in the form of active ester in organic solvent. Carboxyl protected second amino acid was then allowed to react with the polymer derivative to yield peptide directly.

The synthetic procedures of peptides are outlined as follows:



5 → 7 → 8 → 5 + 9

L-Alanine m-nitrophenylester hydrobromide[5](6)(0.58 g, 1.14 mmol) in methylene chloride containing triethyl amine(0.42 ml, 1.71 mmol) was added to the polymer(5)(1.0 g, Cl 0.57 meq/g). The reaction mixture was stirred for 24 hr at a room-temperature to afford sulfenyl derivative of L-alanine m-nitrophenyl ester(IR 1760 cm^{-1}, L-Ala-OPhNO$_2$(m) content 0.43 mmol/g)(7). The polymer derivative(7) was suspended in methylene chloride containing 1,8-diaza-bicyclo-[5,4,0]undecene-7(DBU)[6](0.46 g, 1.71 mmol) and glycine benzylester p-toluene sulfonate(0.67 g, 1.14 mmol) was added. The mixture was stirred for 24 hr at a room-temperature yielding a protected peptide(IR 1630, 1730 cm^{-1})(8). On treatment with a 0.5 N hydrogen chloride in dioxane it afforded L-alanylglycine benzyl ester hydrochloride(9). The yield of 9 based on 7 was 58 % and 5 was regenerated in about 70 % recovery. When p-nitrophenylester is used as an active ester which should be bound to 5, side reactions such as polymerization etc. always occur. Hence m-nitrophenylester which is less active than p-nitrophenylester was used.

These novel experimental operations for peptide synthesis are straightforward and simple as other solid phase methods ; moreover, resulting peptides can be purified without any difficulties.

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