Amino Acids and Peptides. Preparation and Reactions of a Polymer Diazomethylene

By PHILIP H. CHAPMAN and DEREK WALKER*†

(*Chemical Process Development Department, Glaxo Laboratories Limited, Ulverston, Cumbria* LA12 9DR)

Summary The synthesis of a polymer diazomethylene is described; the diazomethylene groups in the new polymer react rapidly and efficiently with carboxylic acids, giving the corresponding polymer ester.

THE increasing interest in polymer-supported reagents and catalysts, and in polymer-supported synthesis, has highlighted the limitations and deficiencies of currently available reactive polymers.[1,2] We have now found that beads of poly(styrene–2% divinylbenzene) can be functionalised with diazomethylene groups (Scheme).

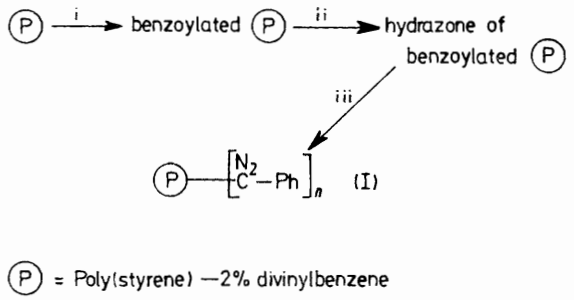
The aromatic rings in the poly(styrene–2% divinylbenzene) were benzoylated as described previously[3] except that we used tetrachloroethylene as solvent. The degree of benzoylation was controlled by varying the quantity of $PhCOCl$-$AlCl_3$ complex and by optimising time-temperature parameters. Most of the work described here was carried out using a polymer containing 3·15 mmole of keto groups/g of polymer.

Reaction of this keto polymer with hydrazine hydrate was effected by refluxing in Bu^nOH for 24 h. Excess of hydrazine was removed by slurrying the filtered beads in Bu^nOH and washing with MeOH and CH_2Cl_2. Elemental analysis of the dried product showed the presence of 2·95 mmol of hydrazone groups/g of polymer, indicating an efficient conversion of keto groups into hydrazone groups.

The hydrazone groups were transformed into diazomethylene groups by adding a slight excess of 38% w/w peroxyacetic acid in $MeCO_2H$ (1·3 mol/mol of $=N{\cdot}NH_2$ groups) to a slurry of the hydrazone polymer in CH_2Cl_2 at *ca.* 0 °C.

† Present address; Bristol-Myers Company, Industrial Division, P.O. Box 657, Syracuse New York 13201. Copies of reprints available from the Librarian, Glaxo Ltd., Ulverston.

Sufficient tetramethylguanidine was added to the slurry to neutralise all the $MeCO_2H$, together with a trace of iodine



SCHEME. *Reagents*: i, $PhCOCl–AlCl_3$ in $Cl_2C{=}CCl_2$; ii, $N_2H_4.H_2O$ in Bu^nOH (reflux); iii, $MeCO_2OH–Me_2NC(=NH)NMe_2–I_2$ catalyst in CH_2Cl_2.

(2·14 mmol/mol of hydrazone) as catalyst.[4] The conversion of hydrazone groups into diazomethylene groups was almost quantitative. Based on the nitrogen evolved when treated with an organic acid in $CHCl_3$, each g of polymer (I) contained 2·89 mmol of diazomethylene groups. The nitrogen content determined in this way was in good agreement with that found by microanalysis. The deep magenta polymer diazomethylene (I) exhibited the expected bands in its i.r. spectrum (*cf.* diphenyldiazomethane). On storage in the dark at 0 °C for 6 months, polymer (I) containing 3·6 mmol of diazomethylene groups/g lost 6·7% of its activity, as determined by nitrogen evolution. Another sample of the same polymer lost 39% of its activity when stored similarly for 6 months at 20 °C.

When 5 g of a polymer containing 2·89 mmol of diazomethylene groups/g was stirred for < 1 h in $CHCl_3$ at 20 °C with 19·6 mmol of (1*S*,3*S*,5*R*,6*R*)-3-carboxy-6-phenylacetamidopenam 1-oxide [penicillin G 1(*S*)-oxide], nitrogen was evolved and the deep magenta colour of polymer (I) faded to pale-yellow. The excess of penicillin G 1(*S*)-oxide was recovered as its acetone solvate by washing the polymer beads with CH_2Cl_2, evaporation, and triturating the residue in acetone. The weight gain of the polymer, and the recovery of unchanged acid, indicated that 2·86 mmol of penicillin G 1(*S*)-oxide was covalently bonded to each gram of (I). The i.r. spectrum of the polymer ester was almost identical to that of the analogous diphenylmethyl ester.

This reaction procedure has been used for the efficient immobilisation of cephalosporin acids, and of *N*-t-butyloxycarbonylglycine. In the case of the t-Boc-glycine polymer ester the t-Boc group was selectively cleaved by treatment with anhydrous HCl in dioxan,[5] and the free base form of the glycine polymer ester converted into glycylglycine (84·5% from the t-Boc-glycine polymer ester) using standard methods (dicyclohexylcarbodi-imide coupling, CF_3CO_2H cleavage). The use of 'polymer diphenylmethyl esters' in peptide synthesis has been previously described.[6]

The polymer hydrazone can be used to immobilise penicillin G 1(*S*)-oxide without separate oxidation of the hydrazone groups to diazomethylene groups. The immobilisation can be achieved in high efficiency by adding peroxyacetic acid to a mixture of the polymer hydrazone and penicillin G 1(*S*)-oxide, in $CHCl_3$ and CH_2Cl_2, in the presence of iodine as catalyst. The reaction conditions were similar to those previously described for the preparation of diphenylmethyl esters.[7]

The transformation of polymer-supported penicillins and cephalosporins into other products has been demonstrated. Polymer-supported penicillin G 1(*S*)-oxide has been converted into polymer-supported (6*R*,7*R*)-7-phenylacetamido-3-methylceph-3-em-4-carboxylate. Polymer-supported cephalosporins undergo a wide variety of reactions, including the PCl_5 cleavage of the 7-acylamido group, sulphoxidation, desulphoxidation, and nucleophilic substitution. The cephalosporins can be efficiently removed from the polymers by trituration in CF_3CO_2H. The spent polymer trifluoroacetate can be converted back into polymer diazomethylene by refluxing the spent polymer with aqueous 30% HNO_3, treating the filtered polymer with aqueous NaOH, and converting the resultant benzoylated poly(styrene–2% divinylbenzene) into the diazomethylene as described above.

The multistage transformation of cephalosporins immobilised on polymers provides support for the recently expressed view[1] that molecular modification in general may be advantageously carried out on substances bonded to polymers.

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