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PREPARATION OF BENZHYDRYL POLYSTYRENE RESINS AS A SOLID SUPPORT FOR PEPTIDE SYNTHESIS[1]

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Abstract—The preparation of benzhydryl and ring substituted benzhydryl polystyrene resins as the halide and carbinols are reported. The resins are useful supports for solid phase peptide synthesis.

THE protection of carboxyl functions with benzhydryl groups in conventional peptide synthesis is advantageous because of the ease with which the benzhydryl group can be cleaved at the appropriate stage of synthesis.[2] In an earlier report,[3] we described the use of a benzhydryl polystyrene resin in conjunction with the 2-benzoyl-1-methylvinyl nitrogen protecting group for synthesizing peptides by the solid phase method. In this report, the conversion of polystyrene to a form suitable for attachment of N-protected amino acid esters via a benzhydryl ester is described (Scheme 1).

Polystyrene, 2% cross-linked with divinylbenzene was benzoylated with benzoyl chloride using $AlCl_3$ or $SnCl_4$ as catalyst. Aluminum chloride with nitrobenzene as solvent allowed the use of less benzoyl chloride and, thus, became the method of choice. Benzoylated polystyrene (I) was reduced to the carbinol (II) in quantitative yield. Dry HCl or HBr converted the carbinol to the halide in a quantitative yield also. Attempts to chlorinate with purified thionyl chloride resulted in resins containing more than the theoretical amount of chlorine and significant quantities of sulfur. Bromination with phosphorous tribromide was unsuccessful.

Both the *p*-methoxy and *p*-chloro benzhydryl resins were prepared by procedures similar to those used for preparation of the unsubstituted benzhydryl resin.

EXPERIMENTAL

Polystyrene-2% divinylbenzene copolymer resin (200–400 mesh), purchased from Bio-Rad Laboratories, Richmond, California, was used as starting material.

Benzoylstyrene-2% divinylbenzene copolymer resin

Procedure A. Styrene-2% divinylbenzene copolymer resin (200–400 mesh), 425 g, was suspended in 2400 ml nitrobenzene at 0°. To the stirring suspension were added 100 ml (850 mmoles) benzoyl chloride followed by 57 g (425 mmoles) $AlCl_3$ in 3 portions. After addition was complete, the mixture was stirred at 0° for 30 min and then at room temp for 3 hr. The resin was collected by filtration and successively washed with 2 l, each of dioxan, dioxan:3N HCl(3:1), dioxan, and MeOH and then was dried *in vacuo* at 40° overnight. The O_2 content of the resin was 0·79 mmole/g, and an IR analysis gave the expected 1662 cm^{-1} absorption of the carbonyl.

Procedure B. To 5 g styrene-2% divinylbenzene copolymer resin (200–400 mesh) stirring in 20 ml benzoyl chloride was added 0·4 ml $SnCl_4$, and the mixture was heated at 70° for 17 hr. The resin was collected by filtration, washed with 70 ml dioxan, 160 ml dioxan:3N HCl (3:1), 50 ml dioxan, 100 ml methylene chloride and was dried *in vacuo* at 40°. The O_2 content of the resin was 1·4 mmoles/g resin. and an IR analysis gave the expected 1662 cm^{-1} absorption of the carbonyl.

Procedure C. A mixture of 100 g styrene-2% divinylbenzene copolymer resin (200–400 mesh) and 400 ml benzoyl chloride was stirred 30 min at 0°. To the mixture were added 17 g $AlCl_3$ and stirring was continued at 0° for 1 hr and room temp for 1 hr. The resin was collected by filtration, washed successively with 1400 ml dioxan. 1600 ml dioxan: 3N HCl(3:1). 100 ml dioxan. 1100 ml methylene chloride and was dried in a vacuum oven at 100° for 5 hr. The O_2 content of the resin was 1·04 mmol/g resin. and an IR analysis gave the expected 1662 cm^{-1} absorption of the carbonyl.

Phenylcarbinolstyrene-2% divinylbenzene copolymer resin

To 100 g benzoylstyrene-2% divinylbenzene copolymer resin were added 550 ml diglyme. and the mixture was cooled at 0°. $NaBH_4$ (3 g) suspended in 100 ml diglyme was added with a dropping funnel while stirring the mixture at 0°. After 15 min at 0°, the mixture was heated at 60° for 16 hr. The mixture was cooled to 0°. and 40 ml concentrated HCl were added dropwise. After collection by filtration, the resin was washed with hot water and hot EtOH and then was dried *in vacuo* at 40°. The O_2 content of the resin was 0·79 mmole/g and an IR analysis gave the expected OH stretching at 3600 cm^{-1} and was without the carbonyl absorption at 1662 cm^{-1}.

Phenylbromomethylstyrene-2% divinylbenzene copolymer resin

HBr gas was bubbled through a suspension of 70 g phenylcarbinolstyrene-2% divinylbenzene copolymer resin, containing 0·79 mmole hydroxy/g resin. in 840 ml methylene chloride for 1 hr. The resin was collected by filtration. washed with methylene chloride and dried. The bromide content of the resin was 0·81 mmole/g resin.

Phenylchloromethylstyrene-2% divinylbenzene copolymer resin

To 20 g phenylcarbinolstyrene-2% divinylbenzene copolymer resin containing 0·73 mmole OH/g resin were added 150 ml toluene and 15 ml $SOCl_2$. The mixture was refluxed for 24 hr, filtered, and the resin was washed with 200 ml toluene and 200 ml methylene chloride and then dried overnight *in vacuo.* The chloride content of the resin was 1·03 mmole/g resin and the sulfur content was 0·65 mmole/g.

Phenylchloromethylstyrene-2% divinylbenzene copolymer resin

HCl gas was bubbled through a suspension of 42 g phenylcarbinolstyrene-2% divinylbenzene copolymer (0·79 mmole OH/g resin) in 400 ml methylene chloride for 1 hr. The resin was collected by filtration. washed with methylene chloride and was dried *in vacuo.* The chloride content of the resin was 0·80 mmole/g resin.

p-*Methoxybenzoylstyrene-2% divinylbenzene copolymer resin*

To 10 g styrene-2% divinylbenzene copolymer resin (200–400 mesh) in 50 ml nitrobenzene were added 3·4 g (20 mmoles) anisoylchloride. The mixture was stirred while adding 2·6 g (20 mmoles) $AlCl_3$ dissolved in 60 ml nitrobenzene and the mixture was stirred an additional 19 hr. The resin was collected by filtration and washed successively with 200 ml each nitrobenzene, dioxan, dioxan:3N HCl(3:1), dioxan, MeOH. and dried *in vacuo* at 60° for 3 hr The O_2 content of the resin was 2·0 mmoles/g of resin or 1 mmole substitution/g. An IR analysis gave the expected 1663 cm^{-1} absorption of the carbonyl.

p-*Methoxyphenylcarbinolstyrene-2% divinylbenzene copolymer resin*

To 10 g *p*-methoxybenzoylstyrene-2% divinylbenzene copolymer resin, (1 mmole substitution per gram) in 100 ml diglyme was added, at 0° with stirring, 1 g $NaBH_4$ suspended in 30 ml diglyme from a dropping funnel. The mixture was stirred at 0° for 10 min and then at 55° for 21 hr. After cooling to 0°, the borohydride was destroyed by the slow dropwise addition of 10 ml of conc HCl to the stirring mixture. The resin was collected by filtration, washed successively with 200 ml each hot water and hot EtOH and then was dried *in vacuo* at 60° for 3 hr. An IR analysis gave the expected 3600 cm^{-1} absorption of the carbinol and no keto absorption.

p-*Methoxyphenylchloromethylstyrene-2% divinylbenzene copolymer resin*

HCl gas was bubbled through 5 g *p*-methoxyphenylcarbinolstyrene-2% divinylbenzene copolymer resin for 1 hr. The resin was collected by filtration, washed with methylene chloride and dried *in vacuo.* The chloride content of the resin was determined to be 1·19 mmole/g resin.

p-Chlorobenzoylstyrene-2% divinylbenzene copolymer resin

To 10 g styrene-2% divinylbenzene copolymer resin (200–400 mesh) in 60 ml nitrobenzene at 0° were added with stirring 5 ml *p*-chlorobenzoylchloride and 1·7 g $AlCl_3$. The mixture was stirred 30 min at 0° and then at 50° for 1 and 3/4 hr. The resin was collected by filtration, washed successively with 200 ml each of dioxan, dioxan: 3N HCl(3:1), dioxan, methylene chloride and MeOH and then was dried *in vacuo*. The O_2 content of the resin was 1·23 mmole/g resin and the chloride content was 1·12 mmoles/g resin. An IR analysis gave the expected 1670 cm^{-1} absorption of the carbonyl.

p-Chlorophenylcarbinolstyrene-2% divinylbenzene copolymer resin

To 10 g *p*-chlorobenzoylstyrene-2% divinylbenzene copolymer resin (1·23 mmole Cl/g resin) in 60 ml diglyme at 0° were added 1·4 g $NaBH_4$ suspended in 60 ml diglyme with a dropping funnel. After the addition was complete, stirring was continued at 0° for 30 min and at 50° for 16 hr. The mixture was cooled to 0°, and the borohydride was destroyed by the slow addition of 20 ml 6N HCl. After stirring for 30 min at room temp, the resin was collected by filtration, washed with 500 ml hot water, 500 ml hot EtOH and was dried *in vacuo* at 40° overnight. An IR analysis gave the expected 3600 cm^{-1} absorption of the carbinol and no keto absorption.

p-Chlorophenylchloromethylstyrene-2% divinylbenzene copolymer resin

Dry HCl gas was bubbled through 10 g *p*-chlorophenylcarbinolstyrene-2% divinylbenzene copolymer resin in 100 ml methylene chloride for 1 hr. The resin was filtered and washed with methylene chloride and dried *in vacuo* at room temp. The chlorine content of the resin was determined to be 2·36 mmoles/g resin corresponding to 1·18 mmoles alkyl chloride/g resin. The 3600 cm^{-1} absorption band of the carbinol was absent from the IR spectra.

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