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Simple and Efficient Synthesis of 2-Chlorotritylchloride Resin

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Abstract: The laboratory synthesis of 2-chlorotritylchloride polystyrene resin was described. Polystyrene was acylated with 2-chlorobenzoyl chloride, reacted with phenyl lithium and finally converted to trityl chloride in the presence of dimethyl sulfoxide and trimethylsilyl chloride. A process for the regeneration of the resin is described.

Since its introduction by Barlos[1-4] the 2-chlorotritylchloride resin has been a valuable tool for the synthesis of protected peptide fragments with C-terminal glycine and proline using the Fmoc-technique. If prepared in good quality and stored carefully, the advantage of this resin is that 1) the loss of the peptide chain at dipeptide phase is negligible even with C-terminal glycine or proline, 2) the contamination generally observed with benzylalcohol-type resins, the formation of aldehyde groups and the side rections due to this contamination under exposure to air are essentially absent, 3) the triphenylcarbinol resin (formed in the hydrolysis of the 2-chlorotrityl chloride or in the cleavage of the peptide chain from the resin) cannot be acylated under regular peptide coupling conditions. This is why the quality of the peptide fragments is generally excellent as the peptide is not contaminated by shorter fragments.

Due to the resin's relatively high price and to our interest[5] in convergent peptide synthesis[6,7] which makes use of intermediates containing C-terminal glycine and proline, we attempted to synthesize this resin in a quality similar to the commercially available products. During the development of the procedure efforts were made to preserve the resin's physical properties (good swelling), thus the original procedures were modified by shortening the resin's exposure to high temperature to achieve complete reaction. This procedure is a modification of the original procedure developed by Fréchet and Nuyens[8], only instead of the long reaction with phenyl magnesium bromide phenyl lithium was utilized to achieve quick and complete reaction.

2-chlorobenzoyl polystyrene (2-chlorobenzophenone resin)

Into a three-necked flask, equipped with mechanical stirrer, reflux condenser and dropping funnel, 20 g of polystyrene (200-400 mesh, 1%divinylbenzene) and 200 ml of carbon disulfide was measured. After a few minutes of stirring allowing the resin to swell completely 6.53 g (49 mmol) of aluminum chloride was added. The reaction mixture was heated to its boiling point and slowly 8.75 g (50 mmol) of freshly distilled 2-chlorobenzoyl chloride was added within approximately 30 min. The reaction mixture was refluxed for further 4 h, then cooled, filtered and washed sequentially on the filter several times with dioxane-water-cc.HCl=5:1:1, N,N-dimethylformamide, dioxane:water=5:1, methyl ethyl ketone, warm water, N,N-dimethylformamide, methyl ethyl ketone, methanol, diethyl ether and finally dried *in vacuo* to yield 28.0-29.5 g of pale yellow resin. Chlorine content: 5.5-6.5%.

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(2'-chlorophenyl, phenyl, hydroxy)methylpolystyrene (2'-chlorotriphenylcarbinol resin)

Phenyl lithium was prepared under argon atmosphere from 3.4 g (0.48 mole) granulated lithium and 39 g (0.24 mole) bromobenzene in 200 ml of ether and filtered. To the solution 200 ml of tetrahydrofuran (distilled from $LiAlH_4$) and 25,5 g of 2-chlorobenzoyl polystyrene (previously dried as follows: the resin was suspended in toluene and the toluene distilled off *in vacuo* three times) were added under stirring. The reaction mixture was refluxed for 1 h. (In the presence of sufficient excess of phenyl lithium the color of the resin turns to light brown.) The reaction mixture was diluted with 100 ml of N,N-dimethylformamide and filtered. Then it was washed sequentially on the filter with N,N-dimethylformamide:methanol=3:1, N,N-dimethylformamide:water=2:1 (the resin becomes warm and some foam appears), dimethylformamide, dichloromethane, dichloromethane:acetic acid=4:1, isopropanol, methanol and diethyl ether then dried *in vacuo* to yield 33-35 g light yellow colored resin containing 5.5-6.4 % of chlorine.

(2'-chlorophenyl, phenyl, chloro)methylpolystyrene (2'-chlorotrityl chloride resin)

33.86 of the 2'-chlorotriphenylcarbinol resin was suspended in 700 ml of dichloromethane, then 70 ml of trimethylsilyl chloride and 7 ml of dimethyl sulfoxide were added[9]. The mixture was stirred for 90 min then the resin was filtered off, washed thoroughly several times on the filter with dichloromethane and benzene. (This resin is suitable for peptide synthesis but it has some unpleasant odor possibly due to dimethyl sulfoxide derivative(s).) The wet resin was transferred to a round-bottomed flask, 350 ml of benzene and 56 ml of acetyl chloride was added and refluxed for 30 min, cooled to room temperature, filtered, washed on the filter with toluene, dichloromethane, diethyl ether, toluene, diethyl ether and dried *in vacuo* to yield 32-34.5 g of deep yellow resin with 9.0-10.5% of chlorine content.

Using this procedure the resin can be regenerated at least two times if relatively short peptides (5-12) have been prepared on the resin, with slowly decreasing amount of attached C-terminal amino acid (0.5-0.45 mmol/g).

Using the standard procedure for attaching the first Fmoc-amino acid to the resin[10], the observed loading will not be higher than 0.65 mmol/g even with glycine. That is why we use the amino acids for loading in slight excess which makes the attachment of the first amino acid more stable in amount (for various amino acids the loadings obtained are between 0.45 and 0.65 mmol/g).

REFERENCES

1. Barlos, K.; Chatzi, O.; Gatos, D.; Stavropoulos, G. *Int. J. Pept. Prot. Res.* **1991,** *37*, 513.
2. Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Yao, W. Q.; Schafer, W. *Tetrahedron Lett.* **1989,** *30*, 3943.
3. Barlos, K.; Gatos, D.; Kapolos, S.; Papaphotiu, G.; Schafer, W.; Yao, W. Q. *Tetrahedron Lett.* **1989,** *30*, 3947.
4. Barlos, K.; Gatos, D.; Kapolos, S.; Poulos, C.; Schafer, W.; Yao, W. Q. *Int. J. Pept. Prot. Res.* **1991,** *38*, 555.
5. Bódi, J.; Süli-Vargha, H.; Ludányi, K.; Vékey, K.; Orosz, G. *Tet. Lett.* **1997,** *38*, 3293.
6. Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Tetrahedron* **1993,** *49*, 9307.
7. Albericio, F.; Lloyd-Williams, P.; Giralt, E. *in: Methods in Enzymology* **1997,** *289*, 313.
8. Fréchet, J. M. J.; Nuyens, L. J. *Can. J. Chem.* **1976,** *54*, 926.
9. Snyder, D. C. *J. Org.Chem* **1995,** *60*, 2638.
10. White, P. in 97/98 Novabiochem Catalog & Peptide Synthesis Handbook, p. S11.

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