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A Simple Method for the Generation of Chloromethyl Polystyrene on the Multipin™ Solid Support.

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Abstract. *A novel route for the chloromethylation of polystyrene grafted Multipin supports (Synphase™ Crowns) has been developed. Aminomethylated polystyrene was converted into chloromethylated polystyrene via a simple diazotisation reaction. The modified graft polymer was assessed by solid phase synthesis of a model dipeptide.*

Derivatisation of a polymeric support with a suitable anchoring point for attachment of a linker system is the first step in solid phase synthesis. Depending on the functionality being produced and the exact method of manufacture, the derivatisation process can lead to further cross-linking of resins beyond what is expected from the known quantity of divinylbenzene (or other alternative cross-linking agents) used in the polymerisation process.[1] The degree of cross-linking is a primary determinant in the swelling characteristics, hence diffusion and reactivity properties, of beaded-type resins. Consequently, it is prudent to use the same batch of derivatised resin for both chemistry development/validation and library generation.[2] This is a simple acknowledgment that chemistry translation between resin types (monomer, bead size, loading, cross-linking, etc.) can be problematic. As part of a program to develop novel grafted supports[3] for solid phase organic chemistry, we needed to minimise the variables resulting from different derivatisation methods. Chloromethylated polystyrene is readily functionalised with carboxylic acids and can, via ester or ether linkages, be coupled with a variety of linkers. Aminomethylation is the other main polystyrene derivatisation method for linker coupling.[4] However, it is not a straightforward matter for the two derivatisation methods to yield functionalised polystyrene with identical swelling and loading characteristics.[5] The original Merrifield method[1] can be difficult to control as chloromethylation takes place at both the *p*-position, and to a lesser extent, the *o*-position on the aromatic ring. The process is frequently accompanied by further cross-linking.[6,7] As a consequence, proper choice of solvent, catalyst and extensive optimisation studies are required for successful chloromethylation on new surfaces. Here, we describe an alternative method to generate the chloromethyl moiety on polystyrene by converting an existing aminomethyl group into the chloromethyl moiety. This approach uses a simple and inexpensive procedure which involves the diazotisation of the aminomethyl-group in a two-step reaction as outlined in Scheme 1.

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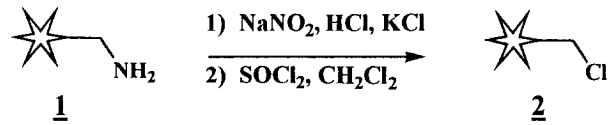
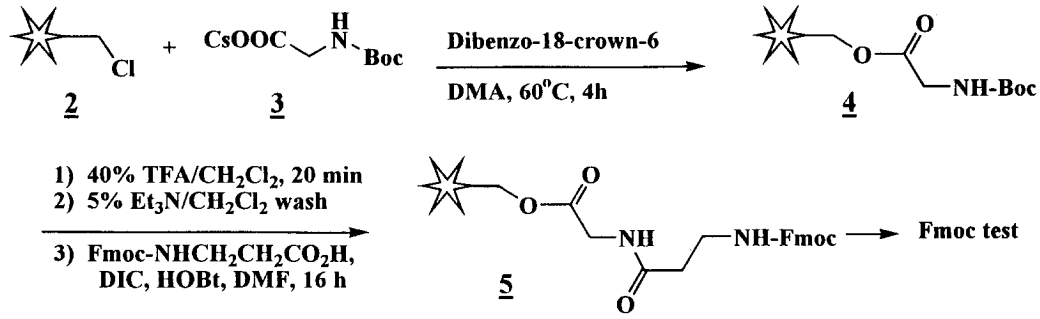


Scheme 1. Preparation of the Chloromethyl group on Polystyrene-grafted Synphase Crowns.

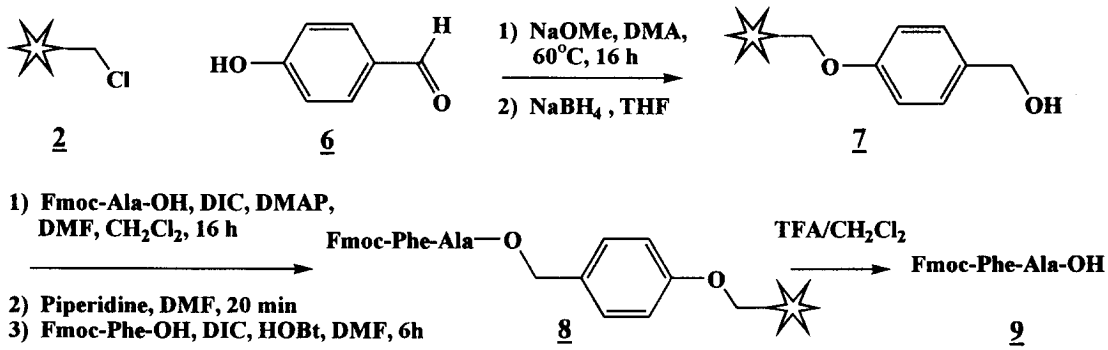
Aminomethylated crowns **1** (I-series, loading = 19 μmol/crown) were treated with $NaNO_2$ in 30% HCl(aq) containing KCl for 3 h with sonication.[8] Completion of the reaction could be confirmed by amine stain tests with TNBSA.[9] After being washed with DMF and CH_2Cl_2, the resulting product was immediately treated with 2% thionyl chloride in CH_2Cl_2 for 3 h to give **2**. Under these conditions, chloromethylation proceeded with *ca.* 70% overall yield (13.4 μmol/crown) as determined by the Fmoc test procedure[10] (Scheme 2). Briefly, chloromethylated crowns (**2**)(five I-series crowns, loading = 13.4 μmol/crown) were treated with the cesium salt of Boc-Gly-OH (**3**) (1 mmol) in the presence of dibenzo-18-crown-6 (1 mmol) in DMA (10 mL) at 60°C for 4h.[11] After Boc deprotection with 40% TFA/CH_2Cl_2, the derivatised crowns were coupled with Fmoc-b-Ala-OH/DIC/HOBt[12] to give **5**. Fmoc-deprotection and spectrophotometric quantitation of released Fmoc group established the substitution level of the crowns. X-ray Photoelectron Spectroscopy[13,14] also confirmed the presence of chlorine and absence of nitrogen on the surface of the crowns.



Scheme 2: Loading Determination of Chloromethyl Polystyrene Crowns.

To evaluate the quality of the chloromethyl product, crowns **2** (O-Series, loading = 5.6 μmol/crown) were subjected to the reaction sequence described in Scheme 3. Reaction of **6** with **2**, followed by reduction with $NaBH_4$ afforded the Wang linker derivatised solid support **7**.[15] The model dipeptide **9** was synthesised using the Fmoc strategy.[12] Treatment of crowns **8** with 50 % TFA in CH_2Cl_2 released the target **9** in 90% purity and 63 % overall yield from **1**. As shown in Table 1, HPLC and ES-MS spectra indicated that a product of similar quality was prepared on chloromethylated polystyrene crowns, which were derivatised by the Merrifield approach (Table 1).[16] The purity of product **9** prepared on the chloromethylpolystyrene surface, derived via diazotisation, was comparable to that obtained using the Merrifield method. The percentage yield obtained using the diazotisation route was slightly less than that obtained via the traditional approach. Furthermore, a similar result (78 % purity, 55% yield) was obtained on cross-linked polystyrene resin.[17] The loading of

chloromethylpolystyrene generated by the diazotisation route is dependent on the number of aminomethyl moieties available on the crown surface, giving equivalence of loading and graft polymer characteristics without the concerns of differential cross-linking which exists with the Merrifield approach. Furthermore, the approach avoids the use of the carcinogenic reagent chloromethylmethyl ether.[18]



Scheme 3. Synthesis of Model Dipeptide 9.

Table 1. Comparison of 9 prepared on chloromethylated crowns.

Method for preparation of chloromethylated crowns	Rt(HPLC)[19]	Observed ES-MS[20,c] $[M + H]^+$	% Yield	% Purity [19,e]
Diazotisation route[a]	8.32 min	459.3	63[d]	90
Merrifield approach[b]	8.31 min	459.4	76	83

a: O-series aminomethylated polystyrene SynPhase Crowns (Loading = 5.6 μmol/crown) were converted into chloromethyl-PS crowns and used in this study. b: O-series chloromethylated polystyrene SynPhase Crowns (Loading = 10 μmol/ crown) were prepared by Merrifield approach. c: Calculated $[M + H]^+$ = 459.3. d: Crude overall yield was calculated from 1 (6 steps). e: Percentage Purities were determined by HPLC peak area at 214 nm.

In summary, a simple method for generation of chloromethylated polystyrene via the diazotisation reaction on polystyrene grafted crowns has been described. The preparation conditions are straightforward, safe and suitable for laboratory scale conversion of the aminomethyl moiety into the chloromethyl moiety on the solid support.

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References and Notes:

Abbreviations: Boc: *tert*-butoxycarbonyl, DIC: diisopropylcarbodiimide, DMA: *N,N*-dimethylacetamide, DMAP: dimethylaminopyridine, DMF: dimethylformamide, ES-MS: electrospray mass spectrometry, Fmoc: 9-fluorenyl-methoxycarbonyl, HOBt: 1-hydroxybenzotriazole, TFA: trifluoroacetic acid, THF: tetrahydrofuran, TNBSA: 2,4,6-trinitrobenzene sulfonic acid.

1. Merrifield, R.B., *J. Am. Chem. Soc.*, **1963**, *85*, 2149.
2. Czarnik A.W., *Biotechnol. Bioeng. (Comb. Chem.)*, **1998**, *61*, 77.
3. Maeji, N.J.; Valerio, R.M.; Bray, A.M.; Campbell, R.A.; Geysen, H.M., *Reactive Polymers*, **1994**, *22*, 203.
4. Mitchell, A.R.; Kent, S.B.H.; Engelhard, M.; Merrifield, R.B., *J. Org. Chem.*, **1978**, *43*, 2845.
5. Feinberg, R.S.; Merrifield, R.B., *Tetrahedron*, **1974**, *30*, 3209.
6. Repper, K.W.; Paisley, H.M.; Young, M.A., *J. Chem. Soc.*, **1953**, 4097.
7. Belen'kii, L. I., Vol'kenshtein, Y. B.; Karmanova, I.B., *Russian Chemical Reviews*, **1977**, *46*, 891 and references therein.
8. Twenty crowns (from Chiron Technologies Pty. Ltd., I-series, loading = 19 μmol/crown) NH_2-CH_2-PS crowns (1) were suspended in 30% HCl(aq) (50 mL) containing KCl (2.5g, 33.5 mmol). The mixture was sonicated while $NaNO_2$ (10 g, 145 mmol) was added in portions over 3 h. (After 3 h the TNBSA stain test was negative.) The crowns were then washed (5 min per wash) with CH_2Cl_2 (20 mL x 2), DMF (20 mL x 2) and CH_2Cl_2 (20 mL x 2) and then incubated with 2% $SOCl_2$ in CH_2Cl_2 (100 mL) for 4 h at ambient temperature. Crowns were finally washed with CH_2Cl_2 (20 mL x 2), DMF (20 mL x 2) and CH_2Cl_2 (20 mL x 2) and dried under reduced pressure for 4 h to afford Cl-CH_2-PS crowns (2) (loading = 13.4 μmol/crown).
9. Stewart, J.M.; Young, J.D., Solid Phase Peptide Synthesis, Second Edition, Pierce Chemical Company, Rockford, Illinois, USA, **1984**, p107.
10. The loading was determined by spectrophotometric determination of a 20% piperidine/DMF solution at 301 nm following cleavage of the Fmoc group (extinction coefficient = 7800 $M^{-1}cm^{-1}$). Loading (nmol/crown) = (Absorbance/0.0078)/(Volume in mL).
11. Sharma, S.; Pasha, S., *Bioorganic & Medicinal Chemistry Letters*, **1997**, *7*, 2077.
12. Valerio, R.M.; Bray, A.M.; Maeji, J.N., *Int. J. Peptide Protein Res.*, **1994**, *44*, 158.
13. Beamson, G.; Briggs, D., High Resolution XPS of Organic Polymers - The Scienta ESCA300 Data Base, Wiley, Chichester, 1992.
14. Chan, C.-M., Polymer Surface Modification and Characterization, Hanser Publishers, New York, 1993, p 237.
15. Wang, S.W., *J. Am. Chem. Soc.*, **1973**, *95*, 1328.
16. Wendeborn, S.; Beaudegnies, R.; Ang, K.H.; Maeji, N.J., *Combinatorial Chemistry*, **1998**, *61*, 89.
17. 400-500 μm polystyrene resin (PL-CMS, 1.9 meq/g) from Polymer Laboratories Ltd.
18. Laskin, S.; Kuschner, M.; Drew, R.T.; Capiello, V.P.; Nelson, N., *Arch. Environ. Health*, **1971**, *23*, 135.
19. Reverse phase high performance liquid chromatography (RP-HPLC) was conducted with Rainin, Microsorb-MV Cat.# 86-200-F3, 50 x 4.6 mm column. Gradient 0-100% B over 11.5 mins. Flow rate: 1.5 mL/min. Solvent A: 0.1% H_3PO_4 in H_2O. Solvent B: 0.1% H_3PO_4 in CH_3CN/H_2O (9:1, v/v). Detection: 214 nm and 254 nm.
20. ES-MS analysis was performed on a Perkin-Elmer Sciex API III.