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# Non-nucleophilic base (KHMDS) mediated nucleophilic conversion of Merrifield resin into aminomethyl resin

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**Abstract**—During a series of alkylation reactions on Merrifield resin involving a number of alkoxides, generated in situ by the treatment of alcohols with a variety of bases (NaH, LiHMDS, etc.), it was determined that treatment of the resin with a number of hexamethyldisilazide bases gave rise to high yields of aminomethyl resin, presumably by nucleophilic displacement of the chloride. The reaction was optimised as a simple one-step process for the generation of aminomethyl resin from chloromethyl polystyrene. The resulting resin was used to synthesise a tripeptide. © 2001 Elsevier Science Ltd. All rights reserved.

Aminomethyl polystyrene resin is one of the most widely used functionalised supports for solid-phase synthesis and is commercially synthesised by either the direct amidomethylation of polystyrene resin[1] or the reaction of Merrifield resin[2] with potassium phthalimide[3] followed by hydrazinolysis. During the course of studies aimed at the attachment of alcohols to Merrifield resin (1% DVB, 1.82 mmol/g), an unexpected side reaction, leading to the high yielding synthesis of aminomethyl resin was discovered. Thus, when the alkoxide was formed using excess sodium bis(trimethylsilyl)amide, elemental analysis of a resin sample showed a high nitrogen content and the resin sample also gave a very positive ninhydrin test,[4] indicating that the nitrogen was present as a primary amine. Since the only source of nitrogen present in the reaction was the base it indicated that this supposedly non-nucleophilic base had displaced the chloride to form the silyl protected benzylamine which had subsequently been deprotected to give aminomethyl resin during work-up.

This phenomenon was therefore further investigated. Thus, 12 Merrifield resin samples (1% DVB, 1.82 mmol/g) were refluxed with lithium, sodium or potassium hexamethyldisilazide[5] (4.5 equiv., 5.0 mmol), with or without 15-crown-5 (3.0 equiv., 3.3 mmol) and/or potassium iodide (0.2 equiv., 0.2 mmol) in THF (10 mL), for 48 h. The resins were washed with THF/water and analysed to give the data shown in Fig. 1. Fmoc analysis[6] was undertaken after the quantitative coupling of Fmoc-Gly-OH, under standard carbodiimide conditions[7], also shown in Fig. 1.

Fig. 1 shows that the highest conversions were obtained when KHMDS was used, with little additional effect following the addition of either 15-crown-5 or KI. In the best case, starting with a Merrifield resin loading of 1.82 mmol/g, the nitrogen content was 1.30 mmol/g indicating a conversion of 77%.

However, although the nitrogen levels were high, chlorine microanalysis was also high and thus confusing if displacement had taken place. However, extensive washing of the resin (resin **3a**: Microanalysis: N = 0.96 mmol/g, Cl = 0.33 mmol/g) by refluxing in THF/water overnight and MeOH/water overnight, removed the halogen content. The nitrogen content remained fixed (resin **3a**: microanalysis, N = 1.06 mmol/g, Cl = 0.06 mmol/g), indicating that any halogen present was actually trapped as the salt within the resin (i.e. KCl). Washing of Merrifield resin under the same conditions gave little change in the chlorine content of the resin i.e. 1.69 mmol/g was only reduced slightly after washing to 1.63 mmol/g).

Three control experiments were undertaken to assess the possibility of by-products of the base being involved in the reaction, since the base could be considered as a potential source of either hexamethyldisilazane or ammonia in the presence of moisture, either of which

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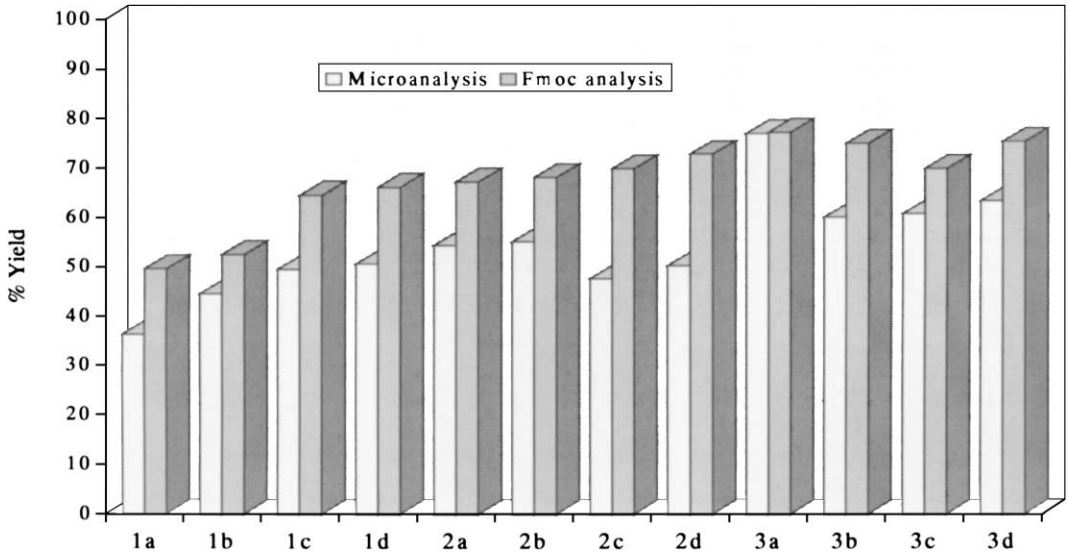


**Figure 1.** Conversion of chloromethylpolystyrene to aminomethylpolystyrene based on elemental analysis for nitrogen and Fmoc quantification.(**1** = LiHMDS, **2** = NaHMDS, **3** = KHMDS, **a** = base, **b** = base+KI, **c** = base+15-crown-5, **d** = base+15-crown-5+KI).

might displace the chloride from the resin. Therefore, Merrifield resin was refluxed with a solution of ammonia in THF or 1,1,1,3,3,3-hexamethyldisilazane in THF. Un-derivatised polystyrene resin was refluxed with KHMDS in order to assess if other side reactions were occurring, not associated with the chloromethyl part of the resin. Microanalysis for nitrogen and ninhydrin tests were negative in all three cases.

The 'new' aminomethyl resin was used for the synthesis of a small peptide to test its applicability under standard peptide synthesis conditions. Thus, the Knorr linker[8] was attached to the resin (**3a**) and the peptide H-Phe-Val-Ala-$NH_2$ was synthesised using Fmoc chemistry and standard carbodiimide couplings.[7] The tripeptide was produced in 76% isolated yield with a purity of 100% (as determined by HPLC, $\lambda = 220$ nm).[9]

These results clearly suggest that KHMDS reacts with Merrifield resin in a nucleophilic manner to give, following work-up, an aminomethyl support. Thus, this is potentially an alternative method to prepare aminomethyl resins on a small scale.

## Acknowledgements

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5. Conversion of Merrifield resin to aminomethyl resin: To an aliquot of resin (0.61 g, 1.1 mmol), under argon, was added a 1.0 M solution of either LiHMDS or NaHMDS (4.5 equiv., 5 mL, 5.0 mmol) or solid KHMDS (4.5 equiv., 1.0 g, 5.0 mmol). Each reaction was made up to 10 mL with THF. KI or 15-crown-5 was added as required. The mixture was refluxed for 48 h then washed with THF/water (3×16/4 mL), DCM (2×20 mL) and methanol (20 mL). The resin was dried in vacuo.
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7. Fmoc protected Knorr linker, Fmoc-Ala-OH, Fmoc-Val-OH and Boc-Phe-OH were coupled to the aminomethyl resin as follows: The resin (0.40 g, 0.38 mmol) was pre-swollen with DCM (1 mL). The linker or protected amino acid (2.0 equiv., 0.76 mmol) and HOBt (2.0 equiv., 0.76 mmol) were dissolved in DCM/DMF (2/1 mL). DIC (3.0 equiv., 1.14 mmol) was added and the mixture stirred for 15 minutes. The solution was added to the resin and agitated overnight. The resin was washed with DMF (5 mL), DCM (3×5 mL) and methanol (5 mL). The resin was dried in vacuo.
   The Fmoc protecting group was removed with 20% piperidine in DMF (5 mL) for 20 minutes. The resin was washed with DMF (5×5 mL), DCM (3×5 mL) and methanol (5 mL).
   The peptide was deprotected and cleaved from the resin by treatment with a solution of 47% TFA/47% DCM/5% water/1% TIS (5 mL) over 3 h. The resin was filtered and washed with the cleavage solution (5 mL). The combined filtrates were evaporated (to ca. 1 mL) and precipitated into cold ether (50 mL). The tripeptide was lyophilised to give a white solid.
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9. Data for the tripeptide: Yield: 76%, $R_f$ (10% methanol/DCM): 0.20, $\delta_H$ (300 MHz, $d_6$-DMSO): 0.88 (6H, m,

$CH(C\underline{H}_3)_2$), 1.22 (3H, d, *J* 7, $CHC\underline{H}_3$), 1.97 (1H, m, $C\underline{H}(CH_3)_2$), 3.01 (2H, AB part of ABX, *J* 6 7 14, $CHC\underline{H}_2Ph$), 4.13–4.24 (2H, m, $C\underline{H}CH_3$ & $C\underline{H}CH(CH_3)_2$), 6.99 & 7.28 (2H, 2×s, $CON\underline{H}_2$) 7.16–7.32 (5H, m, $Ar\underline{H}$), 8.03 (1H, d, *J* 7, $N\underline{H}$), 8.52 (1H, d, *J* 8, $N\underline{H}$). $\delta_C$ (75 MHz; $d_6$-DMSO): 18.3 & 18.4 ($CH(\underline{C}H_3)_2$), 19.2 ($CH\underline{C}H_3$), 30.8 ($\underline{C}H(CH_3)_2$), 37.2 ($Ph\underline{C}H_2$), 48.1 ($\underline{C}HCH_3$), 53.2, ($\underline{C}HCH_2Ph$), 57.9 ($\underline{C}H(CH_3)_2$), 127.1 (*p*-$\underline{C}$ Ar), 128.5 (*m*-$\underline{C}$ Ar), 129.6 (*o*-$\underline{C}$ Ar), 134.9 ($\underline{C}$ Ar), 168.0 & 169.9 ($\underline{C}ONH$), 174.0 ($\underline{C}ONH_2$), IR (max: 1635 $cm^{-1}$ (C=O), 3337 (NH), HPLC (A = water/0.42% TFA, B = MeCN/0.1% TFA. Gradient is 100% A to 100% B over 20 min, $\lambda = 220$ nm): 5.94 min, *m*/*z* (APCI+): 335 (30%) M+H, mp (uncorrected): 205–220°C dec.