New Method for the Preparation of Benzhydrylamine Resins

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Benzhydrylamine and related resins can easily be prepared by treatment of lithiated resins with *N*-trimethylsilyl imines followed by hydrolysis.

Benzhydrylamine-resins provide one of the most useful polymeric supports for solid-phase peptide synthesis. The use of such polymeric supports is advantageous for the synthesis of peptides with a *C*-terminal amide such as gastrin tetrapeptide.[1]

Benzhydrylamine-resins, starting from polystyrene–divinylbenzene cross-linked polymer, have been synthesized by the methods shown in Scheme 1.[2,3] Reduction of the oxime intermediate in method (a) with metal hydrides was reported to lead to a large proportion of secondary amine,[3] and so this method is not a particularly suitable one. In method (b), the possibility of unwanted cross-linking by alkylation of the aminomethyl sites with unchanged bromobenzyl groups could not be avoided. Method (c) *via* Leuckart reduction appears to be superior. However, all these methods require many steps and severe conditions in some cases when the unchanged reagents and by-products may accumulate on the resin leading to decreased purity of the resulting aminated resins.

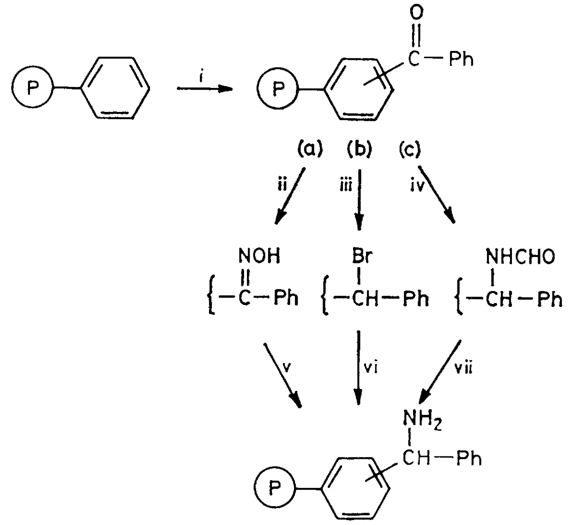
We have recently found a new method for synthesis of primary amines by the reaction of *N*-trimethylsilyl imines with organolithium reagents followed by hydrolysis [reaction (1)]; excellent (sometimes quantitative) yields were obtained.[4]

$$R^1R^2C{=}N\text{–}SiMe_3 + R^3Li \rightarrow\rightarrow R^1R^2R^3C\text{–}NH_2 \qquad (1)$$

For example, benzhydrylamine was obtained in 94% isolated yield by the reaction of *N*-(trimethylsilyl)phenylmethanimine with phenyl-lithium in diethyl ether.

We now report an alternative procedure for the preparation of benzhydrylamine-resin by applying this reaction to systems using polymeric lithium reagents.

All the reactions shown in Table 1 were carried out on a lithiated resin prepared by the reaction of 1% divinylbenzene-styrene copolymer, Bio-Beads SX-1, with butyl-lithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine complex in cyclohexane (65 °C, 3 h), according to the procedure reported by Farrel and Fréchet.[5] The degree of lithiation by this method



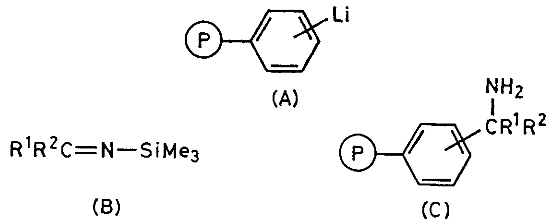
Scheme 1. *Reagents:* i, PhCOCl, $AlCl_3$; ii, $HONH_2$; iii, $NaBH_4$ then HBr; iv, HCO_2H, HCO_2NH_4; v, $LiAlH_4$; vi, NH_3; vii, HCl.

was found to be 27% per phenyl ring of the polymer. A resin with lower loading was obtained using a shorter reaction time. Under nitrogen, 2.0 g (5.1 mequiv. Li) of the lithiated resin was suspended in dry cyclohexane (10 ml) and *N*-(trimethylsilyl)phenylmethanimine (1.76 g, 10 mmol) was added at 0 °C. The mixture was stirred at 30 °C for 5 h, 1 M-HCl (5 ml) was added for complete hydrolysis, and the resin was filtered off and suspended in tetrahydrofuran (THF)–2 M-NaOH (2:1; 20 ml) for 1 h. After filtration, the resin was washed repeatedly with THF–water (3:1), water, THF, and finally methanol. After drying, 2.50 g of benzhydrylamine-resin was obtained. Microanalysis showed that the resin contained 2.0 mequiv. of amine group per gram which corresponds to 27% of ring substitution. The yield was thus almost quantitative based on the lithiated resin.

We have treated the lithiated polystyrene with *N*-(trimethylsilyl)phenylmethanimine to give benzhydrylamine-resins having a substitution of 0.8—2.0 mequiv. amine/g. To explore its application to the preparation of other related aminated resins, a number of reactions were studied. In all cases the aminated resins were obtained *in situ* from the lithiation of resins and sequential treatment with *N*-trimethylsilyl imines followed by hydrolysis. The results are excellent, except for the case using *N*-(trimethylsilyl)diphenylmethanimine where the reaction is sluggish probably owing to steric hindrance.[4]

This method should provide a reliable procedure for the preparation of clean benzhydrylamine-type polymeric supports with a predictable degree of substitution. The degree of substitution can be controlled by the lithiation step and lower levels of functionalization which have been suggested to be best for peptide synthesis can be achieved by reducing the amount of *N*-trimethylsilyl imine used.

Table 1. Preparation of benzhydrylamine and related resins from the reactions of lithiated resins (A) with *N*-trimethylsilyl imine derivatives (B).[a]



Degree of lithiation in (A)[b]	R^1	R^2	Degree of amination in (C)	% Yield of (C)
0.10	H	Ph	0.099	99
0.27	H	Ph	0.27	100
0.10	H	C_6H_4Me-*p*	0.093	93
0.10	H	C_6H_4OMe-*p*	0.097	97
0.10	H	C_6H_4Cl-*p*	0.092	92
0.27	Ph	Ph	0.089	33

[a] The reactions of the lithiated resins with a 2 molar excess of *N*-trimethylsilyl imines were carried out in cyclohexane at 30 °C for 5 h. This lithiation has been studied by Evans *et al.*,[6] who showed that both *meta*- and *para*-lithiation occurred with a *meta*:*para* ratio of 2:1 on the polymer. The resulting aminated polymers were therefore a mixture of *meta*- and *para*-substituted amine resins. [b] The degrees of resin lithiation were estimated by a literature method (R. T. Taylor, D. B. Crawshaw, J. P. Paperman, L. A. Flood, and R. A. Cassell, *Macromolecules*, 1981, **14**, 1134). The lithiated resin was cooled to 0 °C and excess of chlorotrimethylsilane (2 equiv. based on BuLi) added. The usual work-up afforded the silylated polymer, the degree of silylation of which was determined by i.r. and elemental analysis. The degree of silylation was considered to correspond to the initial level of resin lithiation.

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