



# High-loading scavenger resins for combinatorial chemistry

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**Abstract**—The synthesis of high-loading resins functionalised with triazine dendrimers, suitable for use as scavengers in the purification of combinatorially derived products is described. A comparison of their efficacy with respect to some commercial resins is also presented. © 2001 Elsevier Science Ltd. All rights reserved.

The use of scavenger resins for the purification of reaction products is becoming increasingly widespread,<sup>1</sup> particularly for applications in combinatorial chemistry. There are a number of such resins available commercially, however there is considerable scope for improvement. One of the drawbacks of these resins is that quite a high quantity is required to clean up a typical product and this can present physical difficulties since the beads themselves swell in solvent,<sup>2</sup> especially problematic on a small scale. In order to overcome these difficulties we decided to make high-loading resins through the construction of dendritic architectures on the solid phase resin. This strategy has previously been used for the synthesis of dendrimers<sup>3</sup> and hyper-

branched architectures<sup>4</sup> themselves and the preparation of super-high-loading resins for supported chemistry,<sup>3,5</sup> but it has not been tried for preparing new chemical reagents such as scavenger resins. Interestingly however, the commercially available PS–Tris resins could be considered a prototype for this class of resin. This communication describes the synthesis of a number of novel scavenger resins (e.g. Fig. 1) and demonstrates how they can be used to remove both nucleophiles and acids.

We chose to grow the dendritic wedges on Wang functionalised polystyrene resin<sup>6</sup> to enable us to cleave them from the support and subject them to chemical

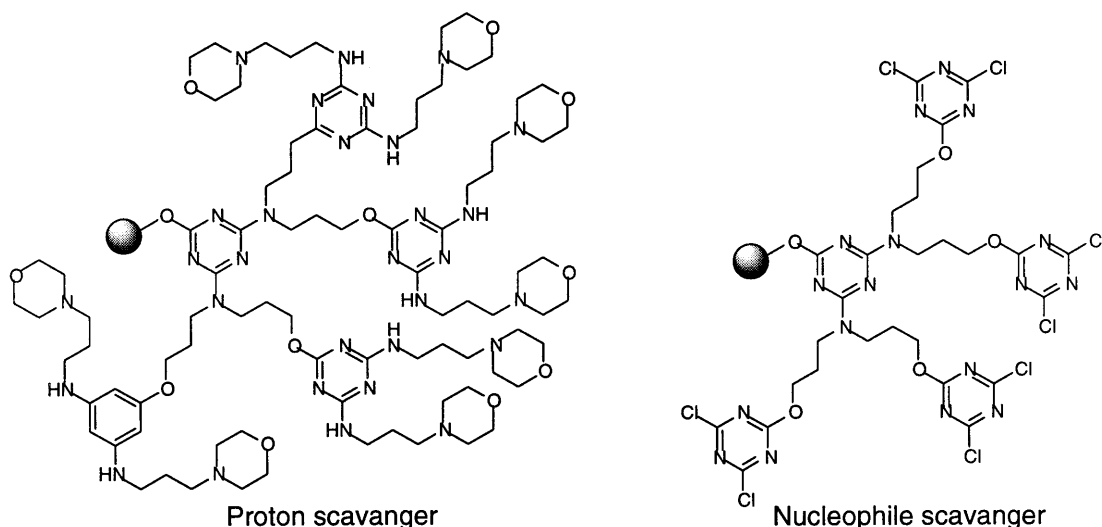


Figure 1.

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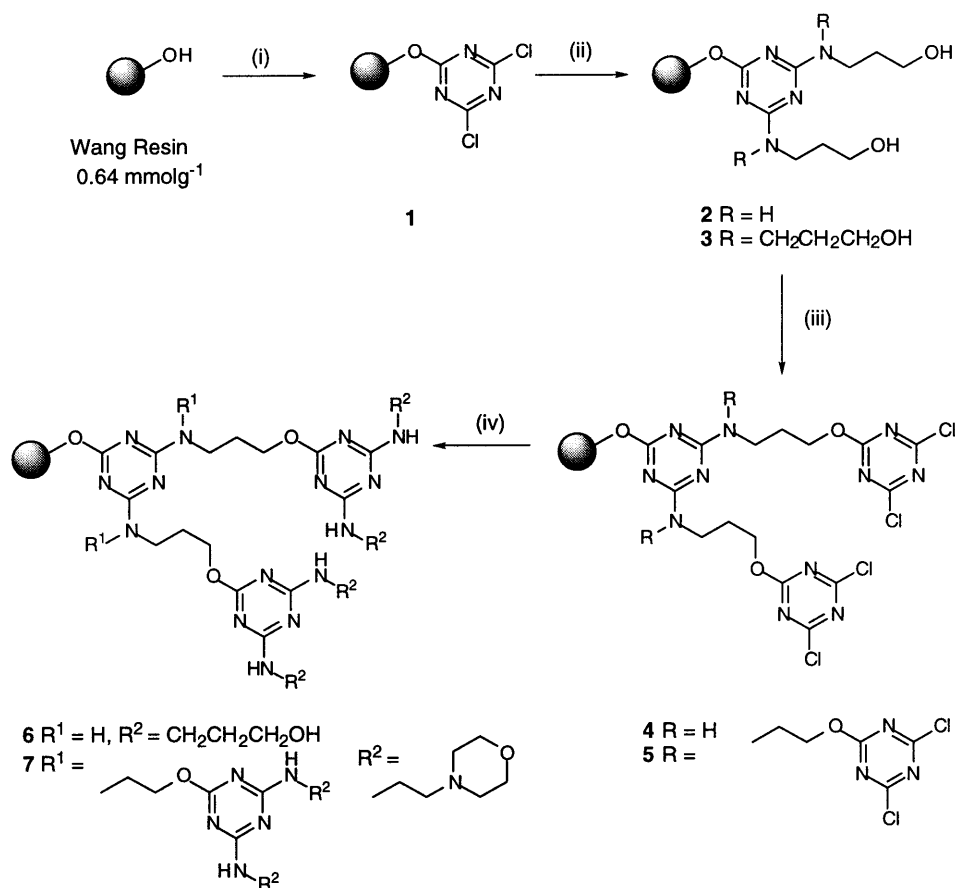
analysis. The preparation of the wedges themselves was found to be considerably facilitated by using a solid support: attempts to prepare related dendrimers in solution met with considerable difficulty during the purification of these polar molecules.<sup>7</sup> The synthesis of the core framework is outlined in Scheme 1. Wang resin was reacted with trichlorotriazine and the resulting dichloride **1** substituted<sup>8</sup> with either propanolamine to give **2** or 1,7-dihydroxy-4-azaheptane to give **3**. These alcohols were found to be rather unreactive and required deprotonation with LDA prior to reaction with more trichlorotriazine giving **4** and **5**. Attempts to functionalise a shorter linker derived from ethanolamine were unsuccessful apparently due to the extremely low reactivity of the ethanolamine oxygen or oxyanion, perhaps for steric reasons.

The resultant dichloro intermediates (**4** and **5**) are rather reactive and were not characterised, instead they were reacted further with a suitable amine nucleophile to give compounds **6** and **7**. These compounds, along with intermediate **3** were cleaved from the resin for analysis by <sup>1</sup>H NMR, IR and mass spectrometry<sup>9</sup> (compounds **8** and **9**, Scheme 2). It was found that the morpholino derivative **9** proved difficult to characterise as the free base after trifluoroacetic acid cleavage.

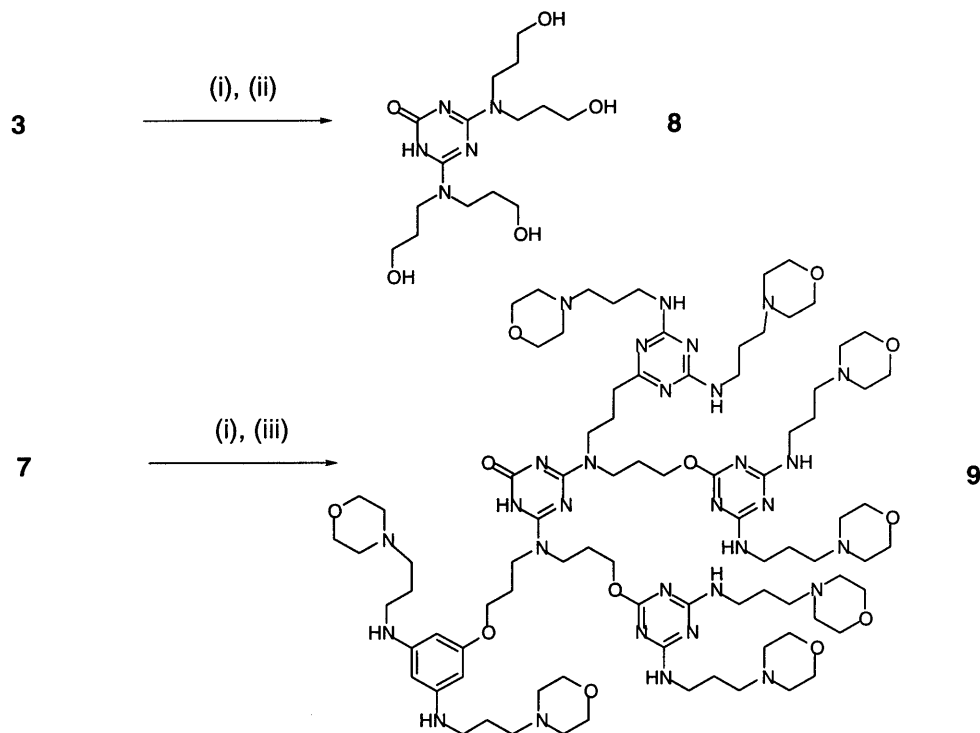
Hence for the purposes of more readily characterising a generation 1.5 dendrimer, intermediate **4** was reacted further with propanolamine giving **6** which was also cleaved from the resin giving compound **10** (structure not shown).

To demonstrate the efficacy of these resins for chemical synthesis we used them for the preparation of a secondary amide, a reaction which has been demonstrated for commercial scavenger resins.<sup>10</sup> In these reactions we used a generation 1 morpholino substituted dendrimer, **7** as the proton scavenger and a generation 1 dichlorotriazine resin **5** as the excess nucleophile scavenger (Scheme 3). The crude acylation reactions were analysed by <sup>1</sup>H NMR and GC. Table 1 shows the results of these experiments.

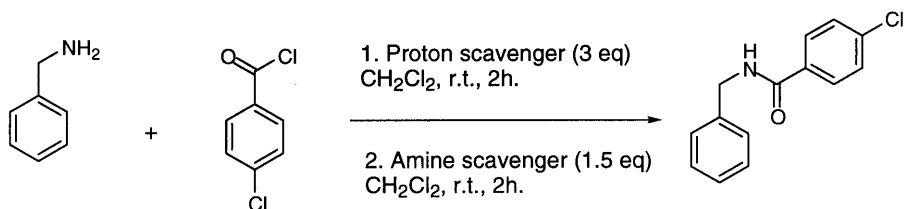
It is noteworthy that in the case of the dendritic scavengers the number of equivalents were calculated on a molar basis. This has the result that approximately half the mass and volume of resin was required to achieve similar scavenging efficiency. A second test reaction was also used to explore the utility of these resins, namely the tosylation of a primary amine (Scheme 4). The results were comparable to those obtained with commercially available resins (Table 2).



**Scheme 1.** Reagents and conditions: (i) trichlorotriazine, Hünig's base, THF, rt; (ii) propanolamine, Hünig's base, DMF 80°C (R = H); HN(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, Hünig's base, DMF, 80°C (R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH); (iii) LDA, THF, rt, then trichlorotriazine; (iv) morpholino CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> or propanolamine, Hünig's base, DMF, 80°C.



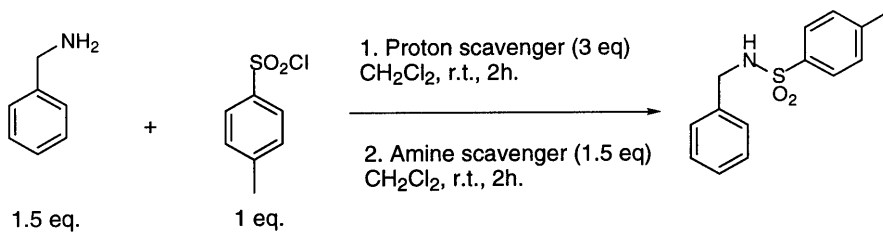
**Scheme 2.** Reagents and conditions: (i) 5% CF<sub>3</sub>COOH in CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h; (ii) MeOH; (iii) 2 M NaOH, then Sephadex chromatography.



**Scheme 3.**

**Table 1.**

Expt	<b>5</b> (g)	PS-NCO (g)	<b>7</b> (g)	PS-NMM (g)	Benzylamine <sup>a</sup> (%)	Acid chloride <sup>a</sup> (%)	Product <sup>b</sup> (%)
1	0.12	–	0.12	–	<1	<1	77
2	–	0.20	0.12	–	<1	<1	77
3	0.12	–	–	0.26	<1	<1	75
4	–	0.20	–	0.26	1.5	0.3	83

<sup>a</sup> Determined by GC.<sup>b</sup> Determined by mass and <sup>1</sup>H NMR.

**Scheme 4.**

Table 2.

Expt	5 (g)	PS-NCO (g)	7 (g)	PS-NMM (g)	Benzylamine <sup>a</sup> (%)	Tosyl chloride <sup>a</sup> (%)	Product <sup>a</sup> (%)
1	0.12	–	0.12	–	0.2	1	74
2 <sup>b</sup>	–	0.20	–	0.26	n.d.	n.d.	89 <sup>b</sup>

<sup>a</sup> Determined by GC.<sup>b</sup> See Ref. 10.

In summary, we have prepared a range of triazine based dendrimers which have found application as high-loading scavenger resins. They give comparable efficiency to commercial resins at significantly lower concentration thanks to the increase in the number of active functional groups. The preparation of dendrimers substituted with an ethylenediamine linker which is more reactive towards further substitution allowing growth of higher generation dendrimers will be reported in a further publication.

### Acknowledgements

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- Purchased from NovaBiochem, 200–400 mesh, loading 0.64 mmol g<sup>-1</sup>.
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- Hünig's base (as used, for example, in: Seto, C. T.; Mathias, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, 115, 1321) was found to be superior to either inorganic base (cf. Kaiser, D. W.; Thurston, J. T.; Dudley, J. R.; Schaefer, F. C.; Hechenbleikner, I.; Holm-Hansen, D. *J. Am. Chem. Soc.* **1951**, 73, 2984) or collidine (cf. Koopman, H.; Uhlenbroek, J. H.; Haeck, H. H.; Daams, J.; Koopmans, M. J. *Rec. Chim. Trav. Pays-Bas* **1959**, 78, 967).
- Data for compound **8**:  $\delta_{\text{H}}$  (300 MHz, CD<sub>3</sub>OD) 3.52 (16H, m, 8×CH<sub>2</sub>), 1.79 (8H, m, 4×CH<sub>2</sub>)  $\nu_{\text{max}}$  3298 (br.), 3123, 2932, 1752, 1682, 1561, 1518, 1342, 1171, 1013, 810 cm<sup>-1</sup>;  $m/z$  (FAB<sup>+</sup>) 360 (M<sup>+</sup>), 281, 147;  $m/z$  (ESI<sup>+</sup>) 383 (M+Na<sup>+</sup>); data for compound **9**:  $\delta_{\text{H}}$  (300 MHz, CD<sub>3</sub>OD) 4.35 (8H, m, 4×CH<sub>2</sub>), 4.01 (16H, m, 8×CH<sub>2</sub>), 3.72 (16H, m, 8×CH<sub>2</sub>), 3.51–3.45 (40H, m, 20×CH<sub>2</sub>), 3.11 (32H, m, 16×CH<sub>2</sub>), 2.10–1.99 (24H, m, 12×CH<sub>2</sub>);  $\nu_{\text{max}}$  3261, 3016, 2970, 2943, 2868, 1741, 1671, 1592, 1197, 1122 cm<sup>-1</sup>;  $m/z$  (MALDI, dithranol matrix) 1920.8 (M+Ag<sup>+</sup>); data for compound **10**:  $\delta_{\text{H}}$  (300 MHz, D<sub>2</sub>O) 4.55 (4H, m, 2×CH<sub>2</sub>), 3.70–3.30 (20H, m, 10×CH<sub>2</sub>), 2.07 (4H, m, 2×CH<sub>2</sub>), 1.81 (8H, m, 4×CH<sub>2</sub>);  $\nu_{\text{max}}$  3286 (br.), 2933, 1749, 1680, 1618, 1436, 1200, 1138, 723 cm<sup>-1</sup>;  $m/z$  (ESI<sup>+</sup>) 717 (M+Na<sup>+</sup>) 694 (M<sup>+</sup>).
- PS-NCO = polystyrene bound isocyanate; PS-NMM = polystyrene bound *N*-methyl morpholine; see: *Polymer Reagents and Scavengers*; Argonaut Technologies, 1998.