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Report

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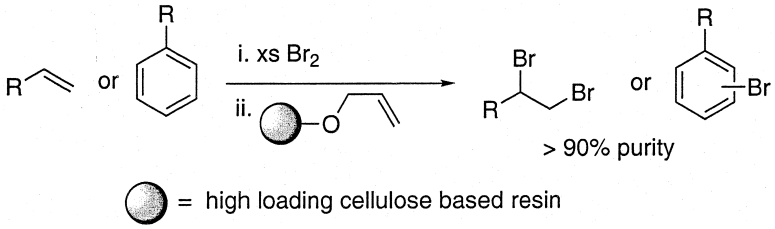

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Reports

High Loading Cellulose Based Poly(alkenyl) Resins for Resin Capture Applications in Halogenation Reactions

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Introduction

The advent of combinatorial chemistry has seen a focus on synthetic methodologies which permit the rapid synthesis of large numbers of compounds, chemical libraries, in the minimum number of operations.[1] While the recent trend has moved away from the preparation of mixtures to arrays of discrete compounds, there is still the requirement that a sufficient degree of purity is attained. The majority of the methods reported have been based on the principles of solid phase organic synthesis (SPOS) in which the substrate is attached to the polymer support and excesses of reactants and reagents can theoretically be used to drive each step of the sequence to completion. After each step simple filtration affords a polymer bound product. While this approach is undoubtedly effective, there are a number of drawbacks which include the requirement for additional chemical steps to attach starting material and cleave products and the need to develop synthetic methodology for the solid phase. More recently, solution phase methods, which circumvent these difficulties, have been introduced as alternatives to SPOS.[2] These include the use of equimolar quantities of reagents in high yielding reactions, high throughput chromatography methods,[3] novel liquid−liquid extraction methodologies in which the different solubilities of the product and reagents are exploited,[4] and polymer assisted solution phase synthesis (PASP).[5] This last technique involves sequestrating either the product or excess reagents and byproducts from the reaction mixture using an insoluble polymer. Purification can then be achieved by simple filtration and evaporation.

To date, the scavenging of excess reagents from solution phase reaction mixtures has focused on either acid−base interactions using ion-exchange resins[6] or the use of amino resins for the sequestration of excess acylating agents (e.g., isocyanates, acid chlorides, and sulfonyl chlorides) and aldehydes (in conjunction with borohydride).[7] Consequently, there is a need for new scavenger resins which can extend the scope of this technique. In contrast to supports designed for synthesis in which interactions between proximal sites can be problematic, these, ideally, should possess a high effective concentration of scavenging group to maximize the efficiency of the sequestration process. Similarly, whereas a range of swelling profiles is desirable for synthetic supports, a broad solvent tolerance is required for scavenging reagents to enable use without requiring additional solvent manipulations

In this communication we wish to report the use of a high loading poly(alkenyl) resin, derived from a carbohydrate source, as an efficient solvent versatile resin which may be used to scavenge excess electrophilic reagents from alkene and arene addition reactions.

Results and Discussion

As part of a general program looking at alternative base matrixes to the polystyrene and PEG based resins commonly used in SPOS and PASP applications, we have been examining the use of various beaded cellulose supports. These show different solvent swelling profiles relative to those exhibited by the standard organic polymers and, being biomolecules, are biodegradable.[8]

Since the early reports by Frank, derivatized cellulose has found widespread application in the synthesis of peptides and oligonucleotides in both combinatorial and high throughput parallel synthesis format.[9,10]

In most situations this has involved the use of cellulose sheets or membranes, and in this case the use of segmented cellulose supports allows for the synthesis to be carried out in a flow through arrangment with the paper disks packed in a column percolated by the appropriate monomer unit.[10,11] Similar advantages of divisibility have also been recently demonstrated for functionalized cotton thread supports.[12] The alternative strategy has involved the absorption of reagent solutions onto a functionalized cellulose surface in the presence of an activating reagent, SPOT synthesis.[13] This removes the need for mixing as the reaction is driven to completion by diffusion of the liquid into the paper. Despite these precedents, alternative cellulose supports, notably beads which can offer considerably higher loading levels than that obtained with planar supports, seem not to have been widely exploited as supports for SPOS.[14] Beaded cellulose can be easily prepared by the coagulation−regeneration technique involving the addition of a solution of a soluble cellulose

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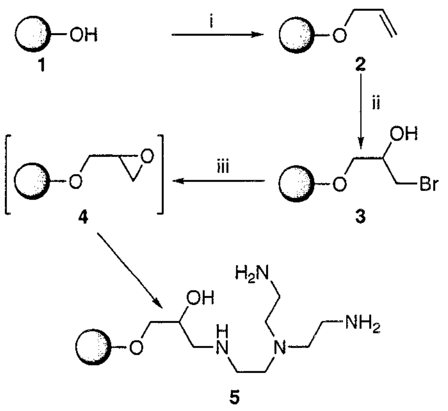
Scheme 1. Preparation of Resins **2** and **5**



[a] Reagents: (i) NaOH, $BrCH_2CH{=}CH_2$; (ii) HOBr; (iii) $N(CH_2CH_2NH_2)_3$, MeOH.

derivative, commonly the xanthate[15,16] or acetate,[17] to a rapidly stirred, inert, immiscible solvent. The beads, thus formed, are precipitated either by a sol−gel process or by a reduction in reaction temperature. Chemical regeneration of the hydroxyl groups and seiving produces the active beads with the desired size distribution.

A wide variety of physical properties can be rapidly introduced into cellulose by simple chemical modification of the basic polymer unit.[18,19] Cellulose undergoes facile alkaline etherification which, given the availability of up to three hydroxyl groups per glucopyranose residue, offers the potential to provide very high loading resins. This derivatization can be achieved either in solution, prior to bead formation, or once the bead has been prepared with the required physical size and porosities. The latter strategy is the most common and has been used to prepare polymers with a number of interesting characteristics such as variable water solubility. Such materials have been employed in the food, agrochemical, and biochemical/biotechnological fields,[20,21] although, to the best of our knowledge, applications in combinatorial chemistry have not been reported.

Owing to ready availability, we opted to use the Perloza MT-100 resin which exhibits suitable manual handling properties. Related Perloza resins have previously been successfully derivatized, and relatively large peptides have been attached to the surface either by direct synthesis[22] or by immobilization via a chemical spacer.[23] The resultant materials have been employed as chromatography adsorbents, for the purification of biomolecules from crude feedstocks,[24] although application in SPOS or PASP has not been explored.

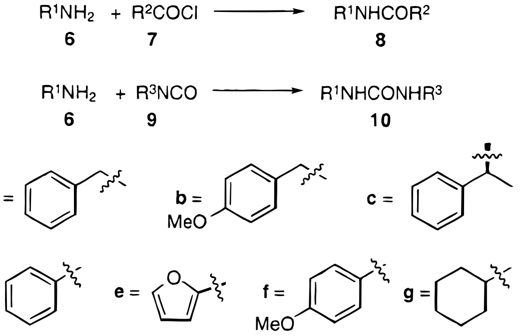
Following established protocols,[25] the resin can be allylated using NaOH and allyl bromide[26] and the resultant allyl resin converted to the tris-(2-aminoethyl)amine resin by sequential treatment with bromine water and tris-(2-aminoethyl)amine in methanol, Scheme 1. This last transformation presumably proceeds via the intermediacy of the epoxy substituted resin. Analysis by bromine titration and elemental analysis indicated that the loadings for the resins were 1.9 mmol/g of allyl groups and 2.2 mmol N/g, respectively. Furthermore these resins show high and uniform swelling properties in a broad range of solvents including water, which is not normally a viable solvent for many polystyrene based matrixes, Table 1.[8,27,28] Although, with more forcing conditions, higher resin loadings can be achieved (up to 4 mmol/g allyl groups), for ease of preparation all scavenging experiments were carried out using the lower loadings.

Table 1. Swelling Volume of 1 g of Resin **2** in Various Solvents[8,29]

solvent	volume mL[a]	solvent	volume mL[a]
water	10	tetrahydrofuran	9 (5)
1,4-dioxane	9 (5.5)	methanol	9 (4)
dichloromethane	8.4 (5)	ethyl acetate	8.7
toluene	8 (4)	acetonitrile	8.8 (3)
dimethylformamide	9 (5)	diethyl ether	10 (1)

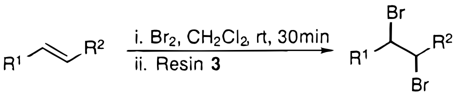
[a] Values in parentheses refer to swelling volumes obtained for a sample of Argonaut PS Trisamine resin under identical conditions.

Table 2. Yields and Purities of Amides **8** and Ureas **10** Prepared Using Resin **5**



amine	acylating agent	product	% yield	% purity (HPLC)
6a	**7d**	**8ad**	99	>95
6a	**7e**	**8ae**	74	>95
6a	**9f**	**10af**	97	>95
6a	**9g**	**10ag**	84	>95
6b	**7d**	**8bd**	95	>95
6b	**7e**	**8be**	96	>95
6b	**9f**	**10bf**	93	>95
6b	**9g**	**10bg**	91	>95
6c	**7d**	**8cd**	93	>95
6c	**7e**	**8ce**	89	>95
6c	**9f**	**10cf**	95	>95
6c	**9g**	**10cg**	97	>80

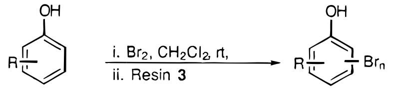
Table 3. Bromination of Alkenes with Excess Bromine

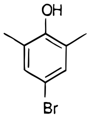
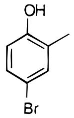
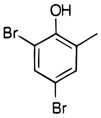
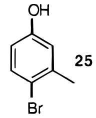
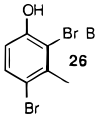
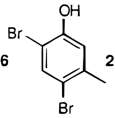
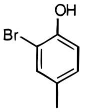
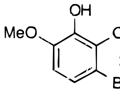
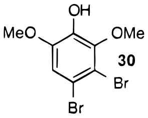
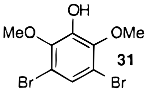


R1	R2	product	% yield	% purity[a] (HPLC)
C_6H_5	H	**11**	95	>95
4-$CH_3C_6H_4$	H	**12**	98	>85
3-$CH_3C_6H_4$	H	**13**	98	>95
3-$O_2NC_6H_4$	H	**14**	100	>95
4-ClC_6H_4	H	**15**	94	>95
4-$MeOC_6H_4$	H	**16**	95	>95
C_6H_{11}	H	**17**	90	>95
1-naphthyl	H	**18**	92	>90
C_6H_5	CH_3	**19**	80	>95
C_6H_5	C_6H_5	**20**	94	>90
$C_6H_5OCH_2$	H	**21**	95	>90[b]

[a] Determined by HPLC. [b] Bromination also occurs on the arene ring to give 2,3-dibromo-1-(4-bromophenoxy)propane.

Table 4. Bromination of Phenols with Excess Bromine



R	Product(s)	% Yield	% Purity[a]
2,6-Me_2	 **22**	97	>87
2-Me	 **23**  **24**	98	>94
3-Me	 **25**  **26**  **27**	98	>90
4-Me	 **28**	78	>78
2,6-$(MeO)_2$	 **29**  **30**  **31**	94	>90

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[a] Determined by HPLC and refers to combined yield of brominated phenol products.

With the resins in hand we demonstrated that cellulose beads could be used in PASP by examining the scavenging of excess electrophiles in simple well-established acylation reactions of several amines using the tris amino resin **5**.[30] In each case the amines were treated with an excess of the acylating reagent (both acid chlorides and isocyanates). After consumption of the amine was complete, the resin was added and the solution filtered and concentrated to afford the amide or urea in essentially pure form, Table 2. Having established that these resins could be used as an alternative to equivalent polystyrene resins, albeit one which swells in a broader solvent range and is biodegradable, we then turned to examine other applications.

Given the efficiency of bromination of the allyl resin it occurred to us that this resin could be used to facilitate workup and isolation of products from simple halogenation reactions. Consequently we treated a range of alkenes and electron rich arenes with an excess of bromine. When the color of the bromine persisted, allyl resin **3** was added and the mixture agitated for 10 min. Simple filtration and concentration afford the desired dibromoalkanes with a high degree of purity as ascertained by HPLC, Table 3. In a similar vein, activated aromatic nuclei undergo direct bromination, and the use of allyl resin **3** in a similar fashion allows the desired bromarenes to be obtained by simple filtration and concentration. No attempt was made to control the regiochemistry of arene bromination, and consequently this process affords mixtures of mono- and dibrominated products.[31] However, the bromo arene products obtained are isolated as the sole products in good yields and purities with no additional purification steps, Table 4.

In conclusion, cellulose based resins have the potential to provide versatile high loading resins that may be easily derivatized to give a variety of functional groups suitable for applications in PASP. In particular, the allyl resin **3** provides an efficient method for the rapid purification of simple halogenation reactions. Work to extend the use of these materials is in progress and will be reported in due course.

Supporting Information Available. Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.
(2) Weller, H. N. *Mol. Diversity* **1999**, *4*, 47−52.
(3) Emiabata-Smith, D. F.; Crookes, D. L.; Owen, M. R. *Org. Proc. Res. Dev.* **1999**, *3*, 281−288.
(4) Curran, D. P. *Med. Res. Rev.* **1999**, *19*, 432−438.
(5) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336.
(6) Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357−3360.
(7) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881.
(8) Chesney, A.; Barnwell, P.; Stonehouse, D. F.; Steel, P. G. *Green Chem.* **2000**, *2*, 57−62.
(9) Frank, R.; Heikens, W.; Heisterberg-Moutsis, G.; Blöcker, H. *Nucleic Acids Res.* **1983**, *11*, 4365−4377.
(10) Frank, R.; Doring, R. *Tetrahedron* **1988**, *44*, 6031−6040.
(11) Dittrich, F.; Tegge, W.; Frank, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2351−2356.
(12) Schwabacher, A. W.; Shen, Y. X.; Johnson, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 8669−8670.
(13) Frank, R. *Tetrahedron* **1992**, *48*, 9217−9232.
(14) Sepharose beads have been used in the solid phase synthesis of pepetides. See: Tegge, W.; Frank, R. *J. Pept. Res.* **1997**, *49*, 355−362.
(15) Determann, H.; Rehner, H.; Wieland, T. *Makromol. Chem.* **1968**, *114*, 268.

(16) Chitumbo, K.; Brown, W. *J. Polym. Sci.* **1971**, *C36*, 279.

(17) Chen, L. F.; Tsao, G. T. *Biotech. Bioeng.* **1976**, *18*, 1507.

(18) Kennedy, J. F. *Cellulose and its Derivatives: Chemical and Biological Applications*; Ellis Horwood: Chichester, 1989.

(19) Ishimura, D.; Morimoto, Y.; Saito, H. *Cellulose* **1998**, *5*, 135−151.

(20) Gemeiner, P.; Benes, M. J.; Stamberg, J. *Chem. Pap.-Chem. Zvesti* **1989**, *43*, 805−848.

(21) Stamberg, J. *Sep. Purif. Method* **1988**, *17*, 155−183.

(22) Englebretsen, D. R.; Harding, D. R. K. *Pept. Res.* **1994**, *7*, 322−326.

(23) Englebretsen, D. R.; Scanlon, M. J.; West, M. L. *Biomed. Peptides, Proteins Nucleic Acids* **1996**, *2*, 47.

(24) Burton, S. C.; Harding, D. R. K. *J. Chromatogr. A* **1997**, *775*, 39−50.

(25) Burton, S. C.; Harding, D. R. K. *J. Chromatogr. A* **1997**, *775*, 29−38.

(26) Lin, M. S.; Huang, C. S. *J. Polym. Sci., Part A: Polym. Chem.* **1992**, *30*, 2303−2312.

(27) Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951−8954.

(28) For a recent alternative to water swellable resins, see: Buchardt, J.; Meldal, M. *Tetrahedron Lett.* **1998**, *39*, 8695−8698.

(29) Upon desiccation Perloza resins are denatured and do not re-swell. Consequently they are always used pre-swollen with mass determined volumetrically.

(30) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886.

(31) Smith, K.; James, D. M.; Matthews, I.; Bye, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1877−1878.

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