ORGANIC LETTERS

2002
Vol. 4, No. 15
2497–2500

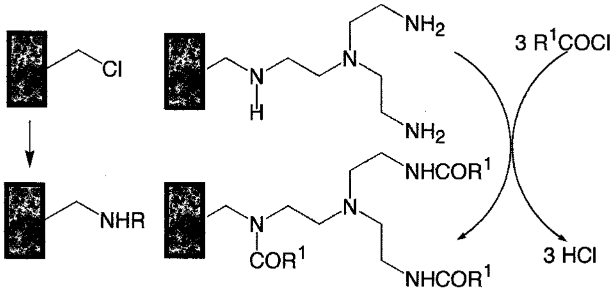
Monolithic Scavenger Resins by Amine Functionalizations of Poly(4-vinylbenzyl chloride-*co*-divinylbenzene) PolyHIPE Materials

Peter Krajnc,*,†,‡ Jane F. Brown,‡ and Neil R. Cameron*,‡

University of Maribor, Faculty of Chemistry and Chemical Engineering,
Smetanova 17, 2000 Maribor, Slovenia, and University of Durham,
Department of Chemistry, South Road, Durham DH1 3LE, U.K.
n.r.cameron@durham.ac.uk

Received May 1, 2002

ABSTRACT



Monolithic polymer supports and scavengers were prepared via nucleophilic displacement of chlorine in poly(4-vinylbenzyl chloride-*co*-divinylbenzene) PolyHIPE materials. Reactions of monolithic PolyHIPE with tris(2-aminoethyl)amine, 4-aminobutanol, tris(hydroxymethyl)-aminomethane, morpholine, and hexamethylenetetramine led to functionalized polymers with amino and hydroxy functionalities with high degrees of conversion. 4-Chlorobenzoyl chloride was efficiently and rapidly scavenged from solution by the tris(2-aminoethyl)amine derivative of monolithic poly(4-vinylbenzyl chloride-*co*-divinylbenzene) PolyHIPE at ambient temperature.

The use of polymer supports in synthetic organic chemistry has recently grown immensely, which is largely due to the rapid development of combinatorial chemistry and parallel synthesis. The suitability of the polymer supports is of vital importance when performing automated parallel experiments. The majority of polymer supports used to date in various methods of solid-supported chemistry come in the form of beads, either gel-type or permanently porous with smaller or larger levels of porosity.[1] Many types of polymer supports in the form of beads are now commercially available; however, their uses have limitations. With gel-type beads, the majority of reactive sites are positioned inside a particle, and swelling is normally essential to enable accessibility of reactive sites. This can limit the range of solvents in which supports can be used. Permanently porous beads do not require pre-swelling and so have greater solvent compatibility; however, the reactive sites inside the porous matrix are accessed by diffusion only, which is a slow process. In addition, porous beads can be fragile and awkward to manipulate due to their propensity for electrostatic charge build up. Furthermore, when using polymer beads in a flow-through rather than a batch method, channeling (flow passing around beads) of the solution severely reduces the efficiency of the support[2] and gel-type resins additionally suffer from compression under flow.

---

* To whom correspondence should be addressed. (N.R.C.) Fax: (+44) 191 384 4737. Tel: (+44) 191 374 3108. (P.K.) E-mail: peter.krajnc@uni-mb.si. Fax: (+386) 2 2527 774. Tel: (+386) 2 2294 422.

† University of Maribor.

‡ University of Durham.

[1] For a review, see: (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650.

10.1021/ol026115k CCC: $22.00

Recent pioneering work by Svec, Fréchet, et al. has shown that porous polymer monoliths under flow-through conditions can overcome many of the problems associated with beads.[3] However, two opposing demands are placed on monolithic supports used in flow-through systems. First, a high permeability of the monolith is required to achieve high flow rates and low back pressures as well as good accessibility of reactive sites. However, high permeability is achieved with larger pore sizes, which results in materials with low surface areas. Thus, there is a tradeoff between permeability and capacity of supports.[4] The Berkeley group elegantly overcame this problem by grafting functional polymer onto the surface of monoliths with relatively large pores, thus producing higher loadings without compromising permeability.[5] An alternative method for producing highly permeable monoliths is to polymerize the continuous phase of a high internal phase emulsion. The resulting material, termed PolyHIPE,[6] has a much more open structure than the monoliths described above (Figure 1) and so would be expected to be more permeable. Furthermore, it can have a high surface area, up to 550m^2/g.[7] Thus, such monoliths could provide highly permeable supports with high surface loadings without the need for grafting. Monolithic PolyHIPE materials have already been utilized in applications such as the separation of heavy metals,[8] as precursors for supported species,[9] and as biocatalyst supports.[10] Functionalization of styrene/DVB- based PolyHIPE materials can be achieved via aromatic substitution[9] or utilization of unreacted double bonds of DVB;[11] however, in order to simplify the processes of obtaining functionalized resins, PolyHIPE materials incorporating 4-vinylbenzyl chloride have been synthesized and their morphology studied.[12] Kirschning and co-workers have recently demonstrated the preparation of chloromethylated polystyrene/porous glass composites, known as PASSflow supports, for use in a flow-through process.[13] These represent an alternative approach to our method for producing permeable monoliths.

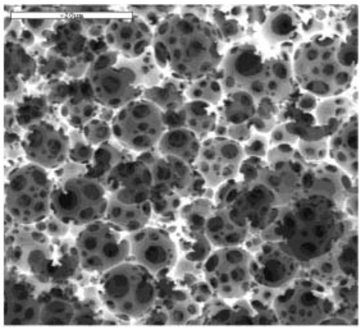


Figure 1. Scanning electron micrograph of VBC/DVB PolyHIPE (molar ratio of VBC/DVB = 6/4; pore volume 90%).

Polymer-supported amines have been used to scavenge excess electrophiles,[14] and Nicewonger et al. reported the use of polymer-supported tris(2-aminoethyl)amine for quenching *trans*-*β*-styrene sulfonyl chloride.[15] With the intention of immobilizing tris(2-aminoethyl)amine moieties, we prepared VBC/DVB (6/4 molar ratio) HIPEs and polymerized these inside PTFE tubes to yield porous monoliths (**1a**) for use in a Quest parallel synthesizer. The remaining HIPE was polymerized in a container, and the resulting material was washed, dried, and cut into ~1 cm cubes (**1b**) for comparative batch reactions. The monoliths were then treated, under flow-through conditions, with a solution of tris(2-aminoethyl)amine in DMF.[16] Initial experiments conducted at 60 °C indicated that additional cross-linking via two amine functionalities of tris(2-aminoethyl)amine could occur, as evidenced by a low residual chlorine content but a lower than expected corresponding nitrogen level, from combustion analysis. Comparable batch reaction studies showed that a lower temperature gave less additional cross-linking but with more time required to reach completion. Reactions with tris-(2-aminoethyl)amine were therefore performed at 45 °C, as opposed to reactions with other amines (vide infra), which were done at 60 °C. From Table 1 it can be seen that these optimized conditions led to a product with 5.3 mmol of NH/

Table 1. Functionalization of Poly(4-vinylbenzyl chloride-*co*-divinylbenzene) PolyHIPE Monolithic Materials[a]

polymer	reaction time/h	calcd % N[b]	found % N	found % Cl	conversion (%)[c]	reactive groups/ (mmol g^{-1})[d]
2a	1	13.87	6.28	5.42	45	3.4
2a	12	13.87	9.85	3.54	71	5.3
2b	1	13.87	3.25	7.39	23	1.7
2b	24	13.87	10.40	2.74	75	5.6
3a	12	5.24	2.22	4.40	42	1.6
4a	1	4.04	2.17	5.18	54	1.6
4a	12	4.04	3.34	1.87	83	2.4
4b	1	4.04	0.48	10.43	12	0.3
4b	24	4.04	2.96	1.55	73	2.1
5a	1	3.70	1.47	6.20	40	3.2
5a	12	3.70	2.26	3.97	61	4.8
5b	1	3.70	0.0	12.56	0	0
5b	24	3.70	2.15	4.61	58	4.6
6a	1	4.06	3.67	2.55	90	2.6
6a	12	4.06	4.02	1.65	98	2.9
6b	1	4.06	1.86	7.86	46	1.3
6b	24	4.06	3.96	1.27	96	2.8

[a] Products **a** are derived from **1a** (4.1 mmol of chloromethyl groups per gram, flow-through method); products **b** are derived from **1b** (4.1 mmol of chloromethyl groups per gram, batch method). [b] Calculated mass percentage of nitrogen for complete conversion and no additional cross-linking. [c] Conversion determined on the basis of combustion analysis for nitrogen. [d] Loading of OH groups in the case of **5a** and **5b**.

---

(2) Rodrigues, A. E.; Lu, Z. P.; Loureiro, J. M.; Carta, G. *J. Chromatogr*. **1993**, *653*, 189.

(3) Peters, E. C.; Svec, F.; Fréchet, J. M. J. *Adv. Mater*. **1999**, *11*, 1169 and references therein.

(4) Viklund, C.; Svec, F.; Fréchet, J. M. J.; Irgum, K. *Chem. Mater*. **1996**, *8*, 744.

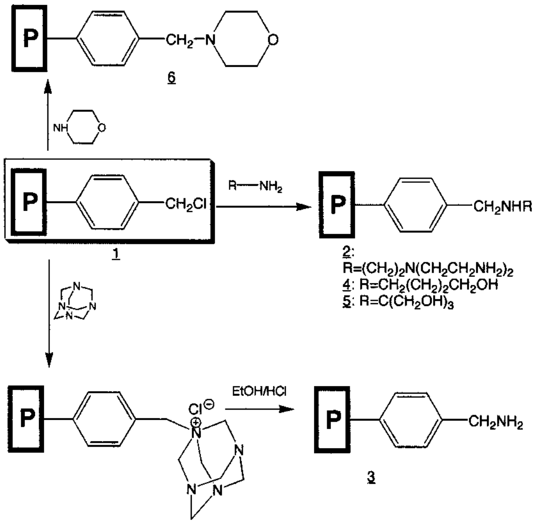
(5) (a) Tripp, J. A.; Stein, J. A.; Svec, F.; Fréchet, J. M. J. *Org. Lett*., **2000**, *2*, 195. (b) Tripp, J. A.; Svec, F.; Fréchet, J. M. J *J. Comb. Chem*. **2001**, *3*, 216.

(6) Barby, D.; Haq, Z. U. S. Pat. 4,522,953, 1985 (PolyHIPE is a Unilever tradename).

(7) Cameron, N. R.; Barbetta, A. *J. Mater. Chem*. **2000**, *10*, 2466.

NH_2 groups per gram under flow-through conditions after 12 h, while after 1 h a product with 3.4 mmol of NH/NH_2 groups per gram was isolated. Reactions under flow-through conditions were considerably faster than batch flask reactions using cubes (**1b**); after 1 h of reaction in the flask, under conditions similar to those used in flow-through, a product with 1.7 mmol of NH/NH_2 groups per gram was formed. For a similar loading, reactions that took 12 h under flow-through conditions took 24 h in a batch reaction. Besides quantitative evaluation of the products by combustion analysis, FT-IR spectroscopy was also used to monitor reactions by observing the disappearance of the C−Cl bond signal at 1265 cm^{-1}.

Scheme 1. Preparation of Functionalized VBC/DVB PolyHIPE Materials



To further test the scope of the chemical modification of VBC monoliths, we undertook a study of their reaction with a range of N-containing species. A route for introducing $-NH_2$ functionalities, known as the Delepine reaction,[17] was investigated (see Scheme 1). Amino-functionalized PolyHIPE has been prepared previously[18] for derivatization to obtain solid-phase peptide synthesis supports; however, this was done with PolyHIPE in granular form. Furthermore, functionalization was obtained by the Gabriel synthesis, which involves harsh conditions (hydrazine) for the cleavage of the initial phthalimide derivative. In this case, after the introduction of hexamethylenetetramine to chloromethylated polystyrene, the functionality is transformed into a primary amine by decomposition with HCl. The reaction was performed under flow-through conditions (using a column in the Quest parallel synthesizer), and approximately 53% conversion of chloromethyl groups to amino was found by combustion analysis.[16] Polymer-supported alcohols as potential scavengers for aldehydes and ketones[19] were also prepared by reaction with amino alcohols (these have been employed previously to functionalize styrene−acrylate polymer beads[20]). 4-Amino-1-butanol was thus used to obtain supported OH groups from VBC moieties on PolyHIPE starting materials. A batch reaction of 24 h of **1b** with 4-amino-1-butanol yielded a product with 2.1 mmol of OH groups per gram of polymer, which corresponds to approximately 73% conversion to **4b** (see Table 1). A 12 h reaction under flow-through conditions resulted in a product with a higher degree of conversion (83%), while approximately 54% conversion was achieved after 1 h (product **4a** with 1.6 mmol of OH groups per gram, Table 1). To increase the loading level, we used an amine containing three OH groups, tris(hydroxyethyl)-aminomethane. Compound **1** reacted readily with tris-(hydroxyethyl)aminomethane to give an amino derivative with a loading as high as 4.8 mmol of OH groups per gram. Reactions under both flow-through and batch conditions for 24 or 12 h gave products with conversions around 60%, thus resulting in high loadings of immobilized OH groups.

Polymer-supported bases have found applications in polymer supported quenching methods where excess acids and acidic byproducts are formed.[21] Morpholine can serve as such a base and can be immobilized onto a polymer matrix via the nucleophilic displacement of chlorine in chloromethylated polystyrene. Reactions of **1a** and **1b** with morpholine yielded products varying from 1.3 mmol (1 h reaction via batch method) to 2.8 mmol (12 h via flow-through) of morpholine moieties per gram, Table 1.

We also performed scavenging experiments, using products **2a** (5.3 mmol of NH/NH_2 groups per gram) and **2b** (5.6 mmol of NH/NH_2 groups per gram) to sequester 4-chlorobenzoyl chloride from solution.[16] The absorbance of UV light at 260 nm was measured to determine the amount of acid chloride remaining in solution.[22] At ambient temperature, when using a 3.35 times molar excess of amino groups (ratio of NH/NH_2 groups to acid chloride: 6.7/1),[23] 96.7% of the acid chloride was quenched after 2 min and 99.1% after 10 min by **2b**. After 1 h of reaction, the acid chloride was no

---

(8) Alexandratos, S. D.; Beauvais, R.; Duke, J. R.; Jorgensen, B. S. *J. Appl. Polym. Sci.* **1998**, *68*, 1911.

(9) Cameron, N. R.; Sherrington, D. C.; Ando, I.; Kurosu, H. *J. Mater. Chem.* **1996**, *6*, 719.

(10) Schoo, H. F. M.; Challa, G.; Rowatt B.; Sherrington D. C. *React. Polym.* **1992**, *16*, 125.

(11) (a) Mercier, A.; Deleuze, H.; Mondain-Monval, O. *React. Funct. Polym.* **2000**, *46*, 67. (b) Mercier, A.; Deleuze, H.; Mondain-Monval, O. *Macromol. Chem. Phys.* **2001**, *202*, 2672.

(12) Barbetta, A.; Cameron, N. R.; Cooper, S. J. *Chem. Commun.* **2000**, 221.

(13) Kirschning, A.; Altwicker, C.; Dräger, G.; Harders, J.; Hoffmann, N.; Hoffmann, U.; Schönfeld, H.; Solodenko, W.; Kunz, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 3995.

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

(15) Nicewonger, R. B.; Ditto, L.; Varady, L. *Tetrahedron Lett.* **2000**, *41*, 2323.

(16) Experimental procedures for the functionalisation of polymers and the scavenging experiments are provided in the Supplementary Information.

(17) Bla evic, N.; Kolbah, D.; Belin, B.; Ŝunjic, V.; Kajfe, F. *Synthesis* **1979**, 161.

(18) Small, P. W.; Sherrington, D. C. *Chem. Commun.* **1989**, 1589.

(19) Hodge, P.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2319.

(20) Zupan, M.; Krajnc, P.; Stavber, S. *J. Polym. Sci. Pt. A*: *Polym. Chem.* **1998**, *36*, 1699.

(21) Creswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppen, M. *Tetrahedron* **1998**, *54*, 3983.

(22) Absorbance values were converted to acid chloride concentrations using a previously constructed calibration curve.

(23) It should be noted that the polymer also quenches 1 mol of HCl produced per mol of acid chloride reacted with NH or NH_2 groups.

Table 2. Scavenging Abilities of **2a** and **2b** (5.3 mmol g^{-1} of NH/NH_2 Groups and 5.6 mmol g^{-1} of NH/NH_2 Groups, Respectively) for 4-Chlorobenzoyl Chloride[a]

polymer	molar ratio of (NH/NH_2) groups/ acid chloride	scavenging time (min)	% of acid chloride scavenged
2a	5.3/1	10.5[b]	86.8
2a	5.3/1	21[b]	98.5
2b	6.8/1	2	96.7
2b	6.8/1	4	97.6
2b	6.8/1	10	99.1
2b	6.8/1	30	99.3
2b	6.8/1	60	100

[a] Quantity of remaining 4-chlorobenzoyl chloride in solution was determined by measuring the absorbance at 260 nm. Total scavenging ability of **2a** = 3.25 mmol g^{-1} of 4-chlorobenzoyl chloride; total scavenging ability of **2b** = 3.39 mmol g^{-1} of 4-chlorobenzoyl chloride. [b] Residence times of 4-chlorobenzoyl chloride solution in monolith, based on a flow rate of 20 mL/h and a monolith volume of 3.5 mL.

longer detectable in the mixture (Table 2). A similar experiment was performed under flow-through conditions. A solution of 4-chlorobenzoyl chloride in dichloromethane was passed through a column containing a monolithic tris-(2-aminoethyl)amine derivative of VBC/DVB PolyHIPE (**2a**, 5.3 mmol of NH/NH_2 groups per gram). At a flow rate of approximately 20 mL/h and ambient temperature, 86.8% of the acid chloride was scavenged after the first pass-through of the solution, increasing to 98.5% after the second pass-through of the same solution. To test the total scavenging ability of **2a**, a solution with excess acid chloride (in relation to NH/NH_2 groups in the polymer) was passed through a column and 3.25 mmol of 4-chlorobenzoyl chloride was scavenged per gram of polymer **2a**, which is in good agreement with the actual amount of nitrogen found by combustion analysis (Table 1). The total scavenging ability of **2b** for 4-chlorobenzoyl chloride was also tested[16] (excess of acid chloride, 30 min. reaction at ambient temperature), and a scavenging ability of 3.39 mmol of acid chloride per gram of resin was found. For comparison, we investigated the scavenging ability of a commercial trisamine resin (Argonaut PS-Trisamine, loading 3.1 mmol g^{-1} NH/NH_2 by elemental anaylsis). Under conditions identical to those used with PolyHIPE materials and employing the same ratio of NH/NH_2 to acid chloride groups, the kinetics of scavenging were found to be slower: 82% of acid chloride scavenged after 2 min, 90% after 10 min, and 99% after 30 min. The total scavenging ability of the commercial resin was found to be 1.92 mmol g^{-1}, compared to 3.39 mmol g^{-1} for the higher loading PolyHIPE resins.

These preliminary results indicate that highly permeable monolithic PolyHIPE supports are advantageous in solution phase organic synthesis. The monolithic format simplifies reagent transfer and other manipulations, furthermore flow-through procedures lead to more rapid transformations. Further uses of these beneficial materials in organic synthesis will be reported in subsequent publications.

Acknowledgment. This research has been supported by a Marie Curie Individual Fellowship (to P.K.) from the European Community, program Monolithic Porous Polymers: Versatile Materials for High Throughput Solid-phase Synthesis (contract HPMF-CT-2000-00845), and the EPSRC (studentship to J.B.). We thank Mrs. J. Dostal for elemental analyses, Ms. Sylvia Bettington and Dr. Andy Beeby for the use of the UV spectrometer, and Drs. Patrick Steel and Leslie Oates for the use of the Quest parallel synthesizer.

Supporting Information Available: Experimental procedures for the preparation and functionalization of PolyHIPE materials. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026115K