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A macroporous polymer-supported cyclic anhydride for efficient sequestration of amines

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ABSTRACT

The efficient removal of primary and secondary amines from organic solutions using a macroporous polymer-supported anhydride is described. The sequestering of primary amines by the anhydride via polymer-bound amide formation is completed within 2–4 h at room temperature. Secondary amines require typically 4 h for complete sequestration.

The use of polymer-supported scavenger reagents for the controlled removal of excess reactants following a reaction has facilitated the development of high throughput parallel solution-phase synthesis of compound libraries.[1] This unique scavenging methodology, in effect a purification technique, relies on the principle of complementary molecular reactivity, in which the polymer-supported reagent reacts chemoselectively with substrates (i.e., the unreacted excess starting material used to drive reactions to completion) in solution to give polymer-bound products that can be removed readily by simple filtration.[2] Such polymer-supported scavengers significantly simplify the reaction work-up and isolation. An extension of the technique is the use of 'sequestration-enabling reagents', including methods that exploit fluorous chemistry, to chemically tag the substrates thus affording readily sequestrable chemical species.[3,4]

A number of polymer-bound electrophilic scavengers, including supported methyl isocyanate,[1b,5] acetaldehyde,[1a,6] benzoyl chloride,[7] and *N*-methylisatoic anhydride[8] for the direct sequestration of amines have been reported. However, since many of these polymer-bound reagents are prepared by the chemical modification of low-crosslinked polystyrene resin beads, they display restricted applicability as they are unsuitable for use in flow reactors or with polar solvents such as acetonitrile and methanol.[9] These restrictions can be overcome by using highly crosslinked polystyrene resins, but these supports tend to be friable and have low bulk densities. In order to overcome these limitations, the use of composite resin supports has been investigated. A highly porous poly(4-vinylbenzyl chloride-*co*-divinylbenzene)-grafted monolithic support has been prepared, derivatized with tris(2-aminoethyl)amine and used as a nucleophilic scavenger.[10] Similarly, poly(2-vinyl-4,4-dimethylazlactone-*co*-divinylbenzene)-grafted monolithic disks were reported to be a useful matrix for sequestration of amines.[11] However, although the grafted monolithic supports are highly functionalized, they are mechanically fragile and hence only appropriate for flow rather than batch sequestration chemistry. A novel polymer-supported ROMPGEL anhydride for sequestering amines and hydrazines was also recently reported.[12] The ROMPGEL polymeric backbone is derived from a ring-opening metathesis reaction, thus resulting in ultra-high loading material. In our hands, although the ROMPGEL anhydride[12b] displays highly efficient scavenging properties, we found that the solid-support undergoes extensive swelling in chloroform to give a gelatinous material. This resulted in handling difficulties, especially in small volumes of solutions.

We therefore envisaged the synthesis of a robust macroporous carboxy anhydride resin as a superior scavenger matrix for the removal of reactive amines. In our considerations, the matrix should be applicable in both flow and batch methods. The poly(methacrylic acid) resin, Amberlite® IRC-50 (16–50 mesh) was deemed to meet many of the desired properties, including the ultra-high density of carboxylic acid units (10–15 mmol g^{-1}) and the stable macroporous structure. Chemically, the carboxylic functionalities are sequentially repeated in a 1,3-relationship on the polymeric

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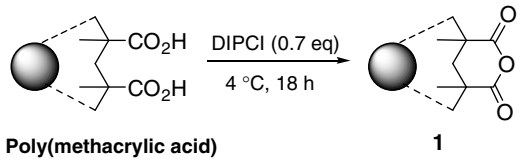
linear hydrocarbon chain, thus resembling repeated units of pivalic acid. From this, the generation of a six-membered cyclic carboxy anhydride is evident. We herein report the synthesis and application of an ultra-high loading polymer-supported cyclic anhydride (5.0–6.7 mmol g^{-1}) **1**.

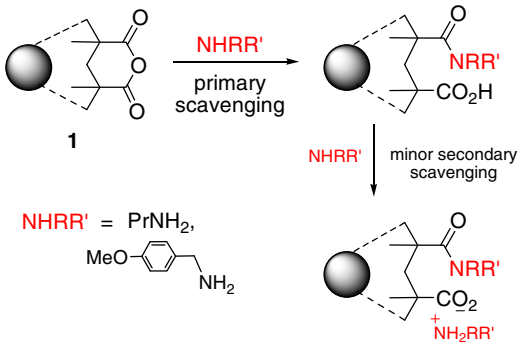
Acetic anhydride treatment (50 °C, 18 h) was initially used for the conversion of the poly(methacrylic acid) to the required poly(methacrylic anhydride) resin **1**. Following Ac_2O treatment, the resin product was washed extensively (DMF and CH_2Cl_2) and dried in vacuo. The chemical conversion was deemed to be successful by FT-IR analysis of the resin product. However, careful analysis of the resin product showed the persistent presence of 'trapped' acetic anhydride. We next considered the use of carbodiimide reagents for the formation of the poly(methacrylic anhydride) resin **1**, and subsequently established a robust method by using 1,3-diisopropylcarbodiimide in a mixture of DMF/CH_2Cl_2 (1:1) (Scheme 1).[13] The purity of the resin product **1** was established by FT-IR, elemental analysis and by suspending a known quantity of the resin in $CDCl_3$ (in the presence of DMSO as internal standard) for 4 h followed by ^1H NMR analysis of the filtrate.

The precise anhydride level was then determined by the condensation of the anhydride resin with 4-chlorobenzylamine (5 equiv, 16 h, DMF), followed by elemental analysis for N and Cl content.[13] As indicated earlier, we have utilized the macroporous matrix due to its low degree of swelling and excellent compatibility with a wide range of organic solvents,[9] as well as good mechanical stability. In fact, the capacity volume of the macroporous anhydride resin **1** ranges from ca. 1.8 (dried state or in CH_2Cl_2 and toluene) to 2.4 mL g^{-1} (in DMF and THF).

In order to quantify the amine-scavenging efficiency of the anhydride resin **1**, a solution of an amine (0.1 mmol) and dimethyl sulfoxide (0.1 mmol, used as the internal reference) in $CDCl_3$ (0.5 mL) was treated with a known amount of anhydride resin **1** at room temperature (Scheme 2). The solution was then quantitatively analyzed by ^1H NMR, in which integration of the signal at δ_H 2.61 due to $(CH_3)_2SO$ was used as the reference. Thus, in preliminary investigations using an equivalent of the anhydride resin **1**, we established that 42% and 61% of 4-methoxybenzylamine was sequestered after 1 h and 4 h treatment, respectively, and that no byproducts were generated or released during the scavenging process.



Scheme 1. The synthesis of the macroporous anhydride resin.



Scheme 2. The sequestering of amines by the macroporous anhydride resin **1**.

Table 1
The sequestering of amines by the macroporous anhydride resin **1** (2 equiv)

Amine		Exposure time (h)	% Scavenged
Primary	Propylamine	1	90
		2	95
		4	>99
	Isobutylamine	1	90
		2	>99
	Benzylamine	1	90
		2	98
		4	>99
Secondary	Piperidine	2	70
		4	>99
	Pyrrolidine	2	95
		4	>99
	Diisopropylamine	2	53
		4	80
Aromatic	4-Methoxyaniline	18	26
		18 (60 °C)	>99

The experiments were carried out in $CDCl_3$ and at room temperature, unless otherwise stated. The percentage scavenged was estimated using ^1H NMR with the aid of dimethyl sulfoxide as the internal standard.

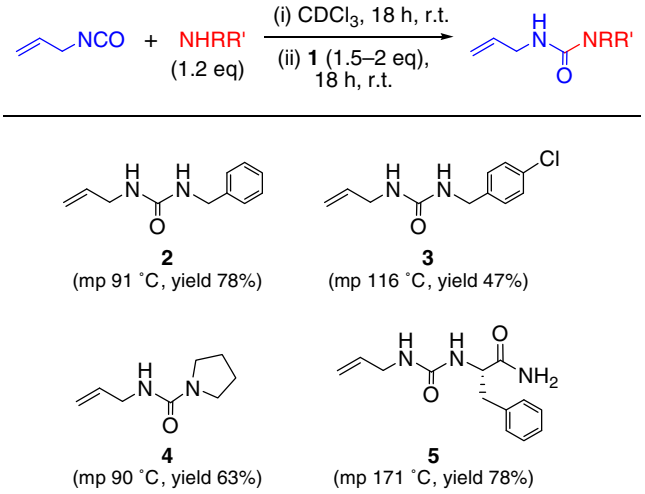
Moreover, following an exposure time of 18 h, the equivalent of anhydride resin **1** scavenged 80% of 4-methoxybenzylamine from a $CDCl_3$ solution. The resin product was collected, and a portion of the sample was additionally washed with 1 M $HCl_{(aq)}$, DMF and CH_2Cl_2. Comparative elemental analyses of both resin samples showed that ca. 10% of the sequestered 4-MeOBnNH$_2$ was due to ionic interactions (Scheme 2); a similar result was observed with PrNH$_2$.

The potential of the poly(methacrylic anhydride) resin for efficient scavenging of amines was then systematically evaluated using a 2 equiv excess of **1** and the results are summarized in Table 1. Propylamine and both isobutylamine and benzylamine were used as illustrative examples of linear and branched primary amines, respectively. As anticipated, though 90% of the available amines were scavenged within 1 h, quantitative removal of these amines was achieved after 2–4 h of exposure to 2 equiv of the anhydride resin **1** at room temperature. In contrast, the sequestering of secondary amines (piperidine and pyrrolidine were used as representative examples of non-hindered secondary amines) was generally incomplete after 2 h, and a minimum of 4 h exposure was necessary for complete removal from the $CDCl_3$ solution. Furthermore, we were gratified to observe that, within 4 h at room temperature, 2 equiv of the anhydride resin **1** sequestered 80% of a sterically-hindered secondary amine, *N*,*N*-diisopropylamine.

We then turned our attention to electron-'rich' anilines, for which 4-methoxyaniline was used as an example. As anticipated, the anhydride resin **1** captured only 26% of the aniline after 18 h at room temperature. However, nearly quantitative removal of the aniline was accomplished when the reaction was carried out at 60 °C in a sealed vessel.

The application of the macroporous anhydride resin **1** within the context of small-scale parallel synthesis of ureas was evaluated, in which an excess of amine (1.2 equiv) was reacted with an isocyanate, followed by sequestering of the unreacted amine by the resin **1** (Scheme 3). For simplicity, 1.5–2 equiv of anhydride resin was used (i.e., 1.3–1.7 equiv in excess for the initial amine content) and the scavenging process was allowed to proceed overnight (18 h). The ureas were isolated in good-to-excellent yields and were of high purity (established by RP-HPLC and elemental CHN analyses).[14]

In summary, we have developed an ultra-high loading macroporous polymer-supported anhydride[15] (5.0–6.7 mmol g^{-1}) **1**, which showed efficient sequestration of both primary and secondary amines, as well as electron-rich anilines from organic solutions.



Scheme 3. Parallel synthesis of *N*-allylureas.

The reactivity per gram of the anhydride resin in fact exceeds that of benzoic anhydride (4.4 mmol g^{-1}). Due to the robustness of the matrix, we anticipate that the poly(methacrylic anhydride) resin will have amine scavenging utility in both batch[1] and flow[16] methods for parallel synthesis of compound libraries.

Acknowledgment

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13. *Typical procedure for the synthesis of the macroporous cyclic anhydride resin* **1**: The poly(methacrylic acid) resin (Amberlite® IRC-50, 10 g, ca. 100 mmol) was washed with 1.0 M $HCl_{(aq)}$ (1 L), distilled H_2O (1 L) and MeOH (500 mL) and subsequently stirred in MeOH (500 mL) for 1 h. The resin was then collected and washed with MeOH (50 mL), THF (50 mL) and CH_2Cl_2 (50 mL) and dried in vacuo overnight to afford the resin material as a white, free-flowing powder (9.70 g). IR (KBr): 3450 (OH) and 1705 (C=O) cm^{-1}. Anal. found C, 58.05; H, 7.77; Cl, 0.38; N, 0.00. The dried resin material (2.00 g, 21.86 mmol; determined by a back-titration method) was suspended in DMF/CH_2Cl_2 1:1 (10 mL), to which was added 1,3-diisopropylcarbodiimide (2.39 mL, 15.30 mmol) and the mixture was stirred at 4 °C for 18 h. The resin was then washed consecutively with warm DMF (500 mL) and CH_2Cl_2 (500 mL), and dried in vacuo to afford the desired reagent as off-white granules (1.53 g, 85%). IR (KBr): 1804 and 1760 cm^{-1} (C(O)–O–C(O)). Anal. found C, 60.02; H, 6.33; N, 0.59.
The macroporous cyclic anhydride resin **1** (100 mg, theoretical 0.68 mmol) was suspended in DMF (0.5 mL). A sample of 4-chlorobenzylamine (0.412 mL, 3.40 mmol) was added and the reaction was stirred for 16 h. The resin was filtered and washed consecutively with 1 M $HCl_{(aq)}$, H_2O, DMF, and CH_2Cl_2 (10 mL each), and dried in vacuo to yield poly(methacrylic acid-*alt*-*N*-4-chlorobenzyl methacrylamide) (151 mg, 99%); IR (KBr): 3375 (OH), 1716 (acid C=O), 1655 (amide I), and 1516 (amide II) cm^{-1}. Anal. found C, 59.11; H, 6.72; N, 5.90; Cl, 12.21; based on chloride content (3.44 mmol g^{-1}), the initial anhydride loading was calculated to be 6.72 mmol g^{-1}.
14. 1-Allyl-3-benzylurea, **2**. To a solution of 1-allylisocyanate (0.106 mL, 1.20 mmol) in $CDCl_3$ (5 mL) was added benzylamine (0.157 mL, 1.44 mmol). The mixture was stirred for 18 h (at this stage, a sample of the solution was typically analyzed by ^1H NMR), after which macroporous anhydride resin **1** (244 mg, 1.64 mmol) was added and the resultant suspension was stirred vigorously for a further 18 h. The suspension was filtered and the resin material was washed with $CDCl_3$. The combined filtrate was evaporated to dryness to afford a white solid (202 mg), which on trituration with hexane gave the compound **2** as a white solid (178 mg, 78%): mp 91 °C, *m*/*z* (+ES) 191.3 (MH^+), calcd 191.2; δ_H (250 MHz, $CDCl_3$) 3.55–3.59 (2H, m), 4.13 (2H, d, *J* 5.8 Hz), 4.93–5.08 (2H, m), 5.59–5.75 (1H, m), 5.85 (1H, t, *J* 5.3 Hz), 6.10 (1H, t, *J* 5.7 Hz), 7.18 (5H, m). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.41; N, 14.72. Found: C, 69.49; H, 7.41; N, 14.79.
1-Allyl-3-(4-chlorobenzyl)urea, **3**: Mp 116 °C; *m*/*z* (+ES) 225.2 (MH^+), calcd. 225.7; δ_H (250 MHz, $CDCl_3$) 3.68–3.74 (2H, m), 4.22 (2H, d, *J* 5.9), 5.03–5.17 (2H, m), 5.21 (1H, t, *J* 5.6), 5.51 (1H, t, *J* 5.6), 5.70–5.85 (1H, m), 7.12–7.28 (4H, m). Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.42. Found: C, 58.69; H, 5.71; N, 12.33.
N-Allylpyrrolidine-1-carboxamide, **4**: Mp 90 °C; *m*/*z* (+ES) 155.2 (MH^+) calcd 155.2; δ_H (250 MHz, $CDCl_3$) 1.85–1.96 (4H, m), 3.34 (4H, t, *J* 6.6), 3.85–3.90 (2H, m), 5.05–5.22 (2H, m), 5.82–5.97 (1H, m). Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.16. Found: C, 61.87; H, 9.06; N, 18.33.
(*S*)-2-(3-Allylureido)-3-phenylpropionamide, **5**: Mp 171 °C; *m*/*z* (+ES) 248.2 (MH^+) calcd 248.3; δ_H (250 MHz, CD_3OD) 2.95 (2H, dd, *J* 6.4 and 13.8), 3.69–3.72 (2H, m), 4.46–4.52 (1H, m), 5.02–5.15 (2H, m), 5.71–5.86 (1H, m), 7.19–7.32 (5H, m). Anal. Calcd for $C_{13}H_{17}N_3O_2 \cdot {}^1/_4$ MeOH, C, 62.33; H, 7.10; N, 16.40. Found: C, 62.41; H, 6.83; N, 16.34.
15. The macroporous polymer-supported cyclic anhydride resin (MP-anhydride resin) is commercially available from Merck Chemicals Ltd.
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