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ROMPGEL Scavengers: A High-Loading Supported Anhydride for Sequestering Amines and Hydrazines

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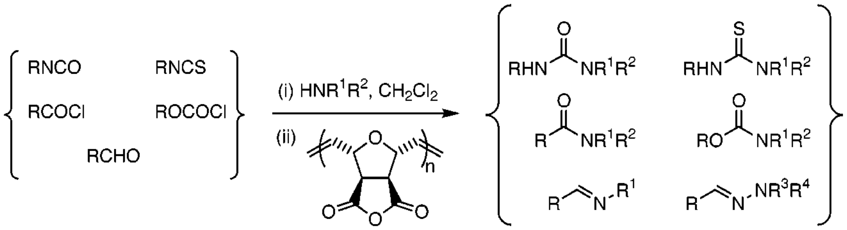
ABSTRACT



A versatile method for sequestering excess amines and hydrazines is reported using a high-loading ROMPGEL anhydride polymer.

Combinatorial chemistry has emerged as a powerful adjunct to drug discovery and catalyst and material development and optimization.[1] During the past decade, interest in methodologies for efficient parallel solution-phase synthesis has emerged. Such methods are appropriate for the preparation of large and diverse libraries yet with simplified analysis and usually shorter development times compared with synthesis on insoluble polymer resin supports. The purification and isolation of target compounds, however, remains a significant problem for solution-phase methodology.[2] Among the diverse techniques developed, the use of scavenger reagents plays an important role in this regard.[3]

Scavengers are usually functionalized insoluble resins which react selectively with excess reagents or side products in a crude reaction mixture, leaving the desired product of enhanced purity remaining in solution. Since the pioneering work of Kaldor and co-workers[4] with polystyrene isocyanate resin (used to scavenge excess amine reactants in the formation of amides), a variety of new polystyrene-supported electrophiles including acid chlorides,[4] isothiocyanates,[5] and aldehydes[6] have emerged. These resins are usually synthesized from Merrifield resin, and as such the issues of resin loading, swelling, and site accessibility come into play.

Several strategies to overcome the low loading of polystyrene have been reported: the use of a higher loading Merrifield resin substituted by isatoic anhydride gave a

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scavenger for amines (anhydride loading 3.2 mmol g^{-1}).[7] Suspension copolymerization of (methacryloyloxy)ethyl isocyanate with 10% divinylbenzene gave an isocyanate resin (isocyanate loading 5.2 mmol g^{-1}).[8] Alternatively, radical copolymerization of 3-isopropenyl α,α-dimethylbenzyl isocyanate with styrene initiated by a TEMPO-functionalized Merrifield resin generated graft copolymer spheres, known as "Rasta" beads (isocyanate loading 2.5 mmol g^{-1}).[9]

In addition to the scavenger resins, ion-exchange techniques have been used for the removal of amine contaminants from nonbasic product. The amine is either removed from solution using a supported acid resin[10] or is first functionalized prior to removal of the derivative by a scavenger resin—a technique known as "tagging". Solution-phase reaction of an amine contaminant with tetrafluorosuccinic anhydride and subsequent sequestration with basic resins was described by Flynn and Parlow to purify amides.[11] Polystyrenesulfonic acid resins have also been reported as amine scavengers.[12]

Herein we report the use of a ring-opening metathesis (ROM) polymer-supported anhydride as a selective high-loading scavenger for amines and hydrazines (we term these polymers "ROMPGELs"). This work is an extension of other recent applications of ROMPGEL reagents for solution-phase parallel synthesis.[13]

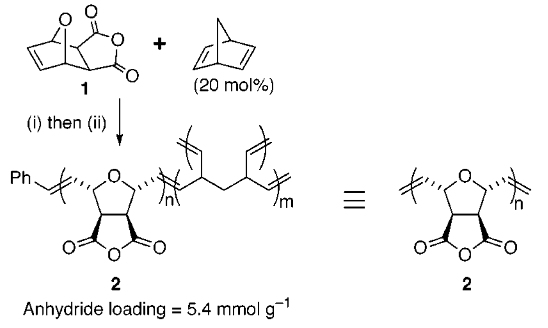
The requirements for a good amine scavenger include effectiveness over a broad range of nucleophilicity (especially toward amines such as anilines), good purity of the products obtained, efficiency (in terms of reaction time), simplicity of the experimental procedure, and especially high loading. Factors such as cost and availability are also important. Most available scavengers are based on a polystyrene support and, although efficient, are frequently slow for complete sequestration. Modest loadings mean that a substantial quantity of resin is required which can prove expensive and volume inefficient, especially once the resin is swollen. Moreover, variation in the quality of the libraries produced has also been noted with different resin batches.

We believe that ROMPGELs have all the qualities and advantages necessary to fulfill the requirements for superior scavengers. First, substituted norbornene and 7-oxanorbornene monomers are readily available (from cyclopentadiene and furan respectively) and inexpensive. Second, all transformations to attach the desired functionality are carried out on the monomer, which is then polymerized in high yield. This is a marked contrast to the synthesis of polystyrene-based scavengers and greatly simplifies the synthesis, authentication and quality control of the ROMPGEL scavenger. Finally the loading of the ROMPGEL scavenger is high because all the monomers are substituted with the desired functionality and hence there is absence of redundant polymer backbone architecture. Moreover, only a small excess of ROMPGEL is required because of the excellent site accessibility and fast scavenging.

ROM polymerization of commercially available anhydride **1** using $Cl_2(PCy_3)_2Ru{=}CHPh$[14] has already been reported by both Grubbs[15] and Buchmeiser,[16] the latter group reporting the affinity between the diacid ROMP derived from **1** by hydrolysis with amines and metal ions.

In our hands, co-ROM polymerization of anhydride **1** with norbornadiene (20 mol %) using the Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ gave a white solid, insoluble in most organic solvents, and with an anhydride loading of 5.4 mmol g^{-1} (Scheme 1).

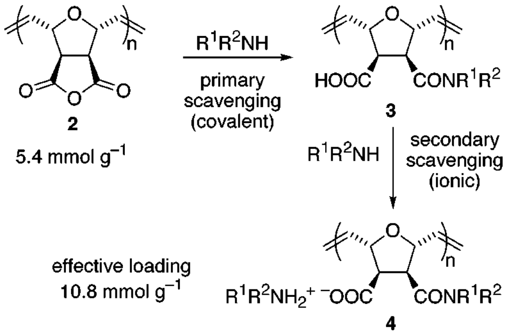
Scheme 1. Synthesis of ROMPGEL Anhydride Scavenger



Reagents: (i) $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2; (ii) $EtOCH{=}CH_2$

To our delight, a slight excess of ROMPGEL **2** (1.5 equiv) rapidly scavenged amines from solution. Additionally, the carboxylic acid function released upon opening the anhydride could also scavenge amines from solution; hence the two functionalities account for a total scavenging potential of 10.8 mmol g^{-1}. Moreover, no byproducts were generated during the scavenging process (Scheme 2).

Scheme 2. Sequestration of Excess Amine



Ureas, thioureas, amides, sulfonamides, carbamates, imines, and hydrazones were synthesized in excellent yields and

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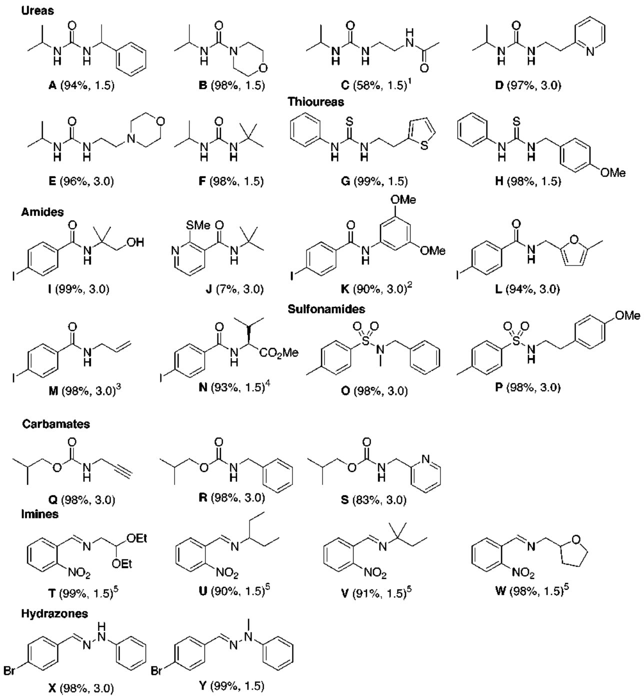
purities by reaction between an excess of amine or hydrazine (3 equiv) with the corresponding isocyanate, isothiocyanate, acid chloride or arenesulfonyl chloride, chloroformate, or aldehyde, respectively (see Table 1). Subsequent removal of the excess nucleophile was performed using the ROMPGEL scavenger **2**.[17]

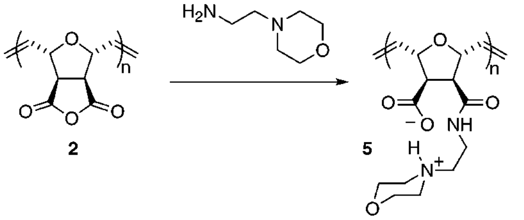
Table 1. Scavenging Results



[a] All the reactions were carried out with 3 equiv of the nucleophile relative to the electrophile. Parentheses refer to the isolated yield and the number of equivalents of anhydride scavenger **2** used (10.8 mmol g^{-1} loading) relative to the excess amine. All the products have been characterized by ^{1}H NMR, ^{13}C NMR, GC/MS (one peak), IR, and HRMS. The superscripts 1−5 refer to the following: 1, product was mostly insoluble in CH_2Cl_2; 2, overnight, room temperature for the scavenging step; 3, ROMPGEL-supported morpholine **8** was used instead of polyvinylpyridine; 4, the hydrochloride salt of the amino ester was used; 5, Et_2O was used instead of CH_2Cl_2 and 4 Å molecular sieves were added to the mixture.

In the case of formation of urea, thiourea, imine, and hydrazone where no hydrogen chloride was produced during the reaction, 1.5 equiv of ROMPGEL **2** (based on the loading of 10.8 mmol g^{-1}) per equivalent of excess amine was needed to cleanly afford the desired product (compounds **A**−**C**, **F**−**H**, **T**−**W**, and **Y**). Surprisingly, even when the nucleophile possessed a second tertiary amine (compounds **D** and **E**) or a basic moiety (compound **X**), the corresponding amino ureas or hydrazones, which could in theory also be scavenged as an ammonium salt, were isolated in excellent yields and purities using 3 equiv of ROMPGEL **2**. Presumably the excess diamine is scavenged as amine salt **5**, thereby tying up the carboxylic acid functionality (Scheme 3).

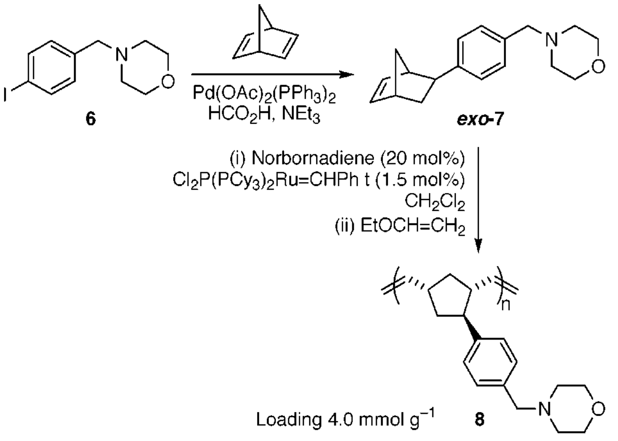
Scheme 3. Sequestring of Diamino Reagent



Amides, sulfonamides, and carbamates (compounds **I**−**S**) were prepared in excellent yields and purities by reaction of excess amines with acyl or arenesulfonyl chlorides or chloroformates. In these cases, polyvinylpyridine was added to the reaction mixture to scavenge hydrogen chloride. Three equivalents of scavenger **2** per equivalent of excess amine were used to trap the unreacted amine. The larger amount was required due to the formation of hydrogen chloride and the necessity to avoid formation of the ammonium salt in the solution phase. Presumably the yield of amide **J** was low under the standard reaction conditions due to poor conversion as a result of steric congestion.

As an alternative to polyvinylpyridine, ROMPGEL-supported morpholine reagent **8** could be used instead. The novel scavenger **8** was readily synthesized from *exo*-*C*-arylation of norbornadiene[18] using iodide **6** and subsequent ROM polymerization of **7** (Scheme 4). Compound **M** was isolated

Scheme 4. Synthesis of ROMPGEL -Supported Morpholine



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(17) **Typical procedure:** To a solution of isocyanate (0.25 mmol) in methylene chloride (3 mL) was added the amine (0.75 mmol). The solution was stirred at room temperature for 3 h before addition of 70 mg of ROMPGEL scavenger **2** (0.75 mmol). The suspension was stirred at room temperature for 3 h, filtered off, and washed with methylene chloride (2 × 3 mL). The solvent was then removed in a stream of nitrogen to give the desired urea.

in 98% yield and excellent purity (>95% by ^{1}H NMR) using 1.5 equiv of ROMPGEL morpholine **8** instead of polyvinylpyridine.

Amine salts (e.g., valine methyl ester hydrochloride) could also be used to prepare amides (compound **N**), and in this case polystyrene-supported guanidine (P-TBD)[19] was used as a proton scavenger with triethylamine as a proton shuttle. The poorly reactive 3,5-dimethoxyaniline (compound **K**) was successfully removed from the reaction mixture upon a longer (overnight) exposure to ROMPGEL scavenger **2** and gave the desired amide in 90% yield and good purity (>95% by ^{1}H NMR). The reaction of amino alcohol (compound **I**) demonstrated the selectivity of the scavenger toward amines in the presence of alcohols. No significant loss of product was detected using the standard scavenging conditions.

In summary, we have developed the use of a high-loading ROMPGEL-supported anhydride scavenger for amines and hydrazines. This readily available ROMPGEL polymer has demonstrated considerable potential in the sequestration of excess of amines and hydrazines. Excellent isolated yields and purities of ureas, thioureas, amides, sulfonamides, carbamates, imines, and hydrazones were obtained. Further applications of ROMPGEL will be reported in due course.

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Supporting Information Available: General procedures for the synthesis and applications of ROMPGELs **2** are provided as well as representative spectra of compound **L** obtained by the ROMPGEL strategy. This material is available free of charge via the Internet at http://pubs.acs.org.

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