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Scavenge–ROMP–Filter: A Facile Strategy for Soluble Scavenging via Norbornenyl Tagging of Electrophilic Reagents

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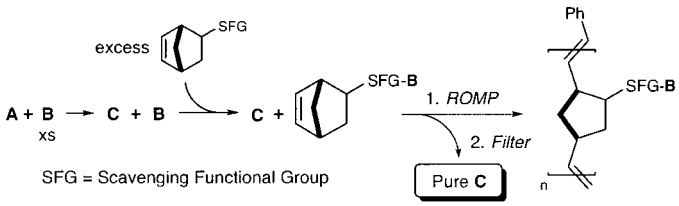
ABSTRACT



A new "chemical tagging" method for homogeneous electrophilic scavenging is described. The method utilizes 5-norbornene-2-methanol to scavenge/tag a variety of electrophiles that are present in excess. Once tagging is complete, the crude reaction mixture is subjected to a rapid ROM polymerization event utilizing the second generation Grubbs catalyst. This process yields a polymer that can be precipitated with methanol or ether/hexane, leaving products in excellent yield and purity.

The development of new technologies to eliminate or lessen the need for chromatographic separation of mixtures is of continued interest in the field of synthetic organic chemistry[1] and combinatorial chemistry.[2] To facilitate impurity removal/product purification, several strategies can be employed, including solid polymer supports[3] and reagents,[4] organic soluble supports and reagents,[5] and scavenger resins.[6] The use of scavenger resins for purification avoids the use of polymers during the actual synthesis and thus offers the convenience of solution phase with the luxuries of solid phase. Limitations to these scavenging resins include sluggish reaction kinetics for removal of solution-phase reactants due to the heterogeneous reaction environment and the limited

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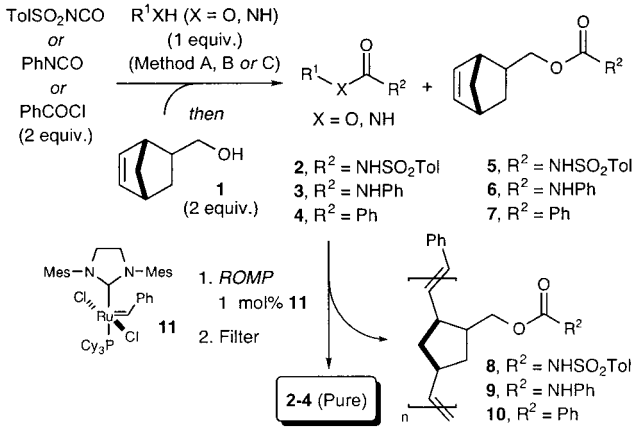
loading capacity (mmol functionality per g of resin) of commonly used scavenging resins.

To overcome these limitations, chemical tagging has recently been employed to facilitate impurity removal.[7] The hallmark of this approach is the inherent ability of a chemical tag to phase-switch or phase-traffic reagents, products, and impurities from one media to another due to the unique "functionality" that is contained in the tag, thus enabling efficient purification. The salient feature that differentiates "chemical tagging" from supported synthesis/reagents is that the reactivity of the reagent is not altered or compromised in the process. Successful examples in this class include fluorous tags,[8] sequestration enabling reagents,[6a,9] precipitons,[10] metal-chelated tagging,[11] PEG tags for soluble-supported scavenging,[12] and Barrett's norbornenyl-tagged annihilation reagent.[13]

Recently, Barrett has taken a ring-opening metathesis polymerization (ROMP) approach to impurity removal with the development of ROMPgel technology[14] utilizing the Grubbs benzylidene catalyst [$(PCy_3)_2(Cl)_2Ru{=}CHPh$]. Our interest in the development of purification protocols based on tagged reagents[9] and ROMP[15] has led us to develop a new chemical tagging approach that we have termed scavenge−ROMP−filter. This new method utilizes 5-norbornene-2-methanol (**1**)[16] as a soluble electrophilic scavenger. This method offers maximum load benefits, is compatible with traditional reaction monitoring methods, and retains the favorable reaction kinetics associated with solution-phase synthesis.

As shown in Scheme 1, the soluble scavenging alcohol **1** is utilized to capture excess electrophilic reagents such as

Scheme 1[a]



[a] Reagents and conditions: method A, (i) TsNCO, CH_2Cl_2, 0 °C to rt, then **1**, 0 °C to rt, (ii) 1 mol % of **11**, CH_2Cl_2, reflux (20−45 min), (iii) Et_2O/hexane (4:1), filter; method B, (i) PhNCO, toluene, reflux, then **1**, reflux, (ii) 1 mol % of **11**, CH_2Cl_2, reflux (20−45 min), (iii) MeOH, filter thru Celite; method C, (i) PhCOCl, Et_3N, CH_2Cl_2, rt or reflux, then **1**, reflux, (ii) 1 mol % of **11**, CH_2Cl_2, reflux (20−45 min), (iii) Et_2O/hexane (4:1), filter thru Celite or SiO_2 plug.

p-toluenesulfonyl isocyanate, phenyl isocyanate, and benzoyl chloride. Subsequent in situ ROM polymerization using 1 mol % of the Grubbs saturated imidazole catalyst $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (**11**)[17] generates differentially soluble polymers[18] **8**−**10** containing the tagged electrophiles **5**−**7**. The products **2**−**4** (Table 1) are readily isolated in solution phase away from the in situ polymerized species **8**−**10** via

Table 1. Formation of Products **2**−**4**[a] via Scavenge−ROMP−Filter[b]

entry	nucleophile	electrophile[a]	pdt	yield (%)	purity (%)
1	*t*-BuOH	$TolSO_2NCO$	**2a**	98	>90[c]
2	BnOH	$TolSO_2NCO$	**2b**	94	>90[c]
3	$BnNH_2$	$TolSO_2NCO$	**2c**	99	>90[c]
4	$C_6H_{11}NH_2$	$TolSO_2NCO$	**2d**	97	>90[c]
5	$PhCH_2CH_2NH_2$	$TolSO_2NCO$	**2e**	99	>90[c]
6	*n*-$BuNH_2$	$TolSO_2NCO$	**2f**	90	>90[c]
7	$MeOPhCH_2OH$	PhNCO	**3a**	99	97[d]
8	geraniol	PhNCO	**3b**	78	98[d]
9	Bn_2NH	PhNCO	**3c**	99	81[d]
10	menthol	PhNCO	**3d**	99	96[d]
11	1-(*4H*)naphthol	PhNCO	**3e**	99	84[d]
12	BnOH	PhCOCl	**4a**	99	94[d]
13	$C_6H_{11}OH$	PhCOCl	**4b**	99	84[d]
14	geraniol	PhCOCl	**4c**	99	89[d]
15	phenol	PhCOCl	**4d**	94	90[d]
16	menthol	PhCOCl	**4e**	98	87[d]
17	morpholine	PhCOCl	**4f**	99	84[d]
18	Bn_2NH	PhCOCl	**4g**	99	95[d]

[a] Reactions performed with an excess of electrophile as outlined in Scheme 1. [b] Polymerization conducted with 1 mol % of Grubbs catalyst **11**. [c] Determined by ^1H NMR (no polymer present). [d] Determined by GC and confirmed by ^1H NMR (no polymer present, see Figure 1 and supplementary spectra).

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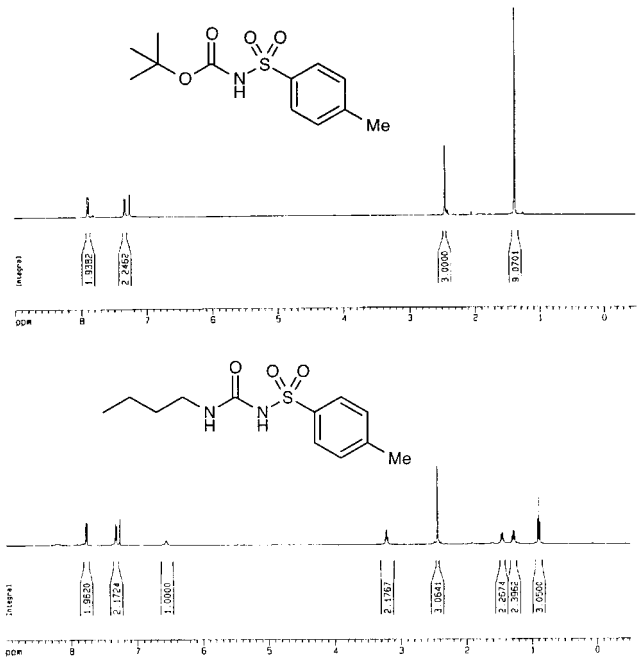

Figure 1. ^{1}H NMR analysis of purified sulfonyl carbamate **2a** and sulfonyl urea **2f**, respectively, using scavenge−ROMP−filter.

precipitation and filtration of the polymers using a suitable solvent. In this method, the desired products remain in solution while the unreacted scavenger **1** and tagged reagents **5**−**7** are co-opted for a rapid in situ ROM polymerization (20−45 min) as a means of filtering them from the reaction mixture.

Using *p*-toluenesulfonyl isocyanate as the electrophile, we looked at the generation of an array of sulfonyl carbamates and ureas **2a**−**f** utilizing a variety of alcohols and amines (entries 1−6, Table 1). One equivalent of the nucleophilic species (amine or alcohol) was added per 2 equiv of the isocyanate. Once the reaction was complete, excess isocyanate was reacted with 2 equiv of 5-norbornene-2-methanol (**1**). Subsequent ROM polymerization of all norbornenyl-tagged molecules (**5** and unreacted **1**), followed by polymer removal, gave the desired sulfonyl carbamates and ureas **2a**−**f** in good to excellent yields and high purity as evident by ^{1}H NMR analysis of crude isolated product (Figute 1).[19]

Initial attempts at reacting phenyl isocyanate with various alcohols/amines (entries 7−11, Table 1) focused on performing the reaction in degassed CH_2Cl_2, thereby eliminating the need to change solvents for the polymerization. Unfortunately, while dibenzylamine reacted efficiently in refluxing CH_2Cl_2, the reaction with the scavenger alcohol **1** and other alcohols was slow. To overcome this reactivity problem, we decided to switch our solvent to toluene which would allow for higher reaction temperatures.

To this end, various alcohols and dibenzylamine were treated with phenyl isocyanate in refluxing toluene to produce carbamates and ureas **3a**−**e** (entries 7−11, Table 1). The reactions were complete in 45 min as indicated by GC analysis. Scavenger **1** was added and the reaction refluxed. Upon completion (GC analysis), the solvent was removed in vacuo and degassed CH_2Cl_2 (0.1 M) was added. Catalyst **11** (1 mol %) was added and the reaction mixture was refluxed for 30−45 min. Analysis by TLC or GC showed that no excess scavenger **1** or tagged carbamate **6** was present. The reaction mixture was then poured into methanol to precipitate the polymer, which was removed by filtration using Celite. The resulting carbamates and ureas **3a**−**e** were isolated in excellent yield and purity.

We also looked at the benzoylation of a variety of amines and alcohols (entries 12−18, Table 1). Benzoylation using 1 equiv of the nucleophilic species and 2 equiv of benzoyl chloride in the presence of 8 equiv of Et_3N gave the benzoylated products **4a**−**g**. The excess of benzoyl chloride was then removed by reaction with 2 equiv of **1**, producing the norbornenyl-tagged compound **7**. Once complete, excess Et_3N was removed under reduced pressure. Subsequent polymerization of **7** and unreacted **1** using 1 mol % of **11**, followed by polymer removal, gave the benzoylated compounds **4a**−**g** in excellent yields and high purity.

In conclusion, we have developed a new scavenge−ROMP−filter strategy that utilizes the second generation Grubbs catalyst.[17] The method lessens the need for chromatographic purification and should be amenable to other reactions as well as the purification of combinatorial libraries. Several advantages are apparent: favorable reaction kinetics,[20] high-load capacity, and conventional monitoring of reaction progress. Furthermore, the method is high yielding and generates products with good to excellent purity.

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Supporting Information Available: Detailed experimental procedures and ^{1}H NMR spectra of crude products obtained by our method. This material is available free of charge via the Internet at http://acs.pubs.org.

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(18) The importance of utilizing the second generation Grubbs catalyst is demonstrated in a comparative study, see ref 15.

(19) ^{1}H NMR spectra of all crude products are available in the Supporting Information.

(20) A comparative experiment of the reaction kinetics was made between the norbornene-based scavenger **1** and its comparable solid-phase equivalent, the hydroxymethyl resin (purchased from Irori). In this study, each alcohol scavenger (1.2 equiv) was tested for its reactivity toward the three electrophiles (1 equiv): *p*-toluenesulfonyl isocyanate, phenyl isocyanate, and benzoyl chloride. In the cases of *p*-TsNCO and the PhCOCl (0 °C to rt), the norbornene-based scavenger reacted instantaneously with the electrophile, depleting its concentration to zero before any analysis could take place; in the PhNCO case, the tagged-scavenger reacted completely with the electrophile in 50 min (toluene, 100 °C). The resin-bound scavenger reacted only slightly slower for the *p*-TsNCO (15 min); however, for PhCOCl and PhNCO, the resin-bound scavenger was dramatically slower (>2 h for PhCOCl and >12 h for PhNCO).