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ROMP-Generated Oligomeric Sulfonyl Chlorides as Versatile Soluble Scavenging Agents

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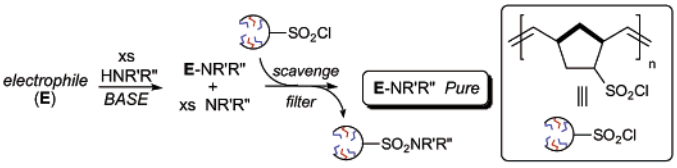
ABSTRACT



A new method for homogeneous nucleophilic scavenging employing oligomeric sulfonyl chloride (OSC) reagents is described. The method utilizes OSC to rapidly scavenge a variety of amines that are present in excess. The OSC reagents are generated from ROM polymerization of 2-chlorosulfonyl-5-norbornene utilizing the second generation Grubbs catalyst to produce oligomers of varying size as stable, free-flowing powders. Following the scavenging event, these oligomers are precipitated with ethyl acetate leaving products in excellent yield and purity.

The evolution of combinatorial chemistry[1] over the past decade has expedited the development of new technologies that strive to eliminate the need for chromatographic separation of mixtures. In turn, this has led to the development of similar technologies in synthetic organic chemistry.[2] Among the more effective tools for impurity removal/product purification are resin-bound supports,[3] reagents,[4] and scavenging agents.[5] Although these revolutionary tools are widely employed, they are limited by nonlinear reaction kinetics and their low-load parameters. To address these deficiencies, two general strategies have emerged: (i) chemical tagging[6] and (ii) the use of soluble, polymeric supports, reagents, and scavenging agents.[7−10] The hallmark of these methods is that they avoid the use of insoluble polymers during the actual synthesis yet retain the virtues of both solution-phase and solid-phase approaches.

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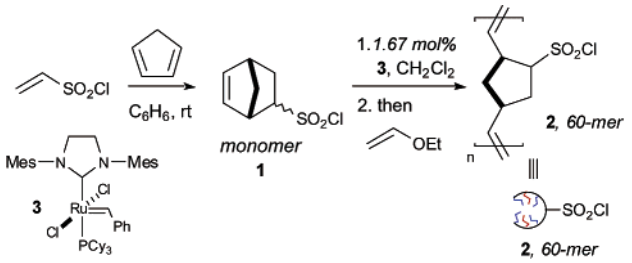
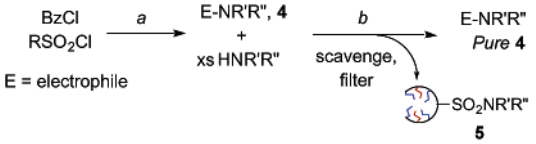
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) electrophile (1.0 equiv), CH_2Cl_2, base (5.0 equiv), and amine (2.0 equiv), from 0 °C to rt (10−60 min). (b) OSC **2** (2.0 equiv), CH_2Cl_2, reflux (30 min), then EtOAc, filter through Celite or a SiO_2 plug.

Regarding the latter strategy, PEG-based soluble polymers are the most prevalent.[7] However, a number of alternative systems have emerged, including several dendritic[9] and polyacrylamide[7] systems and a variety of ROMP-derived polymers pioneered by Barrett and co-workers.[11] In all of these systems, phase-trafficking of supported intermediates is accomplished via judicious choice of solvent systems. Thus, it is of paramount importance to develop new soluble, polymeric scaffolds with vast differential solubility profiles;[12] in general, the wider the profile, the more versatile the reagent will be in phase-trafficking protocols.

Our interest in the development of purification protocols based on norbornenyl-tagged reagents[13] and ROMP strategies[11,14] recently led us to develop a new chemical tagging approach that we termed scavenge−ROMP−filter.[14] This method utilized 5-norbornene-2-methanol as a facile soluble electrophile scavenger that could be co-opted out of solution via in situ ROM polymerization. We now report a new protocol, employing a soluble oligomeric sulfonyl chloride (OSC) reagent,[15] derived from ROM polymerization of a norbornenyl-tagged sulfonyl chloride. We have termed this protocol ROMP−scavenge−filter. This method offers maximum load benefits, flexible oligomer design, and is compatible with traditional reaction monitoring methods. Furthermore, the diverse solubility profile of these oligomers retains the favorable reaction kinetics associated with homogeneous solution-phase synthesis yet requires filtering from EtOAc as the sole purification protocol.

As shown in Scheme 1, 2-chlorosulfonyl-5-norbornene (monomer **1**) can be produced via the Diels−Alder reaction of vinylsulfonyl chloride and cyclopentadiene in benzene at room temperature. Subsequent ROM polymerization with $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (**3**)[16] yields oligomeric sulfonyl chlorides (OSC) **2** of differing lengths dependent upon the mol % of **3** employed. Final quenching with ethyl vinyl ether and precipitation from ethyl ether yields **2** as a stable free-flowing powder that is ready for use. Thus far, we have synthesized and studied the use of a number of soluble oligomers of OSC **2** generated with catalyst **3**, including: 10-mers, 30-mers, 60-mers, and 100-mers. We found that the 60-mer precipitated more readily from ether than the 30-mer and had the best differential solubility of all oligomers tested to date.[17]

We initially investigated the benzoylation of a variety of amines (entries 1−11, Table 1). Facile benzoylation was accomplished in less than 1 h using 1 equiv of benzoyl chloride in the presence of 5 equiv of base and 2 equiv of amine. Subsequent in situ scavenging using the 60-mer of OSC **2** was completed within 30 min. The resulting mixture

Table 1. Formation of Benzoylated Amines **4**[a] Using ROMP−Scavenge−Filter with the OSC 60-mer[a]

entry	amine[b]	base	filter method	product	yield (%)	purity (%)[d]
1	$BnNH_2$	Et_3N[c]	Celite	**4a**	99	>90
2	$BnNH_2$	Et_3N[c]	SiO_2	**4a**	97	99
3	$BnNH_2$	Cs_2CO_3	Celite	**4a**	99	>95
4	$BnNH_2$	pyr	Celite	**4a**	91	>90
5	$C_6H_{11}NH_2$	pyr	SiO_2	**4b**	97	>95
6	morpholine	Et_3N[c]	SiO_2	**4c**	97	>95
7	morpholine	Cs_2CO_3	Celite	**4c**	99	>95
8	morpholine	K_2CO_3	Celite	**4c**	98	>95
9	morpholine	pyr	Celite	**4c**	99	>95
10	$PhCH_2CH_2NH_2$	Et_3N[c]	SiO_2	**4d**	97	>95
11	$CH_3(CH_2)_7NH_2$	pyr	Celite	**4e**	99	99

[a] OSC used was generated using 1.67 mol % Grubbs catalyst **3** (60-mer) unless otherwise noted. [b] Carried out with excess amine as outlined in Scheme 2. [c] OSC used was generated using 3.33 mol % Grubbs catalyst **3** (30-mer). [d] Determined by GC and confirmed by ^1H NMR (no polymer present; see spectra in Supporting Information).

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was concentrated, diluted with EtOAc, filtered, and concentrated under reduced pressure to yield benzoylated products **4a**−**e** in excellent yields and high purity.[18] A variety of bases are compatible with this method, including triethylamine, pyridine, Cs_2CO_3, and K_2CO_3. In addition, both silica gel and Celite can be effectively utilized in the filtering process. The major impurities in all cases were ammonium salts that occasionally came through when using Celite as a filter aid. This problem can be thwarted by using a silica gel plug or a silica gel SPE (see Figure 1).

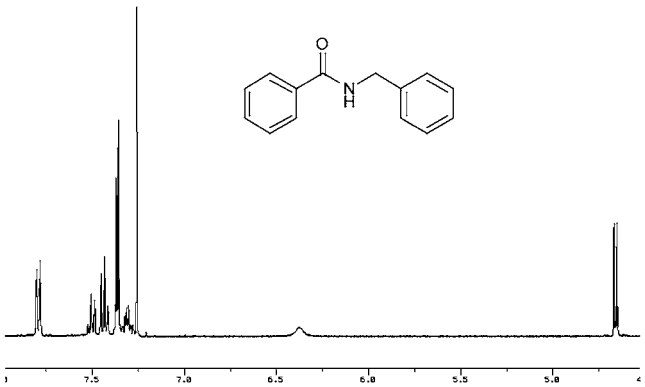

Figure 1. ^{1}H NMR analysis of purified *N*-benzoylbenzylamine **4a** generated using ROMP−scavenge−filter.

We next studied the arylsulfonation of an array of amines (entries 1−10, Table 2) using both *para*-toluenesulfonyl chloride and benzenesulfonyl chloride. Again arylsulfonation was accomplished in less than 1 h using 1 equiv of the arylsulfonyl chloride in the presence of 5 equiv of pyridine and 2 equiv of amine. Subsequent in situ scavenging using the 60-mer of OSC **2** was completed within 30 min. In these examples, the resulting mixture was not concentrated first but was immediately diluted with EtOAc, filtered through silica gel, and concentrated under reduced pressure to yield arylsulfonated products **5** and **6** in good to excellent yields and high purity.[19]

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(17) OSC 60-*mer* is soluble in CH_2Cl_2 (50 mg/mL), THF, and DMF and is insoluble in Et_2O, EtOAc, and MeOH.

(18) ^{1}H NMR spectra of all crude products are available in Supporting Information.

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

Table 2. Formation of Tosylated Amines **5** and **6**[a] Using ROMP−Scavenge−Filter with the OSC 60-mer[a]

entry	amine[b]	electrophile[c]	product	yield (%)	purity[d] (%)
1	$BnNH_2$	*p*-TsCl	**5a**	85	>90
2	$C_6H_{11}NH_2$	*p*-TsCl	**5b**	94	99
3	morpholine	*p*-TsCl	**5c**	99	>95
4	$PhCH_2CH_2NH_2$	*p*-TsCl	**5d**	88	99
5	$CH_3(CH_2)_7NH_2$	*p*-TsCl	**5e**	91	>90
6	$BnNH_2$	$PhSO_2Cl$	**6a**	87	>90
7	$C_6H_{11}NH_2$	$PhSO_2Cl$	**6b**	85	99
8	morpholine	$PhSO_2Cl$	**6c**	79	>90
9	$PhCH_2CH_2NH_2$	$PhSO_2Cl$	**6d**	76	99
10	$CH_3(CH_2)_7NH_2$	$PhSO_2Cl$	**6e**	82	99

[a] OSC used was generated using 1.67 mol % Grubbs catalyst **3** (60-mer). [b] Carried out with excess amine as outlined in Scheme 2. [c] All products were generated using pyridine and filtering with SiO_2. [d] Determined by GC and confirmed by ^{1}H NMR (no polymer present; see spectra in Supporting Information).

In conclusion, we have developed a new ROMP−scavenge−filter strategy that utilizes a soluble oligomeric scavenging agent and lessens the need for chromatographic purification. Several advantages are apparent: favorable reaction kinetics, high-load capacity, and conventional monitoring of reaction progress. Furthermore, the method is high yielding and generates products with excellent purity. Further development of this OSC as a synthetic tool is currently under investigation, and the results will be reported in due course.

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Note Added after ASAP Posting. Daniel L. Flynn's affiliation was listed incorrectly in the version posted ASAP December 28, 2002. The corrected version was posted January 9, 2003.

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

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