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High-Load, ROMP-Generated Oligomeric Bis-acid Chlorides: Design of Soluble and Insoluble Nucleophile Scavengers

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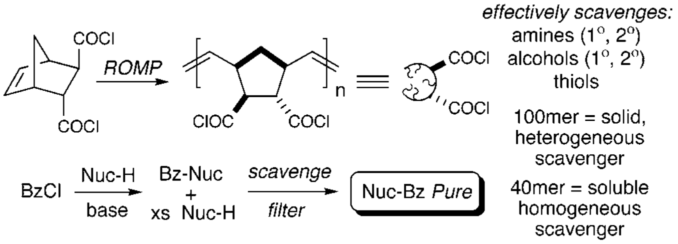
ABSTRACT



An efficient strategy for scavenging a host of nucleophiles utilizing an oligomeric bis-acid chloride (OBAC), generated from the ROM polymerization of *trans*-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride, is described. The reactivity and high load of the OBAC reagent is exploited in the scavenging of amines, alcohols, and thiols that are present in excess following a common benzoylation event. Following the scavenging event, these oligomers can be precipitated with EtOAc and filtered (SiO_2), leaving benzoylated nucleophiles in excellent yield and purity.

The emergence of combinatorial chemistry over the past decade[1] has brought about several technological advances in the area of impurity removal.[2−4] Among these, scavenger resins[5] have emerged as powerful tools that avoid the use of insoluble polymers during the synthesis event yet retain the virtues of both solution-phase and solid-phase approaches. Despite these advances, limitations in both nonlinear reaction kinetics and low-load parameters warrant the continued development of new designer polymers in this area. Two common methods have surfaced to address these issues: (1) chemical tagging[6] and (2) the use of soluble, polymeric supports, reagents, and scavenging agents.[7−10] Regarding the latter strategy, PEG-based soluble polymers are the most prevalent.[7] Recently, 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, it is of paramount importance to develop new

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[1] (a) *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997. (b) Bunin, B. A. *The Combinatorial Index*; Academic Press: New York, 1998. (c) *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed.; The Practical Approach Series 233; Oxford University Press: New York, 2000.

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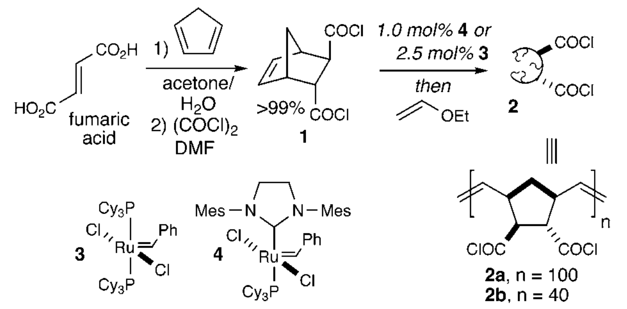
soluble, polymeric scaffolds with vast differential solubility profiles[12] in order to optimize facile phase-trafficking protocols.

Our interest in the development of purification protocols based on norbornenyl reagents[13] and ROMP strategies[11,14] has led us to recently communicate two novel scavenging approaches: (1) a chemical tagging scavenge−ROMP−filter approach[14] that utilizes 5-norbornene-2-methanol as a facile soluble electrophile scavenger that is phase-trafficked out of solution via in situ ROM polymerization and (2) ROMP−scavenge−filter utilizing a "preformed", high-load, oligomeric sulfonyl chloride (OSC) as an effective amine scavenger.[15] We are now reporting a powerful extension to these methods that utilizes a high-load, oligomeric, bis-acid chloride (OBAC) as a general nucleophile scavenger. Unlike its sulfonyl chloride predecessor, this oligomer can now effectively remove alcohols and thiols as well as amines from a reaction mixture. Also, because each monomer unit contains two acid chloride moieties, the OBAC reagent offers a significant increase in load. Like the OSC, this system offers flexible oligomer design and compatibility with traditional reaction monitoring methods. In addition, the OBAC reagent has a wide solubility profile that allows precipitation/filtering from EtOAc as the sole purification protocol.

The OBAC reagent can be introduced into the reaction system as an insoluble solid (100-mer, generated using the second-generation Grubbs catalyst, ^{2G}OBAC$_{100}$)[16] or as an 89 or 40 mg/mL CH_2Cl_2 solution[17] (40-mer, generated from the first-generation Grubbs catalyst, ^{1G}OBAC$_{40}$). Details of the polymer design are outlined below.

The requisite monomer, *trans*-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride (**1**), is produced in a two-step sequence beginning with a Diels−Alder reaction between fumaric acid and cyclopentadiene in 10:1 acetone/water at 50 °C followed by chlorination using oxalyl chloride and catalytic DMF. Subsequent ROM polymerization with either 1 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (second-generation Grubbs catalyst, **4**)[18] or 2.5 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (first-generation Grubbs catalyst, **3**) yields the 100-mer (**2a**) or 40-mer (**2b**) OBAC reagent, respectively.[19] Quenching of the ROM polymerization is carried out in standard fashion with ethyl vinyl ether. The length of the oligomer, in conjunction with its method of formation, is crucial with respect to reagent solubility. We have found that the OBAC reagent is an effective scavenger when added as a solid or as a solution. Using 1 mol % catalyst **4** generates the 100-mer that can be isolated and readily used as a heterogeneous, solid nucleophile scavenger (^{2G}OBAC$_{100}$). We also wished to demonstrate the effectiveness of adding the oligomer as a homogeneous solution; therefore, we carried out the polymerization event using 2.5 mol % catalyst **3**, generating the more soluble 40-mer (^{1G}OBAC$_{40}$). This oligomer could be readily dissolved in CH_2Cl_2 and used as either an 89 or 40 mg/mL stock scavenger solution. Interestingly, when catalyst **4** (second-generation) was used in the production of the 40-mer, it was found that the polymer would not go completely back into solution following precipitation. We believe that this can be partially attributed to the difference in shape (*E*/*Z* ratio of polymer backbone) of the two oligomers that occurs when changing from one catalyst to the other.[13b]

Scheme 1



We initially investigated the benzoylation of a variety of amines present in excess (entries 1−12, Table 1) using the

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(14) Moore, J. D.; Harned, A. M.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847−1849.

(15) Moore, J. D.; Herpel, R. H.; Lichtsinn, J. R.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 105−107.

(16) Oligomeric bis-acid chloride reagent is abbreviated according to the "generation" of Grubbs catalyst used for the polymerization (the superscript before the OBAC) and the length of polymer (the subscript following the OBAC acronym).

(17) It was discovered that the 89 mg/mL stock solution would "gel" upon cooling over a 48 h period. However, simple dilution to a 40 mg/mL stock solution readily overcame this problem. Both solutions scavenged nucleophiles with equal effectiveness.

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(19) Size of the polymer is calculated using the following equation: length = 100/(mol % catalyst). It is important to note that these oligomers are generated as a Gaussian distribution with the most heavily populated region corresponding to the size calculated from this equation.

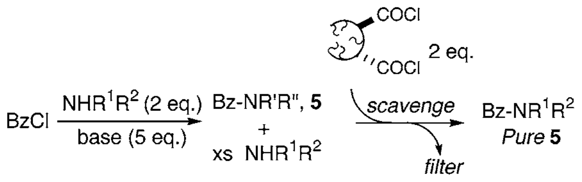
Table 1. Formation and Isolation of Pure of Benzoylated Amines **5** Using ROMP−Scavenge−Filter with ^{2G}OBAC$_{100}$

entry	amine[b]	base	pdt	yield (%)	purity (%)[a]
1	benzylamine	Et_3N	**5a**	99	>95
2	benzylamine	K_2CO_3	**5a**	93	>95
3	benzylamine	Cs_2CO_3	**5a**	94	>95
4	*n*-octylamine	Et_3N	**5b**	98	>95
5	morpholine	Et_3N	**5c**	95	>95
6	phenethylamine	Et_3N	**5d**	83	>95
7	phenethylamine	pyridine	**5d**	96	>95
8	cyclohexylamine	Et_3N	**5e**	93	>95
9	cyclohexylamine	pyridine	**5e**	99	>95
10	methylbenzylamine	Et_3N	**5f**	97	>95
11	dibenzylamine	Et_3N	**5g**	99	>95
12	diallylamine	Et_3N	**5h**	97	>95

[a] Determined by GC and confirmed by ^{1}H NMR (no polymer present; see supplementary spectra in Supporting Information).

solid ^{2G}OBAC$_{100}$ and a variety of bases. Facile amidation was accomplished in less than 1 h using 1 equiv of benzoyl chloride in the presence of 5 equiv of base[20] and 2 equiv of amine. Subsequent in situ scavenging of excess amine utilizing only 1.0 equiv[21] of ^{2G}OBAC$_{100}$ **2a** was completed within 30 min. The resulting mixture was diluted with EtOAc, filtered (SiO_2),[22] and concentrated under reduced pressure to yield the benzoylated amines **5a**−**h** in excellent yields and purities.[23] Following this success, we then investigated the possibility of alcohol scavenging utilizing the ^{2G}OBAC$_{100}$ reagent. Our previously reported OSC scavenger was unable to effectively scavenge alcohols presumably due to the generation of a labile sulfonate ester. Although higher temperatures and 2 equiv of the scavenger were required for efficient scavenging (refluxing DCM, ∼1−2 h), we were pleased to find that a wide scope of alcohols could be scavenged, including allylic, propargylic, and secondary alcohols (Table 2).

Scheme 2[a]



[a] Reagents and conditions: (i) Benzoylation: BzCl (1.0 equiv), CH_2Cl_2, base (5.0 equiv), and amine (2.0 equiv) at rt (20 min). (ii) Scavenging: OBAC **2** (1.0 equiv), CH_2Cl_2, 30 min at rt, then EtOAc, filter via SiO_2 plug.

Table 2. Formation of Benzoylated Alcohols **6** Using ROMP−Scavenge−Filter with ^{2G}OBAC$_{100}$

entry	alcohol[b]	pdt	yield (%)	purity (%)[a]
1	benzyl alcohol	**6a**	94	>95
2	2-allyloxy ethanol	**6b**	99	>95
3	4-MeO-benzyl alcohol	**6c**	91	>95
4	geraniol	**6d**	94	>95
5	propargyl alcohol	**6e**	99	>95
6	2-octanol	**6f**	40	>95
7	3-Me-2-butene-1-ol	**6g**	78	>95
8	(−)-menthol	**6h**	46	>95

[a] Determined by GC and confirmed by ^{1}H NMR (no polymer present; see supplementary spectra in Supporting Information).

As a final extension to this work, we investigated the scavenging of thiol nucleophiles. Again, we were pleased to find that 2 equiv of ^{2G}OBAC$_{100}$ could scavenge thiols from a reaction mixture (Table 3).

Table 3. Formation and Isolation of Pure of Benzoylated Thiols **7**[a] Using ROMP−Scavenge−Filter with ^{2G}OBAC$_{100}$

entry	thiol	pdt	yield (%)	purity (%)[a]
1	methyl thioglycolate	**7a**	83	>95
2	butane thiol	**7b**	86	>95
3	1-dodecane thiol	**7c**	99	>95

[a] Determined by GC and confirmed by ^{1}H NMR (no polymer present; see supplementary spectra in Supporting Information).

We next directed our efforts at the development of a soluble version of the bis-acid chloride oligomer. Following an extensive investigation, it was found that a 40-mer generated with the first-generation Grubbs catalyst (^{1G}OBAC$_{40}$) was ideal. We therefore prepared a stock solution of the ^{1G}OBAC$_{40}$ reagent in DCM (88 or 40 mg/mL stock solution) and studied its reactivity against a panel of amines, alcohols, and thiols.[17] We were pleased to find that the ^{1G}OBAC$_{40}$ was also extremely effective in scavenging all of the substrates outlined in Table 4.

To further assess the synthetic utility of the OBAC scavengers, it was deemed necessary to compare the effectiveness of the OBACs as general nucleophile scavengers versus a commercially available counterpart. Since bis-acid chloride resins are not commercially available, we chose to compare the titled OBAC scavengers with commercially available, polystyrene-based isocyanate resins commonly

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(20) It is noteworthy that excess base is readily removed by either concentration under reduced pressure (Et_3N, pyridine) or filtration (K_2CO_3, Cs_2CO_3).

(21) Equivalents in this context refer to molar equivalents and not load, which we have measured, vide infra. The load value measured in mmols/gram incorporates the mmols of reactive functional groups/gram of polymer (see footnote 25). The weight of polymer used, based on molar equivalents, was determined using the molecular weight of the monomeric bis-acid chloride starting unit.

(22) When using K_2CO_3 or Cs_2CO_3 as the base, no filtration through SiO_2 is necessary, as final products of high purity can be obtained using only precipitation/filtration. However, in the cases of Et_3N and pyridine, a small contaminant of amine salt is evident from ^{1}H NMR analysis. We have found that using a small pad of SiO_2 as a filter aid can remedy this problem.

(23) ^{1}H NMR spectra of all crude products are available in Supporting Information.

Table 4. Scavenging with a Solution of $^{1G}OBAC_{40}$

entry	nucleophile	base	pdt	yield (%)	purity[a] (%)
1	benzylamine	Et_3N	**5a**	99	>95
2	*n*-octylamine	Et_3N	**5b**	99	>95
3	morpholine	Et_3N	**5c**	94	>95
4	phenethylamine	Et_3N	**5d**	85	>95
5	diallylamine	Et_3N	**5h**	98	>95
6	diallylamine	K_2CO_3	**5h**	95	87
7	methylbenzylamine	Cs_2CO_3	**5f**	99	95
8	benzyl alcohol	Et_3N	**6a**	95	>95
9	3-Me-2-butene-1-ol	Et_3N	**6g**	99	>95
10	methyl thioglycolate	Et_3N	**7a**	99	>95

[a] Determined by GC and confirmed by ^1H NMR (no polymer present; see supplementary spectra in Supporting Information).

used in organic synthesis.[24] One clear advantage quickly becomes apparent and pertains to the "load" of the OBAC scavengers, which is higher than the corresponding isocyanate polystyrene resin (8.3 mmol/g[25] vs ~1.3 mmol/g). Thus, the amount of OBAC reagent required for each scavenging reaction is 6.5 times lower than the amount of isocyanate resin for a given experimental procedure. In a typical comparison experiment, we employed 35 mg of OBAC to 250 mg of the polystyrene-based isocyanate.

In addition, both $^{1G}OBAC_{40}$ and the $^{2G}OBAC_{100}$ scavengers performed similarly (yields and reaction times) to the commercially available isocyanate reagent in the cases of benzylamine and methyl thioglycolate and slightly better in the case of benzyl alcohol.[26] In this latter example, it was seen that after 2 h, the OBAC reagents had sufficiently scavenged all the alcohol present, while the reaction containing the commercially available isocyanate scavenger resin still possessed 20% of the starting alcohol.

In conclusion, we have developed high-load, bis-acid chloride oligomers that serve as effective heterogeneous and homogeneous nucleophile scavengers that can be introduced into the reaction system as a solid (100-mer) or as a stock solution (40-mer). In addition, the use of only a *single* equivalent of excess scavenging agent, in combination with the *expedient manner* (<30 min to 2 h) in which the scavenging event occurs, demonstrates the enormous potential of this new method in combinatorial chemistry. The utilization of OBAC reagents in the area of combinatorial library development and organic synthesis is currently under investigation and will be reported in due course.

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

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(25) The theoretical load of this polymer is calculated at 9.1 mmol/g. The actual load was experimentally determined to be 8.1−8.5 mmol/g utilizing ^1H NMR to measure the uptake of benzyl amine by OBAC in refluxing deuterated DCM using allyl phenyl ether as an internal standard and Et_3N as a base. Room temperature uptake was measured at 7 mmol/g.

(26) Exact details of these competition experiments can be found in Supporting Information.