

High-load, oligomeric phosphonyl dichloride: facile generation via ROM polymerization and application to scavenging amines

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Abstract—A new ROMP-derived scavenging reagent, oligomeric phosphonyl dichloride (OPC), with high-load and selectivity is reported. This reagent can be readily generated via the ROM polymerization of bicyclo[2.2.1]hept-5-en-2-ylphosphonic dichloride, which is conveniently assembled from the Diels–Alder reaction of cyclopentadiene and vinyl phosphonic dichloride. The OPC has been exploited in the rapid, efficient scavenging of primary and secondary amines that are present in excess following a common benzoylation event at room temperature (30–60 min) or under microwave conditions in shorter duration (<5 min).
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1. Introduction

The growing demand for high throughput synthetic protocols has spurred efforts directed toward integrating the sciences of organic synthesis and purification in order to streamline drug discovery efforts. The emergence of designer polymers with tunable properties has become a powerful technological advancement in this arena of facilitated synthesis. A primary driver in this advance has been the development of an array of polymer-bound reagents and scavengers,^{1,2} and corresponding technologies, which effectively streamline synthetic methods to simple mix, filter, and evaporate protocols.³ 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. While substantial progress has been noted in this field, several common restrictions encountered include reaction homogeneity (non-linear reaction kinetics), resin-load capacity, and the method for reagent delivery. These prominent issues continue to warrant the development of new polymers for library production. Among these, ring-opening

metathesis (ROM) polymerization has materialized as a commanding platform to develop high-load, immobilized reagents^{4,5} with tunable properties circumventing classical issues associated with conventional immobilized reagents. To this end, we now report the synthesis and utility of a high-load, oligomeric phosphonyl dichloride using ROM polymerization.

Our interest in the development of purification protocols based on norbornenyl reagents and ROMP strategies has led us to recently communicate two novel scavenging approaches: (1) a chemical tagging scavenger-ROMP-filter approach⁶ which utilized 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-scavenger-filter utilizing a ‘pre-formed,’ high-load, oligomeric sulfonyl chloride (OSC)⁷ as an effective amine scavenger, and a higher-load, oligomeric, bis-acid chloride (OBAC)⁸ that effectively removes alcohols and thiols as well as amines from a reaction mixture. In this report, we describe the generation of our highest load oligomer to-date, OPC, which yields a theoretical load of 9.5 mmol/g.

2. Results and discussion

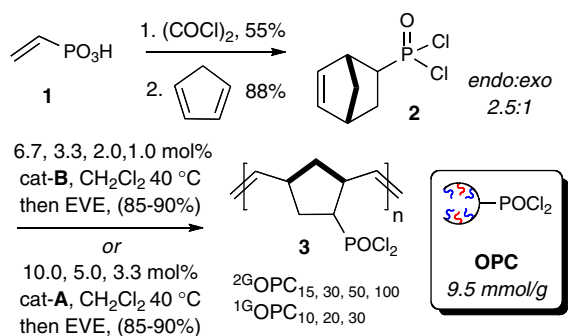
Our efforts to the titled high-load, ROMP-derived phosphonyl dichloride (**3**, OPC) scavenging agent was

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initiated by the preparation of the phosphonyl dichloride monomer. The starting monomer, bicyclo[2.2.1]hept-5-en-2-ylphosphonic dichloride (**2**), was produced in a two-step sequence by first chlorination of vinylphosphonic acid (**1**) using oxalyl chloride and catalytic DMF, followed by a Diels–Alder reaction between vinyl phosphonic dichloride and cyclopentadiene in methylene chloride at 60 °C. Subsequent ROM polymerization with either 6.7, 3.3, 2.0, or 1.0 mol % (IMesH₂)(PCy₃)(Cl)₂Ru=CHPh (cat-**B**)⁹ yielded the corresponding oligomers of 15, 30, 50, and 100 monomeric units (²GOPC_{15,30,50,100}), respectively. Synthesis of 10, 20, and 30-*mer* (¹GOPC_{10,20,30}) was also accomplished using 10, 5, and 3.3 mol % (PCy₃)₂(Cl)₂Ru=CHPh (cat-**A**).¹⁰ Quenching of the ROM polymerization event was carried out with ethyl vinyl ether (EVE) in standard fashion, followed by precipitation into a stirring solution of Et₂O affording the desired oligomers as free-flowing powders (Scheme 1).

We investigated the benzoylation of a variety of amines present in excess (entries 1–12, Table 1) using the solid ²GOPC₁₀₀ using either Et₃N or K₂CO₃ as the base. Simple amidation was accomplished in less than one hour using 1 equiv of benzoyl chloride in the presence

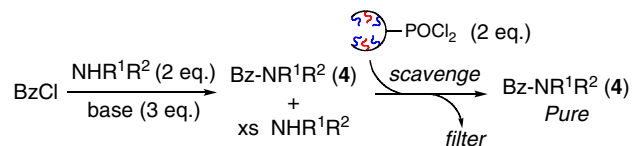


Scheme 1.

of 3 equiv of base¹¹ and 2 equiv of amine. Subsequent in situ scavenging of excess amine utilizing only 2.0 equiv of ²GOPC₁₀₀ was completed in 30–60 min at RT or 5 min at 100 °C in the microwave (Emrys™ Creator). The resulting mixture was diluted with EtOAc, filtered thru a SPE,¹² and concentrated under reduced pressure to deliver the benzoylated amines **4a–l** in excellent yields and purities¹³ (Scheme 2).

It was found that all OPCs efficiently removed both primary and secondary amines from a reaction mixture after a benzoylation event. The only limitations of amine scavenging noted are dibenzylamine and *N*-isopropylbenzylamine. Our justification for the aforementioned results may be due to the steric bulk of these two molecules, in which bulky amines deter OPC from reacting in both cases. However, dibenzylamine may be scavenged with OPC by use of a microwave reactor with extended heating of 10 min instead of 5 min as necessary for the other amines investigated.

Like its counterpart, OBAC, OPC contains two acid chloride moieties that offer a substantial increase in load. The theoretical load for OPC of 9.5 mmol/g accounts for displacement of merely the two chloride ligands. To our surprise we have found the actual load to be 11.5–14 mmol/g. We have reported the load as a range based on the following load studies: OPC was added to known excess amounts of benzylamine and



Scheme 2. Reagents and conditions: (i) Benzoylation: BzCl (1.0 equiv), CH₂Cl₂, base (3.0 equiv), and amine (2.0 equiv) at rt (30 min); (ii) scavenging: OPC **3** (2.0 equiv), CH₂Cl₂, 30–60 min at rt, then EtOAc, filter via SiO₂ plug.

Table 1. Formation and isolation of pure benzoylated amines **4** using ROMP-scavenge-filter with ²GOPC₁₀₀

Entry	Amine	Conditions	Base	Product	Yield (%)	Purity ^a (%)
1	Benzylamine	A	Et ₃ N	4a	93	>95
		B	K ₂ CO ₃	4a	>90	>95
2	Octylamine	A	Et ₃ N	4b	88	>95
3	Phenethylamine	A	Et ₃ N	4c	92	>95
4	Diallylamine	A	Et ₃ N	4d	89	>95
		B	K ₂ CO ₃	4d	>90	>95
5	Morpholine	A	Et ₃ N	4e	97	>95
6	Piperidine	A	Et ₃ N	4f	95	>95
		B	K ₂ CO ₃	4f	>90	>95
7	Dibenzylamine	A	Et ₃ N	4g	—	—
		B ^b	K ₂ CO ₃	4g	>90	>95
8	Ethanolamine	A	Et ₃ N	4h	89	>90
9	<i>N</i> -Isopropylbenzylamine	B	K ₂ CO ₃	4i	x	x
10	<i>n</i> -Pentadecylamine	A	Et ₃ N	4j	98	>90
11	Diethanolamine	A	Et ₃ N	4k	94	>90
12	Cyclohexylamine	A	Et ₃ N	4l	96	>95

Reagents and conditions: (A) rt, CH₂Cl₂ (30–60 min). (B) MW, CH₂Cl₂ (5 min at 100 °C).

^a Determined by GC and confirmed by ¹H NMR (no polymer present, see supplementary spectra).

^b Microwave for 10 min at 100 °C.

4-methoxybenzylamine, respectively, with allylphenyl ether as an internal standard in the presence of Et₃N in methylene chloride.¹⁴ The reaction was allowed to proceed overnight to allow for complete saturation of all reactive sites within OPC, and was then analyzed by ¹H NMR spectroscopy to find the resultant amine to ether ratio.

We attribute this unexpected, extra load to H-bonding of the amine with the oxygen atom of P=O. Several experimental approaches were carried out to support and explain this extremely high load. We believe that formation of a phosphono-iminium species is not a plausible explanation. This hypothesis is supported by two simple experiments revealing only chloride displacement when excess benzylamine was reacted with either norbornene phosphonic dichloride or methyl phosphonic dichloride.

Unlike OBAC that was found to bond with alcohols, amines and thiols, OPC has the ability to selectively bond with amines. Similar benzylation reactions as previously discussed with amines were attempted with benzyl alcohol, phenol, and *n*-butanethiol, in which the OPC was unable to scavenge the excess reagent in each case. To further support this selectivity concept, benzylation of ethanolamine and diethanolamine (entries 8 and 11) result in the formation of amide bonds with free 1° OH group(s). Also, a competition reaction was set up with both benzyl alcohol and benzylamine in the presence of OPC and the expected conclusion of OPC reacting solely with benzylamine was observed. This notable selectivity for amines could potentially be quite advantageous in library synthesis as a simple method for removal of excess amines in the presence of other functional groups.

3. Conclusions

Overall, several high-load, OPC scavengers have been conveniently prepared on large scale from inexpensive and readily available starting materials. These scavenging reagents offer high-load benefits, exceptional selectivity for bonding with primary and secondary amines, and simple removal by silica gel SPE. Additional use in other transformations is underway and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.130.

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- The 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.
- It is worthy to note that excess base is readily removed by either concentration under reduced pressure (Et₃N) or filtration (K₂CO₃).
- When using K₂CO₃ as the base, no filtration through SiO₂ is necessary, as final products of high purity can be obtained using only precipitation/filtration. However in the cases of Et₃N, a small contaminant of amine salt is evident from ¹H NMR analysis. We have found that using a small pad of SiO₂ as a filter aid can remedy this problem.
- ¹H NMR spectra of all crude products are available in the Supplementary data.

14. The theoretical load of this polymer is calculated at 9.5 mmol/g. The actual load was experimentally determined to be 11.5–14.0 mmol/g utilizing ^1H NMR to measure the uptake of benzyl amine by OPC in refluxing CH_2Cl_2 using allyl phenyl ether as an internal standard and Et_3N as a base.