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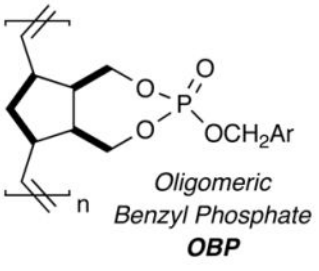
ROMP-derived Oligomeric Phosphates for Application in Facile Benzylation

Toby R. Long[†,‡], **Pradip K. Maity**[†], **Thiwanka B. Samarakoon**[†], and **Paul R. Hanson**[†,‡,*]

[†] Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582

[‡] The Center for Chemical Methodologies and Library Development at the University of Kansas (KU-CMLD), 2034 Becker Drive, Del Shankel Structural Biology Center, Lawrence, KS 66047

Abstract



The development of new ROMP-based oligomeric benzyl phosphates (OBP_n) is reported for use as soluble, stable benzylating reagents. These oligomeric reagents are readily synthesized from commercially available materials and conveniently polymerized and purified in a one-pot process, affording bench stable, pure white, free-flowing solids on multi-gram scale. Utilization in benzylation reactions with a variety of nucleophiles is reported.

The development of new immmobilized reagents for the production of libraries for high-throughput screening is an important element in drug discovery. In this regard, new and improved immobilized reagents with tunable properties have emerged as critical components in facilitated synthetic protocols, particularly within the arena of combinatorial and *green* technologies.[1,2] Consequently, this has driven the development of an array of polymer-bound supports, reagents and scavengers for streamlining synthetic methods into simple mix, filter and evaporate protocols.[1,2] Despite many salient attributes of current immobilized platforms, limitations in load capacity, reaction kinetics, means of delivery and stability continue to warrant efforts in this area. [3] Among these, ring-opening metathesis (ROM) polymerization of functionalized norbornenes has surfaced as a powerful tool in the generation of high-load, immobilized reagents with tunable properties.[4,5,6] In this regard, we report the development of new ROMP-based oligomeric benzyl phosphates (OBP_n) for use as soluble, stable benzylating reagents.

The innate properties of phosphates as leaving groups have inspired the current study aimed at developing oligomeric phosphate-based reagents. While phosphates have been uniquely tailored to play vital roles in nature,[7] only recently have they found widespread use in

phanson@ku.edu.

Supporting Information Available. Detailed experimental procedures and tabulated ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, FTIR, and mass data, and ^{1}H NMR spectra of crude products obtained by the described benzylation method.

synthetic methodology and total synthesis. [8] This resurgence is primarily attributed to their stability, facile assembly and ideal monoanionic pKa profiles.[9] Despite these attributes, synthetic oligomeric-based phosphates and other phosphorous-containing materials have primarily found applications in the production of flame-retardant materials[10] with limited use in novel therapeutic applications.[11] To the best of our knowledge, the literature is void of immobilized phosphate-based alkylating/benzylating agents.

The benzylation of amines and alcohols continues to serve as one of the most utilized protecting group strategies in organic synthesis due to its ease of incorporation and removal. [12,13,7b] In addition, benzylation has emerged as a key diversification reaction in medicinal/combinatorial chemistry approaches as well as diversity-oriented synthesis.[14] This continued use has spurred development of a number of alternative approaches to benzylation. [15, 16] Among these, two ROMP-derived benzylating agents were recently developed in our laboratory.[5c,16b] Interest in further improvements[17] of such protocols has lead to the study reported herein.

The synthesis of oligomeric benzyl phosphate **6** was envisioned to occur via reduction of *endo* norbornenyl anhydride **1** to the corresponding diol, followed by phosphorylation and subsequent condensation with benzyl alcohol. However, repeated attempts to polymerize the *endo* isomer of monomer **5** with a variety of metathesis catalysts resulted in incomplete conversions. Plausibly, both steric and electronic interactions of the P=O bond of the resulting *endo* isomer could interfere with catalyst/olefin activation or the subsequent propagation step.

Attention was next directed towards synthesis of the thermodynamic *exo* isomer (Scheme 1). Several thermal isomerization reactions of the inexpensive *endo* carbic anhydride **1** were performed on large scale using classical methods.[18] Sequential recrystallizations in toluene yielded exo product **2** with diastereomeric ratios progressively increasing and yields decreasing with each recrystallization, i.e., dr = 15:1 and 39% yield after three recrystallizatons, dr = 29:1 and 34% yield after four, up to dr = 84:1 and 20% yield after six. Reduction of **2** with $LiAlH_4$ yielded diol **3** as a clear, viscous oil with good yield. Phosphorylation of the *exo* diol **3** was performed using distilled $POCl_3$ and Et_3N in the presence of catalytic DMAP to yield phosphorochloridate **4** as a white solid in moderate yields.

This was conveniently stored as a solid over argon in a dessicator for use in preparing the various reagents for up to three months.

Addition of **4** into a solution containing benzyl alcohol, NMI, and CH_2Cl_2 at room temperature cleanly afforded the benzyl phosphate **5** in good yields and purity. Polymerization of **5** and other phosphate analogs of this type in the presence of $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (cat. **B**)[19] occurred rapidly at room temperature resulting in formation of insoluble and unusable gels. However, polymerization with $RuCl_2(PCy_3)_2{=}CHPh$ (cat. **A**), [20] cleanly afforded the oligomeric reagent with desirable characteristics.[21] Following polymerization, the reaction was quenched with ethyl vinyl ether (EVE) and stirred for 30 minutes. A basic workup involving the Pederson protocol[22] was applied in the same pot until cat. **A** was visibly removed as indicated by precipitate formation and lack of coloration. The resulting solution was washed several times with water, dried over $MgSO_4$ and concentrated to critical viscosity. [23] Precipitation via dropwise addition into anhydrous Et_2O afforded oligomeric benzyl phosphate (OBP_n) **6** as a free-flowing white solid where n = relative lengths of 20, 50, and 100-mers – each displaying slightly different solubility profiles. [24]

The oligomeric benzyl phosphate 20-mer (OBP_{20}) was then investigated for benzylation of various amines (Scheme 2, Table 1). The reagent was delivered either as a free-flowing powder or as a stock solution in anhydrous $CHCl_3$ alongside a catalytic amount of tetrabutylammonium iodide. [25] During the reaction, precipitation of the resulting oligomeric phosphate monoanion typically occured within a 0.5 – 2 hour period after addition of the nucleophile. The mother liquor was subsequently concentrated over silica or precipitated into Et_2O, filtered via silica SPE and concentrated under vacuum to afford the corresponding the benzylated analog(s) in good to excellent yields and high purity. The resulting monoanionic oligomeric phosphate was found to be water soluble at elevated temperatures and remained soluble on cooling to room temperature. This observation would be of particular importance in potential large-scale applications for the removal of spent oligomer.

A number of cyclic and acyclic amines as well as O, and S nucleophiles were subjected to the established benzylation protocol and were found to proceeed smoothly to afford the desired benzylated products in excellent yields and purities (Table 1). A number of monomeric analogs of OBP were also prepared in good yields using several substituted benzyl alcohols. Subjection of the monomers to the established ROM polymerization protocol afforded the desired oligmeric products in excellent yields as free-flowing white solids. Interestingly, efforts towards production of monomeric phosphates **5a-d** did not afford the desired products. This is likely due to a combination of the substituent mesomeric effect and/or eliminative degradation pathways of these phosphates (Table 2). The corresponding oligomers **6e-l** were subjected to established benzylation conditions utilizing morpholine as a test substrate and conveniently afforded the desired benzylated products in moderate to good yields and purities (Table 3).

The 20-mer of OBP was tested on a select benzofused sultam scaffold for benzylation (Table 4). The reagent was added to a THF solution containing benzothiaoxazepine-1,1-dioxide (**9a**) in the presence of K_2CO_3 and Bu_4NI and stirred at 80 °C overnight. The resulting mother liquor was precipitated from a Et_2O/EtOAc mixture. Subsequent filtration employing a silica SPE cartridge, and evaporation of solvent afforded the desired benzylated product **10a** in excellent yield and high purity. With this result in place, sultams **9a-d** were subjected to benzylation employing OBP derivatives utilizing the conditions established above to afford the desired products (**10b-h**) in good to excellent yields.

In conclusion, we have demonstrated the synthesis and utilization of a ROMP-based oligomeric phosphate for facilitated benzylation of cyclic amines and have applied it towards simple diversification pathways in relevant scaffolds. These oligomeric reagents are readily synthesized from commercially available materials and are conveniently polymerized and purified in a one-pot process affording pure reagent on multi-gram scale. Efforts to widen the scope of this reagent, improvement in synthesis and scale-up and its continued integration into diversity-oriented synthetic protocols is underway. The results of these endeavors will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. (a) The synthesis of oligomeric benzylsulfonium salts requires 5 steps and the use of benzyl bromides. These reagents were not soluble in typical organic solvents (Reference [5c]). (b) The oligomeric sulfonate esters were used in a “catch and release” protocol whereby benzyl alcohols were reacted after polymerization (Reference [16b]).
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21. These characteristics include homogeneity and the ability to achieve the necessary critical viscocity for precipitation.
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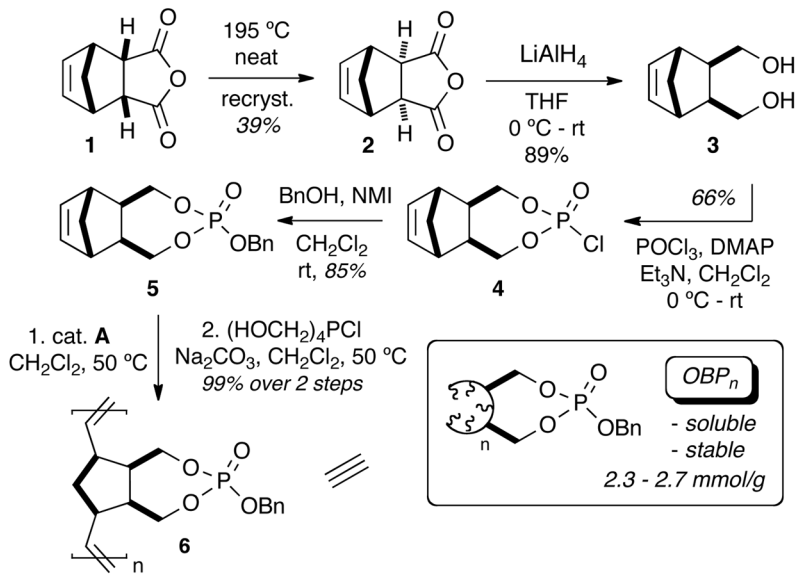
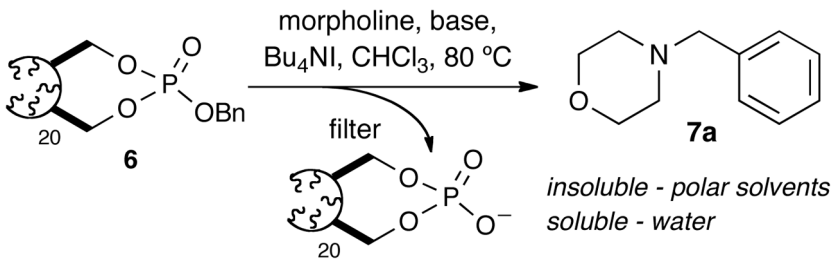
23. Critical viscosity described in these terms is the optimum viscosity to achieve a free-flowing precipitate.
24. See Supporting Information for solubility tables of OBP_n. For information regarding Gaussian distribution of oligomers see ref. [5a].
25. We have recently formulated ROMP-tabs, whereby premeasured OBP_{20} tablets can be conveniently added to the reaction.



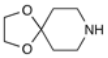
Scheme 1.
Synthesis of the oligomeric benzyl phosphate (OBP)



Scheme 2.
Benzylation of morpholine

Table 1

Benzylation of *N*-, O-, and *S*-nucleophiles using OBP_{20}

nucleophile	pdt	yield (%)[a]	purity (%)[b]
morpholine	**7a**	99	98
thiomorpholine	**7b**	93	98
N-phenylpiperizine	**7c**	98	99
piperizine	**7d**	95	97
pyrrolidine	**7e**	80	99
piperidine	**7f**	73	99
dihydroindole	**7g**	98	85
	**7h**	69	97
phenol	**7i**	80	95
lithium thiophenolate[e]	**7j**	98	96
Bn-NH_2	**7k/l**	99[c]	4:1[d]
Ph-NHEt	**7m**	81	89

[a] Isolated yields after filtration through a silica SPE.

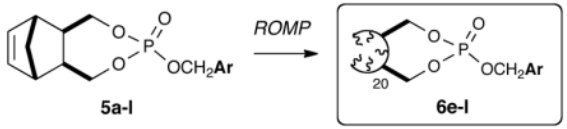
[b] Purities calculated using GC and further confirmed by ^{1}H NMR.

[c],[d] Percent conversion and ratio of mono to dibenzylated amine as found by GC/MS.

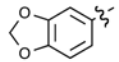
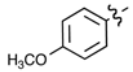
[e] Reaction was performed w/OBP_{50}.

Table 2

Synthesis of various OBP analogs



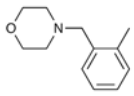
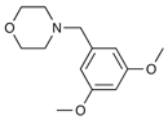
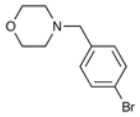
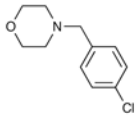
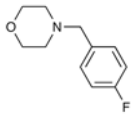
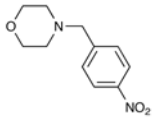
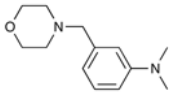
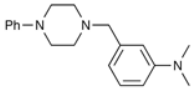
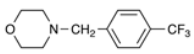
5a-l 6e-l

monomer	Ar	yield (%)	monomer	Ar	yield (%)
5a		23%	**5e**	*o*-CH_3Ph	75%
			5f	3,5-$(OCH_3)_2$Ph	70%
5b		21%	**5g**	*p*-BrPh	79%
			5h	*p*-ClPh	76%
5c		<10%	**5i**	*p*-FPh	80%
			5j	*p*-NO_2Ph	70%
5d		<10%	**5k**	*m*-$N(CH_3)_2$Ph	73%
			5l	*p*-CF_3Ph	77%

[a] Yields correspond to monomeric phosphates. Quantitative conversions were obtained for oligomers **6e-l**. Monomers **5a-d** were not polymerized.

Table 3

Benzylation of amines using various OBP analogs

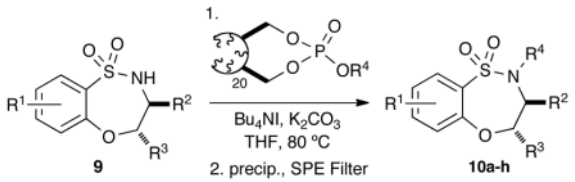
entry	SM	product	yield(%)	purity(%)[a]
1	**6e**	 **8e**	64	94
2	**6f**	 **8f**	54	89
3	**6g**	 **8g**	82	93
4	**6h**	 **8h**	67	97
5	**6i**	 **8i**	70	96
6	**6j**	 **8j**	74	93
7	**6k**	 **8k**[b]	78	98
8	**6k**	 **8k′**[c]	93	98
9	**6l**	 **8l**	68	95

[a] Purities calculated using GC and further confirmed by ^{1}H NMR.

[b],[c] Despite their simplicity, each compound is classified as a NCE.

Table 4

Benzylation of benzothiaoxazepine-1,1-dioxides



SM	R^1	R^2	R^3	R^4	pdt	yield (%)[a]
9a	4-Br	Ph	H	Bn	**10a**	99
9a	4-Br	Ph	H	3,5-diMeO-Bn	**10b**	72
9a	4-Br	Ph	H	4-F Bn	**10c**	85
9b	4-Br	^{i}Bu	H	4-F Bn	**10d**	97
9b	4-Br	^{i}Bu	H	2-Me Bn	**10e**	81
9c	3-Cl	^{i}Bu	H	4-Cl Bn	**10f**	76
9d	5-Cl	Me	Ph	2-Me Bn	**10g**	78
9d	3-Cl	Me	Ph	2-Me Bn	**10h**	83

[a]Yields after filtration through a SiO_2 SPE.