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"Click"-Capture, ROMP, Release: Facile Triazolation Utilizing ROMP-derived Oligomeric Phosphates

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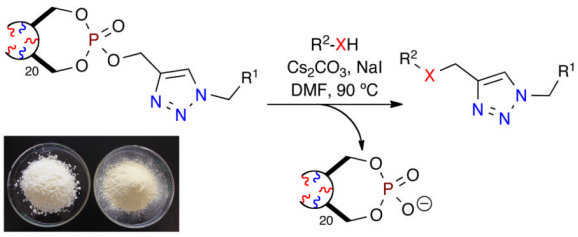
Abstract



Soluble, high-load ROMP-derived oligomeric triazole phosphates (OTP) are reported for application as efficient triazolating reagents of nucleophilic species. Utilizing a "Click"-capture, ROMP, release protocol, the efficient and purification free, direct triazolation of *N*-, *O*- and *S*-nucleophilic species was successfully achieved. A variety of OTP derivatives were rapidly synthesized as free-flowing solids on multi-gram scale from commercially available materials.

Rapid access to collections of diverse molecules in desirable quantities and purity for high-throughput screening is an important challenge in drug discovery. In this regard, methods that integrate synthesis and purification have become powerful tools in the arena of facilitated synthesis.[1,2] This has been driven in recent years by the development of an array of polymer-bound reagents and scavengers for utilization in streamlined protocols to access small molecule libraries.[2] Despite huge advances in this area, limitations in non-linear reaction kinetics (heterogeneous reactions), low resin-load capacities, means of distributing reagents, and solution phase automation technology continue to warrant the development of designer polymers for library production.[3] To this effect, a variety of reagents and scavengers possessing tunable properties have emerged from ring-opening metathesis polymerization (ROMP) technology.[4,5,6] We herein report the development of a new ROMP-derived oligomeric triazole phosphate (OTP) for application as a soluble, efficient triazolating reagent of nucleophilic species. Overall, these reagents are free flowing solids that are easy to handle, non-toxic, soluble, and air stable. In addition, they are easily stored

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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 products obtained by the described methods. This material is available free of charge via the Internet at http://pubs.acs.org.

long-term at room temperature and are readily prepared, vide infra, from commercially available starting materials on multi-gram scale.

The development of new methodolgies for the diversification of biologically interesting core scaffolds with functional handles is of paramount importance. In this regard, triazoles and their derivatives have demonstrated a wide variety of biological activity, with many reports focusing on antifungal activity.[7] Despite this activity, the utilization of solution phase or immobilized reagents to directly triazolate nucleophilic species in a one-step protocol has been limited to reports of a two-step, one-pot propargylation-click protocol.[8]

Oligomeric and polyphosphates are ideal immobilized leaving groups due to the inherint pKa, stability and innate leaving group properties of phosphate anions.[9,10,11] Recently, we reported the generation and application of oligomeric benzyl phosphate (OBP) as an efficient benzylating reagent.[10] We now report the synthesis of ROMP-derived triazolating reagents (OTP) for application in purification free diversifications of nucleophilic species using the title method, termed “Click”-Capture, ROMP, Release. This method utilizes a propargyl-tagged norbornenyl-phosphate to capture an azide in a classical “click” reaction, followed by ROM polymerization to generate the desired soluble oligomeric triazole reagent (OTP) **4**. Subsequent release via S_N2 displacement with nucleophilic species yields triazolated products along with the spent oligomeric phosphate that is readily sequestered via precipitation (Figure 1).

The synthesis of the oligomeric triazole phosphate bearing a 4-MeOPh group OTP **4a**, starts with the exonorbornenyl tagged (Nb-tagged) phosphonyl chloride **1** utilized in the synthesis of previously reported ROMP-derived benzylating reagent OBP.[10,12] Phosphorylation of propargyl alcohol with Nb-tagged phosphonyl chloride **1**, followed by a “Click”-capture event of the corresponding azide, yields the desired monomer **3a** in an efficient fashion. ROM polymerization of monomer **3a** was achieved with $RuCl_2(PCy_3)_2$=CHPh (cat. **A**), followed by basic workup utilizing the Pederson protocol.[13,14] Precipitation via dropwise addition into anhydrous Et_2O afforded the corresponding oligomeric triazole phosphate (OTP_{20}) **4a** as a free-flowing white solid possessing a theoretical load of 2.4 mmol/g (Scheme 1).

Investigation into the utilization of OTP **4a** as a direct triazolating reagent was next studied using reaction conditions reported for the application of OBP.[10] After optimization of reaction conditions for the triazolation of 2,4-dichlorophenol utilizing OTP **4a**, the corresponding triazole ether **5a**, was isolated in excellent yield (99%) and crude purity (>90%) using simple filtration through a Celite® SPE (Scheme 2).

The application of OTP **4a** as an efficient triazolating reagent was extended to a variety of *N*-, *O*- and *S*-nucleophilic species (Table 1). Initially, a variety of phenols were utilized (Table 1, entries 1–3) though reduced yields were observed for sterically hindered napthalene-1-ol. In addition to phenols, thiophenols (Table 1, entry 5) and a variety of amines (Table 1, entries 6 – 10) were successfully utilized to release the corresponding triazole in >90 % crude purity. Building on the success of OTP **4a**, a variety of additional OTP derivatives **4b** – **4i** were synthesized as free-flowing powders on gram scale from ROM polymerization of their corresponding monomers utilizing cat. **A** (Table 2).

With a variety of OTP **4** derivatives in hand, the triazolation of both naphthalene-1-ol and *N*-ethylnaphthalen-1-amine with OTP derivatives **4a** – **g** was investigated (Table 3). All reactions proceeded with good yields with >90% crude purity after Celite® SPE to remove the spent oligomer.

In conclusion, we have developed and demonstrated the synthesis and utilization of oligomeric triazole phosphates for direct triazolation of *N*-, *O*- and *S*-nucleophilic species in a “Click”-capture, ROMP, release protocol. These oligomeric reagents are readily synthesized on multi-gram scale from commercially available materials as soluble, high-load, free-flowing powders. The application of OTP in the diversification of core scaffolds for the synthesis of diverse-collections of small molecules is underway and will be reported in due time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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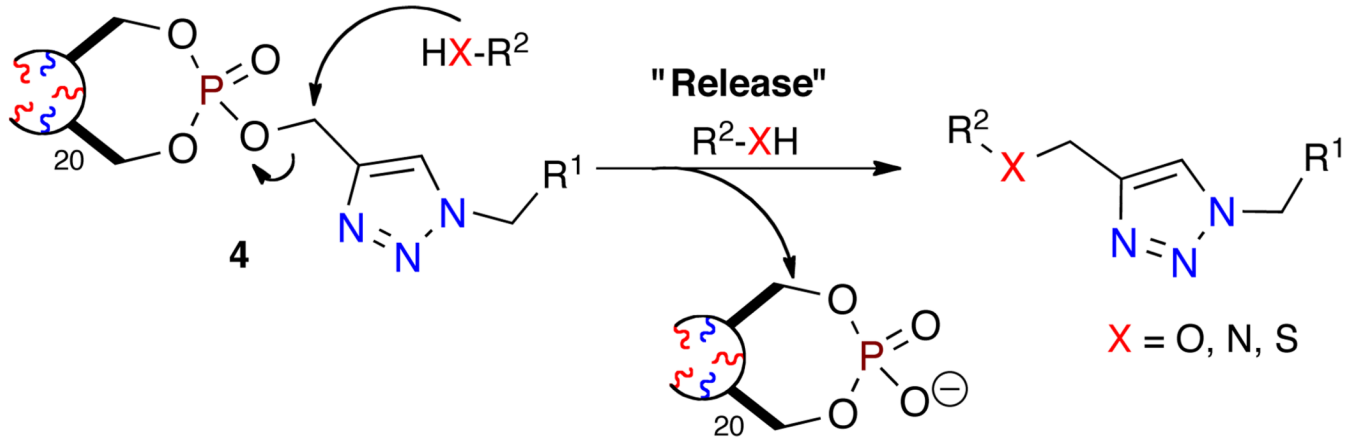
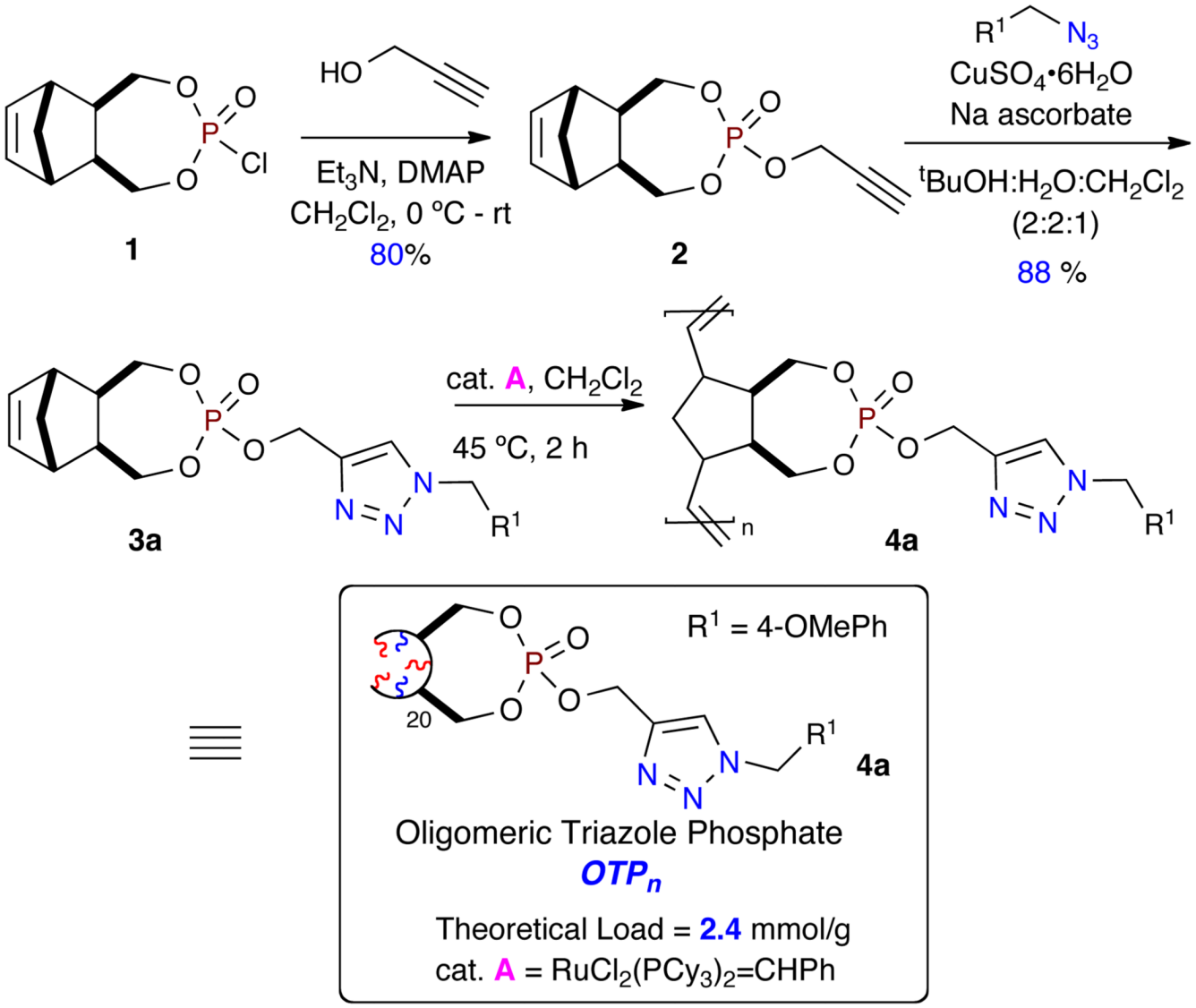


Figure 1.
Reaction of oligomeric triazole phosphate (OTP) **4**

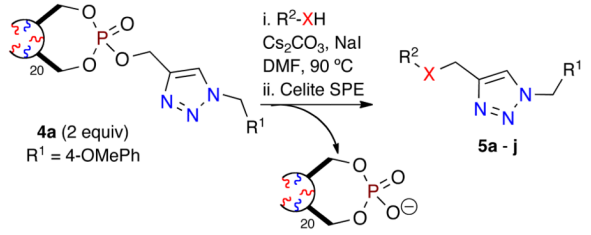


Scheme 1.
Synthesis of oligomeric triazole phosphate (OTP) **4a**

Scheme 2.
Triazolation of 2,4-Cl-PhOH utilizing OTP **4a**

Table 1

Triazolation of N, O and S-Nucleophiles using OTP_{20} **4a**



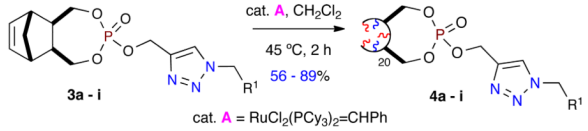
entry	nucleophile	pdt	yield (%)
1	2,4-Cl-PhOH	**5a**	98
2	4-F-PhOH	**5b**	92
3	4-^{t}Bu-PhOH	**5c**	90
4	naphthalene-1-ol	**5d**	69
5	4-SMe-PhSH	**5e**	60
6	Morpholine	**5f**	72
7	Thiomorpholine	**5g**	75
8	1-phenylpiperazine	**5h**	95
9	Indoline	**5i**	88
10	*N*-ethylnaphthalen-1-amine	**5j**	62

[a] Purities >90% observed for all reactions using both GC and ^{1}H NMR.

[b] OTP **4a** utilized as a 20-mer.

Table 2

Synthesis of various OTP analogues **4**

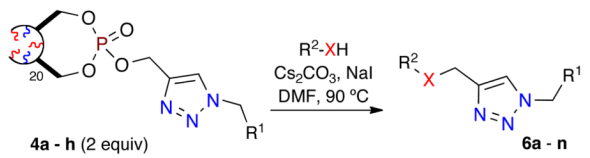


monomer	R^1	pdt	yield (%)[a]
3a	4-OMe-Ph	**4a**	82
3b	4-Me-Ph	**4b**	88
3c	2-Me-Ph	**4c**	77
3d	4-Cl-Ph	**4d**	71
3e	4-F-Ph	**4e**	74
3f	4-CF_3-Ph	**4f**	73
3g	Cylohexyl	**4g**	70
3h	4-Br-Ph	**4h**	89
3i	Furfuryl	**4i**	56

[a]Yields corresponding to metathesis of corresponding monomers.

Table 3

Triazolyation utilizing OTP derivatives **4a – g**.



entry	nucleophile	OTP	pdt	yield (%)[a]
1	naphthalene-1-ol	**4a**	**6a**	72
2	naphthalene-1-ol	**4b**	**6b**	90
3	naphthalene-1-ol	**4c**	**6c**	55
4	naphthalene-1-ol	**4d**	**6d**	68
5	naphthalene-1-ol	**4e**	**6e**	70
6	naphthalene-1-ol	**4f**	**6f**	65
7	naphthalene-1-ol	**4g**	**6g**	49
8	*N*-ethylnaphthalen-1-amine	**4a**	**6h**	62
9	*N*-ethylnaphthalen-1-amine	**4b**	**6i**	52
10	*N*-ethylnaphthalen-1-amine	**4c**	**6j**	63
11	*N*-ethylnaphthalen-1-amine	**4d**	**6k**	51
12	*N*-ethylnaphthalen-1-amine	**4e**	**6l**	50
13	*N*-ethylnaphthalen-1-amine	**4f**	**6m**	60
14	*N*-ethylnaphthalen-1-amine	**4g**	**6n**	66

*[a]*Purities >90% observed for all reactions using both GC and ^{1}H NMR.

*[b]*OTP **4a-g** utilized as a 20-mer.