Organic LETTERS

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Synthesis of Diaryl Diazaphosphonates via 1,6-Hydrophosphonylation of *p*-Quinone Methides with *N*-Heterocyclic Phosphine−Thioureas

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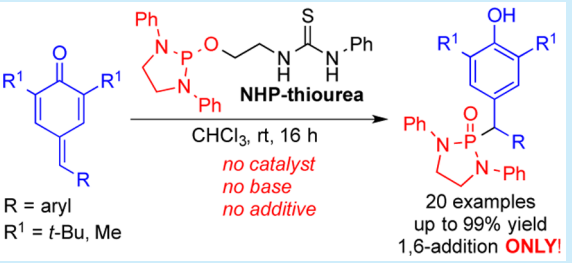
Supporting Information

ABSTRACT: A mild, efficient method for the synthesis of diaryl diazaphosphonates via 1,6-hydrophosphonylation/aromatization of *p*-quinone methides (*p*-QMs) with *N*-heterocyclic phosphine−thioureas has been developed. This transformation proceeds without any additive or catalyst under mild reaction conditions and tolerates a wide range of *p*-QMs. This methodology provides a straightforward access to diaryl phosphonate derivatives in good to excellent yields (up to 99%).



Over the past decade, *p*-quinone methide (*p*-QM) derivatives, a unique structural assembly of reactive carbonyl and olefinic moieties, have gained prominence in synthetic organic chemistry.[1] *p*-QMs are ubiquitous structural motifs present in a wide range of natural products with significant biological activities.[2] They also have been extensively used in biological applications such as lignin biosynthesis,[3] adrenergic receptors,[4] enzyme inhibition,[5] and DNA alkylation[6] as well as cross-linking.[7] Owing to their diverse properties and applications, synthetic transformation of *p*-QMs has been increasingly explored. While the 1,6-conjugate addition reactions of carbon nucleophiles to *p*-QMs are well developed,[8] only a few conjugate addition reactions of heteroatomic nucleophiles have been reported.[9] Mayr has reported hydrazine addition to *p*-QMs via 1,6-conjugate addition reaction to construct C−N bonds of biologically important nitrogen-containing diarylmethine derivatives.[9a] Cheng and co-workers has revealed a phosphoric acid-catalyzed 1,6-addition reaction of thioacetic acid to *p*-QMs for enantioselective C−S bond formation.[9b] Recently, the Anand group has demonstrated a carbene-catalyzed 1,6-conjugate addition reaction of phosphorus nucleophiles to *p*-QMs, providing an efficient route to diaryl-phosphonates.[10] Among the diarylmethine compounds formed with the heteroatomic nucleophiles, the diaryl phosphonates exhibit a broad spectrum of intriguing properties.[11] For instance, they are known as important leukocyte elastase inhibitors **a**[12] and potassium channel modulators **b**[13] (Figure 1). They have been also utilized in the preparation of chemiluminescence materials **c**[14] and flame retardants **d**.[15] In addition, phosphonic diamide derivatives exhibit diverse properties such as fructose 1,6-bisphosphatase inhibitors **e**,[16] P-chiral ligand **f**,[17] and directing groups in organic synthesis **g**[18] (Figure 1).

Existing approaches toward the diaryl phosphonate synthesis include Michaelis−Arbuzov reaction between trialkyl phosphites and alkyl halides (Scheme 1, a),[19] $FeCl_3$-mediated Friedel−Crafts reaction between α-hydroxyphosphonates and arenes (Scheme 1, b),[20] and Pd-catalyzed α-arylation of benzylic phosphine oxides with haloarenes (Scheme 1, c).[21] However, these reactions require harsh reaction conditions (high reaction temperatures), metal catalysts, and additional bases, limited to narrow substrate scope. In addition, to the best of our knowledge, there is no efficient method for the synthesis of the diaryl phosphonates without catalysts or additives under mild reaction conditions. To overcome these limitations, we desired a mild, efficient transformation that could directly produce diaryl phosphonate compounds. With our ongoing research efforts in various C−P bond-forming reactions using bifunctional *N*-heterocyclic phosphine (NHP)−thioureas as efficient phosphonylation reagents,[22] we envisioned that the bifunctional NHP−thiourea could directly activate the *p*-QMs through the hydrogen bond for the 1,6-conjugate addition process. Herein, we report

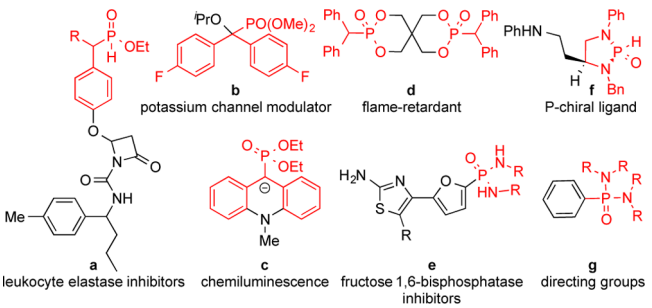


Figure 1. Examples of diaryl phosphonate and phosphonic diamide derivatives.

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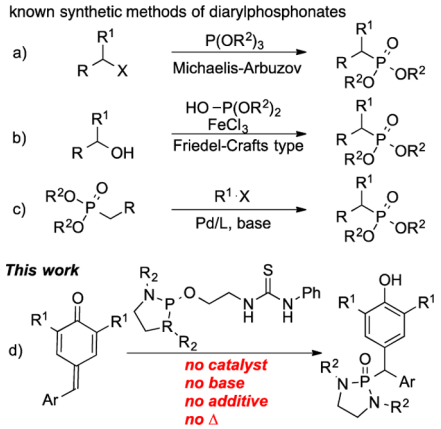
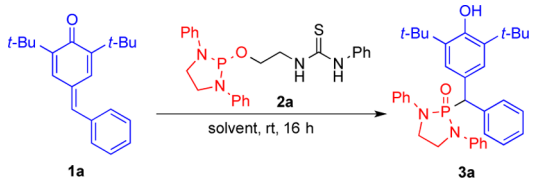
Scheme 1. Synthesis of Diarylmethyl Phosphonates



the synthesis of diaryl diazaphosphonates via 1,6-hydrophosphonylation/aromatization of *p*-QMs with NHP-thioureas of bifunctional phosphonylation reagents.

To test our hypothesis, we began optimization studies by investigating the effect of the ratio between *p*-QM **1a** and NHP−thiourea **2a** on the hydrophosphonylation reaction, and the results are summarized in Table 1. A control experiment between

Table 1. Optimization of Reaction Conditions[a]



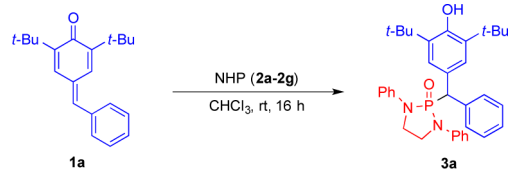
entry	**2a** (equiv)	solvent	yield[b] (%) of **3a**
1	1.0	$CHCl_3$	63
2	1.5	$CHCl_3$	90
3	2.0	$CHCl_3$	98
4	2.0	toluene	90
5	2.0	CH_3CN	95
6	2.0	DCM	94
7	2.0	THF	90
8	2.0	MeOH	94

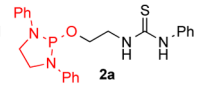
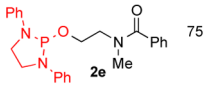
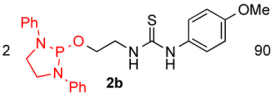
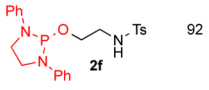
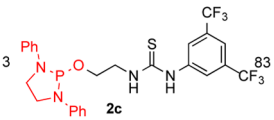
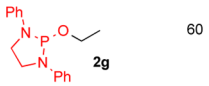
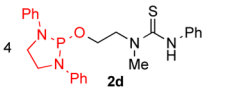
[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), and solvent (0.2 mL) at rt for 16 h. [b]Isolated yield (%).

an equimolar amount of *p*-QM **1a** and NHP−thiourea **2a** provided the corresponding 1,6-hydrophosphonylation product **3a** with 63% yield at room temperature after 16 h. Inspired by this initial result, we explored the effect of different amount of NHP−thioureas on 1,6-conjugate addition reactions (entries 2 and 3). A slight excess of **2a** (2.0 equiv) is needed to obtain the desired product **3a** in 98% yield (entry 3). Having the optimized ratio of the NHP−thiourea, a series of solvents were screened to study the solvent effect on this addition reaction. It was found that both polar and nonpolar solvents worked equally well for the conjugate addition reaction, affording the products in 90−98% (entries 3−7). Interestingly, methanol as an environmentally friendly solvent also furnished the addition product **3a** in excellent yield (94%, entry 8). Among all screened solvents, $CHCl_3$ was found as the optimum solvent.

With the optimized reaction conditions in hand, we investigated the effect of Brønsted acids of different NHPs on the addition reaction with *p*-QM **1a**, and the results are described in Table 2. The parent NHP−phenylthiourea **2a** provided the

Table 2. Screening of Different NHPs[a]



entry	NHP	yield (%)[b]	entry	NHP	yield (%)[b]
1	 **2a**	98	5	 **2e**	75
2	 **2b**	90	6	 **2f**	92
3	 **2c**	83	7	 **2g**	60
4	 **2d**	77			

[a]Reaction conditions: **1a** (0.05 mmol), **2** (0.1 mmol), and $CHCl_3$ (0.2 mL) at rt for 16 h. [b]Isolated yield (%).

diaryl diazaphosphonate **3a** in excellent yield 98% (entry 1). Next, we studied the electronic effects of the Brønsted acids on the conjugate addition reaction (entries 2 and 3). The electron-withdrawing group on the Brønsted acid motif diminished the reactivity and resulted in a slightly lower yield than that of electron-rich thiourea (entry 2 vs 3). The *N*-methyl-substituted NHP−thiourea **2d** and NHP−amide **2e** significantly reduced the reactivity of the addition reaction and provided moderate yields of 77% and 75%, respectively (entries 4 and 5), probably due to the retarding of the intramolecular nucleophilic substitution process. We further examined the effect of different Brønsted acids such as sulfonamide on the substitution process. The sulfonamide moiety did not exhibit a significant effect on this reaction (entry 1 vs 6). On the other hand, NHP−ethane **2g** without the Brønsted acid moiety drastically reduced the reactivity of the 1,6-addition reaction with *p*-QM **1a** under the standard reaction conditions (entry 7). These experimental results strongly support the importance of tethering of the Brønsted acids on the NHP scaffolds.

Next, we examined the scope of NHP−thioureas and *p*-QMs for the 1,6-hydrophosphonylation reaction summarized in Scheme 2. The electron-rich NHPs **2h,i** were well tolerated and gave the corresponding 1,6-addition products **3b,c** in 83% and 88% yields, respectively. When the 2,6-diisopropylphenyl-NHP **2j** was employed under the optimized reaction conditions, the reaction did not proceed. This is presumably due to the adverse steric interaction between the bulky *ortho* substituents on the benzene rings of the NHP scaffold and the *p*-QMs. In addition, *p*-QM derivatives with various substituents on the phenyl moiety were evaluated under the standard reaction conditions. *p*-QMs having electron-donating and -withdrawing groups on the phenyl group (**1b−j**) were efficiently transformed to the desired addition products (**3e−3m**) with good to excellent

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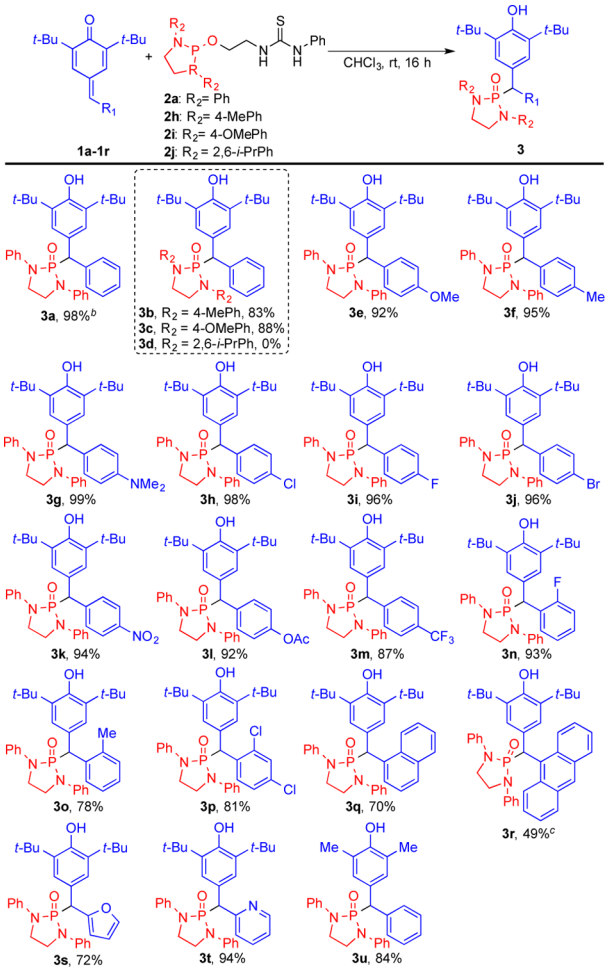
Scheme 2. Scope of NHP−Thioureas and *p*-QMs[a]

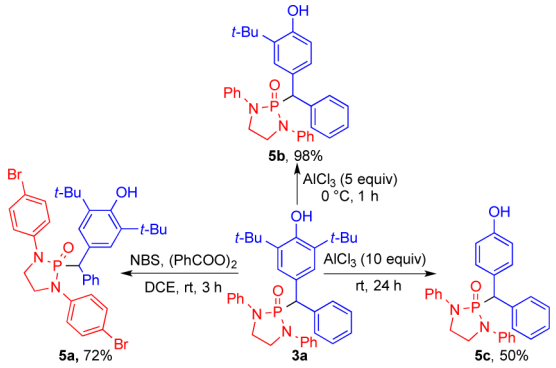


[a]Reaction conditions: **1** (0.05 mmol), **2** (0.1 mmol), and $CHCl_3$ (0.2 mL) at rt for 16 h. [b]Isolated yield (%). [c]Reaction run at 60 °C for 44 h.

yields. On the other hand, *p*-QMs with *ortho*-substituents on the phenyl ring (**1k−m**) significantly reduced the formation of the 1,6-conjugate addition products (**3n−p**) except for the *p*-QM with an *ortho*-fluoro substituent on the benzene ring (**3n**, 93% yield). In the case of *p*-QM with the multisubstituted phenyl ring **1m**, the corresponding product **3p** was obtained in 81% yield. Polyaromatic substituents on *p*-QMs **1n,o** were also tolerated and afforded the desired products **3q,r** in 70% and 49% yields, respectively. In addition, the *p*-QMs with heteroaromatic substituents **1p,q** proved to be suitable substrates for this addition reaction, affording the target products **3s,t** in 72% and 94% yields, respectively. Furthermore, 2,6-dimethylphenol-*p*-QM **1r** smoothly underwent the 1,6-addition reaction to furnish the desired product **3u** in 84% yield. In order to demonstrate the synthetic feasibility of this transformation, we conducted a large-scale experiment on 1.0 mmol scale and found that the reaction was equally efficient, affording the desired product in excellent yield (95% yield).[23]

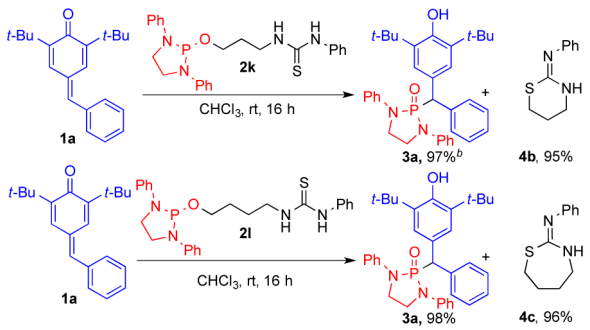
To explore the synthetic utility of this transformation, we conducted synthetic manipulation of the 1,6-hydrophosphonylation product **3a** (Scheme 3). With the potential application of the halogenated diaryl phosphonates as phosphorus-containing flame retardants,[24] **3a** was treated with NBS in the presence of benzoyl peroxide to afford the only aryl-brominated product **5a**. The selective removal of one *tert*-butyl group of **3a** using $AlCl_3$ (5 equiv) delivered **5b** in excellent yield (98%). In addition to the selective removal of one *tert*-butyl group, removal of both *tert*-butyl groups using $AlCl_3$ (10 equiv) was also successfully demonstrated at room temperature in 24 h, providing the desired product **5c** in moderate yield (50%).

Scheme 3. Synthetic Transformations



To understand the reaction mechanism, we performed additional experiments by using NHPs **2k,l** with a three-carbon chain tether and a four-carbon chain tether, respectively (Scheme 4). Both **2k** and **2l** produced the desired diaryl diazaphosphonate

Scheme 4. Conjugate Addition Reaction with NHPs 2k and 2l



[a]Reaction conditions: **1** (0.05 mmol), **2** (0.1 mmol), and $CHCl_3$ (0.2 mL) at rt for 16 h. [b]Isolated yield (%).

3a in 97% and 98% yields, respectively. We also isolated the 1,3-thiazinan-2-imine **4b** and 1,3-thiazepan-2-imine **4c** in 95% and 96% yields, respectively. It was found that the experiments using a different length of tether linkages **2k,l** for 1,6-conjugate addition reaction provided the same outcomes as with the parent NHP-thiourea **2a**. On the basis of the results of our experiments and previous reports,[8i,22] a plausible reaction pathway is illustrated in Scheme 5. The 1,6-conjugate addition of the bifunctional NHP **2a** to the *p*-QM **1a** activated through hydrogen bond with the thiourea Brønsted acid generates a diazaphoshonium intermediate **A**. A sequential proton transfer led to an anionic thiourea intermediate **B**, which promotes the intramolecular nucleophilic displacement of the diazaphoshonium **A** by the anionic thiourea moiety to furnish the addition product **3a** and thiazolidine **4a**.

In summary, we have developed an efficient method for the synthesis of diaryl diazaphosphonates via 1,6-hydrophosphonylation/aromatization of *p*-QMs with NHP-thioureas under catalyst and additive free conditions. This method is compatible with a wide range of *p*-QMs under mild reaction conditions, providing the corresponding diaryl phosphonate derivatives in excellent yields (up to 99%). This transformation is readily

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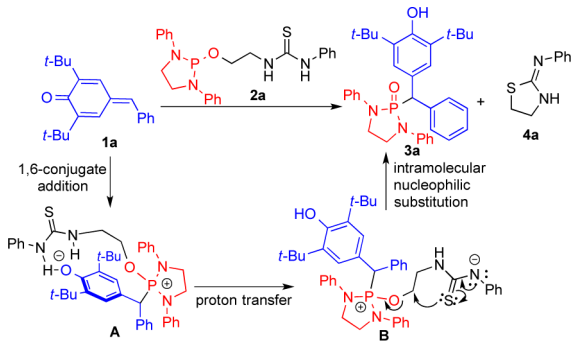
Scheme 5. Proposed Reaction Pathway



scalable without compromising the reactivity. In addition, the synthetic utility of 1,6-hydrophosphonylation products was demonstrated by transforming to an aryl-brominated diaryl diazaphosphonate. The selective removal of *tert*-butyl groups on **3a** was readily achieved. Further studies of enantioselective construction of C−P bonds of the diaryl diazaphosphonates are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00261.

Experimental details (PDF)
Spectral data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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