Organic LETTERS

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Amine-Catalyzed Phospha-Michael Reaction of α,β-Unsaturated Aldehydes and Ketones with Multifunctional *N*-Heterocyclic Phosphine-Thioureas as Phosphonylation Reagent

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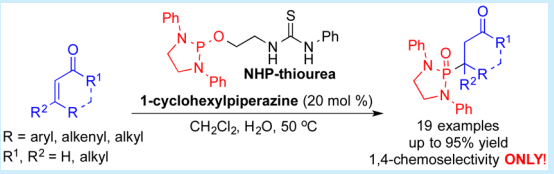
Supporting Information

ABSTRACT: An efficient amine-catalyzed phospha-Michael addition reaction of α,β-unsaturated aldehydes/ketones with *N*-heterocyclic phosphines for the synthesis of γ-ketodiazaphosphonates has been developed. With freedom from nucleophile additives, this mild process affords a range of structurally diverse γ-ketodiazaphosphonates in moderate to excellent yields. Importantly, various α,β-unsaturated ketones were also tolerated in this process and gave moderate yields.



The phospha-Michael addition reaction has emerged one of the most versatile and powerful synthetic tools for carbon−phosphorus bond formation because of its atom- and step-economic approach and because many different products with various substitution patterns, depending on both the acceptor and the donor nucleophiles, are available.[1] Highly functionalized and valuable phospha-Michael adducts are generated under the reaction conditions in one step.[2]

Among the phospha-Michael adducts, γ-ketophosphonates and their phosphonic acid derivatives have received significant attention in recent years owing to their both biological properties and pharmaceutical applications as analogues of α-substituted phosphonates and phosphonic acids (Figure 1).[3] They exhibit a

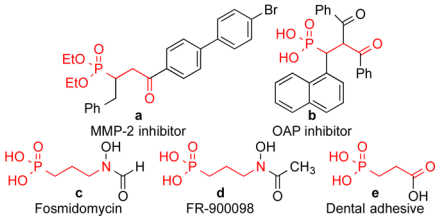


Figure 1. Biologically active and pharmaceutically important γ-ketophosphonates and their derivatives.

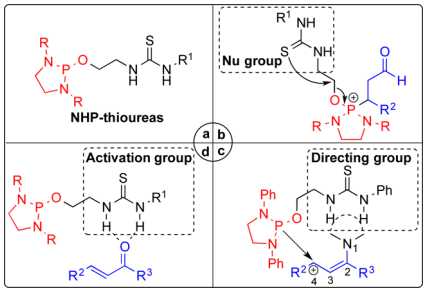
wide range of enzyme inhibitions such as matrix metalloprotease (MMP-2) inhibitor (**a**)[4] and osteoclastic acid phosphatase (OAP) inhibitor (**b**).[5] In addition, they are versatile precursors for the synthesis of important γ-aminophosphonate compounds of antimalarial drugs including fosmidomycin (**c**) and FR-900098 (**d**).[2a,6] Furthermore, 3-phosphonopropionate (**e**) has been identified as a promising dental adhesive.[7]

Dialkyl phosphonate or trialkyl phosphites are the common Michael donors of this phospha-Michael addition in which only trivalent phosphite form of the active nucleophile undergoes 1,4-addition to α,β-unsaturated carbonyls to form the γ-ketophosphonates.[2f,k] With various methods available for the tautomerism in favor of the phosphite form between the phosphite and phosphonate equilibrium, dialkyl phosphonate Michael donors have been successfully applied for the synthesis of γ-ketophosphonates.[2f−i] On the other hand, application of the trialkyl phosphites to the phospha-Michael reaction is limited to a handful of examples and currently requires complex reaction conditions.[2a,b] In 2007, Jørgensen and co-workers reported a pyrrolidine-catalyzed enantioselective phospha-Michael addition of trialkyl phosphite ($P(O\text{-}i\text{-}Pr)_3$) to the α,β-unsaturated aldehydes for β-phosphonylation in combination with the required Brønsted acid ($PhCO_2H$) and an external nucleophile (NaI).[2a] In addition, synthetic application of the precedent amine-catalyzed phospha-Michael addition reaction of the trialkyl phosphites to α,β-unsaturated aldehydes still faces two major synthetic hurdles: (1) The crucial step, the transformation of P(III) to P(V),[2a] must be performed via nucleophilic attack by additives. (2) Chemoselectivity is also another inherent difficulty in this type of addition due to the reversibility of the nucleophilic attack and competition between 1,2- and 1,4-addition.[2a,b,d,e,i] With our ongoing efforts in the construction of C−P bonds using *N*-heterocyclic phosphine (NHP)-thioureas (Scheme 1, a), we hypothesized that the NHP-thiourea exhibits multiplex roles in the phospha-Michael reaction as follows: (1) an internal nucleophile that could promote the transformation of P(III) to P(V) without additives (Scheme 1, b);[8] (2) a hydrogen-bond-mediated directing group that efficiently inhibits the undesired 1,2-addition (Scheme 1, c); and (3) an activating group that

Received: July 20, 2016

DOI: 10.1021/acs.orglett.6b02121
Org. Lett. XXXX, XXX, XXX−XXX

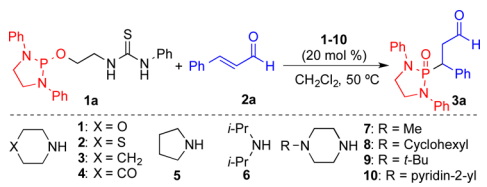
Scheme 1. Multiplex Roles of NHP-thioureas in the Phospha-Michael Addition Reaction



helps the iminium intermediate formation between α,β-unsaturated ketones and amines (Scheme 1, d). Given the great importance of cyclic phosphonamide reagents in organic synthesis,[9] we herein report an amine-catalyzed phospha-Micheal addition reaction of α,β-unsaturated aldehydes/ketones with multifunctional NHP-thioureas for the synthesis of γ-ketodiazaphosphonates under additive-free, mild reaction conditions.

To test our hypothesis of the amine-catalyzed phospha-Michael addition reaction without nucleophile additives, NHP-thiourea **1a**, transcinnamaldehyde **2a**, and amines (**1**−**10**) in CH_2Cl_2 were used to screen for the optimal reaction conditions described in Table 1.[10] We began with the examination of the

Table 1. Optimization of the Reaction Conditions[a]



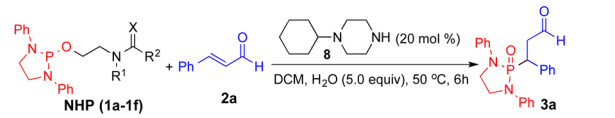
entry	amine	H_2O (equiv)	yield of **3a**[c] (%)
1	**1**		28
2	**2**		65
3	**3**		58
4	**4**		28
5	**5**		47
6	**6**		52
7	**7**		67
8	**8**		71
9	**9**		69
10	**10**		40
11	**8**	H_2O (1.0)	75
12	**8**	H_2O (5.0)	80
13	**8**	H_2O (8.0)	76
14[b]	**8**	**H_2O (5.0)**	**95**

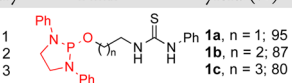
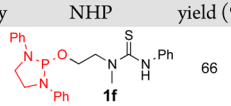
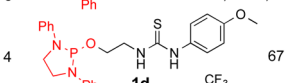
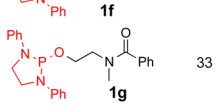
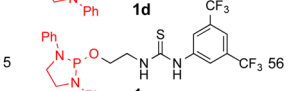
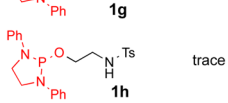
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), and catalyst (20 mol %) in CH_2Cl_2 (0.5 mL) at 50 °C for 6 h. [b]0.3 mmol of **2a** was added. [c]Isolated yield.

catalytic activity of amines. Morpholine **1** with 20 mol % loading demonstrated the catalytic turnover of the reaction, providing the phospha-Michael adduct **3a** with 28% yield without external nucleophiles. With this promising result, we next tested various heterocyclic amines (entries 2−5); among the evaluated amines, thiomorpholine provided the highest product yield (entry 2, 65%), probably due to the strong nucleophilicity. However, acyclic amine was inferior to the cyclic amine (entry 6 vs 2). With the advantage of strong nucleophilic amines for iminium intermediate formation, we explored *N*-alkyl- or aryl-substituted piperidines for optimization of the catalytic system (entries 7−14). Gratifyingly, optimized reaction conditions of this phospha-Michael addition reaction were obtained using 1-cyclohexylpiperazine **8** with addition of a 5.0 equiv of H_2O (entry 14, 95%); a large excess of H_2O was found to cause a significant decomposition of the NHP to ethylenedianiline, resulting in a reduced product yield (entry 13, 76%).

Next, a systematic study of the effect of Brønsted acid motif on the intramolecular nucleophilic substitution reaction process was conducted (Table 2). The phenyl-substituted parent thiourea **1a**

Table 2. Scope of NHP-thioureas[a]



entry	NHP	yield (%)[b]	entry	NHP	yield (%)[b]
1 2 3		**1a**, n = 1; 95 **1b**, n = 2; 87 **1c**, n = 3; 80	6	 **1f**	66
4	 **1d**	67	7	 **1g**	33
5	 **1e**	56	8	 **1h**	trace

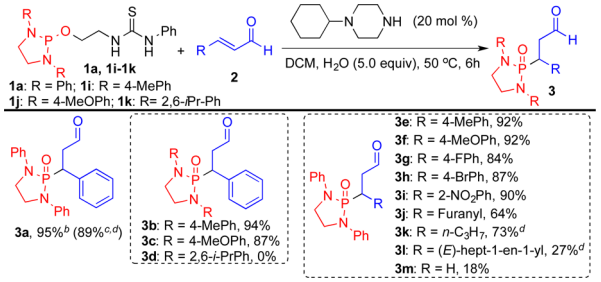
[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.3 mmol), H_2O (5.0 equiv), and **8** (20 mol %) in CH_2Cl_2 (0.5 mL) at 50 °C for 6 h. [b]Isolated yield.

generated the phospha-Michael adduct **3a** in excellent yield (95%) with exclusive 1,4 addition product (entry 1). Following optimization study of the bifunctional NHPs revealed that the length of the tether between the NHP motif and the Brønsted acid played a pivotal role in an effective hydrogen-bond activation of the aldehyde. For example, NHPs with a longer tether provided lower product yields (entry 1 vs entries 2 and 3). To investigate the electronic effects of the thiourea motif on this transformation, 4-MeO- and 3,5-(CF_3)-phenyl thiourea-NHPs (**1d,e**) were subjected to the standard reaction conditions with the catalyst **8**, and the results showed that none of them were superior to the parent thiourea (entries 4 and 5 vs 1). Having a methyl substituent on the nitrogen atom at the Brønsted acid motif, the reaction also provided a lower yield (entries 6 and 7), presumably due to impediment of the intramolecular nucleophilic substitution reaction. The replacement of thiourea group with sulfonamide significantly reduced the reaction efficiency (entry 8). Lastly, it should be noted that triethyl or diethyl phosphite, previously known phosphonylation reagents,[2a,b,f−i] did not proceed to form Michael adducts under the standard reaction conditions.

With the optimized reaction conditions established, we explored the scope of this reaction by treating NHP-thioureas and aldehydes (Scheme 2). The electronic effects of the NHP motifs (**1i,j**) on this reaction had a negligible influence (**3b,c**), whereas the steric effects induced by the *ortho*-substituents on the NHP scaffold (**1k**) completely suppressed the reactivity (**3d**). Aldehydes with *para*-substituted phenyl rings containing electron-donating groups (**2e,f**) or withdrawing groups (**2g,h**) were well tolerated and provided the corresponding products in

DOI: 10.1021/acs.orglett.6b02121
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of α,β-Unsaturated Aldehydes for Phospha-Michael Addition Reaction[a]

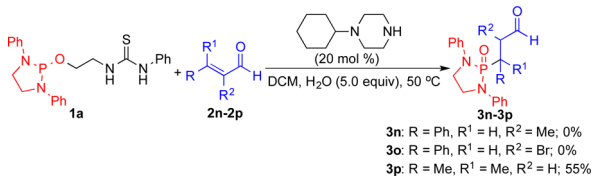


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), H_2O (0.5 mmol), and **8** (20 mol %) in CH_2Cl_2 (0.5 mL) at 50 °C for 6 h. [b]Isolated yield. [c]Scale-up experiment with 2.3 mmol of **1a** loading. [d]Reaction run for 24 h.

high to excellent yields (**3e**−**h**). In addition, a Michael acceptor with *ortho*-substituted phenyl ring (**2i**) proceeded smoothly to furnish a phospha-Michael adduct in excellent yield (**3i**, 90%). Heteroaromatic α,β-unsaturated aldehyde (**2j**) also succeeded in producing the desired adduct in a moderate yield (**3j**, 64%). Furthermore, aliphatic α,β-unsaturated aldehyde, (*E*)-hex-2-enal (**2k**), was also suitable for this reaction to produce the corresponding product (**3k**) in 73% yield. Moreover, (2*E*,4*E*)-deca-2,4-dienal (**2l**) with the NHP-thiourea (**1a**) delivered an allylphosphonate in an acceptable yield (**3l**, 27%). We also studied the reactivity of acrolein, but a poor product yield was obtained due to the instability of the product (**3m**). Finally, it is noteworthy that a scale up of this reaction (2.3 mmol) was performed without sacrificing the product yield (Scheme 2, **3a**, 89%).[11]

To further explore the influence of steric hindrance on the Michael acceptor, several α,β-unsaturated aldehydes containing various substituents were examined under the standard reaction conditions (Scheme 3). The results showed that α,β-unsaturated

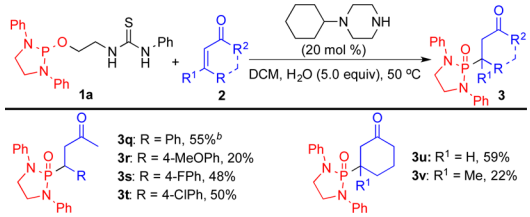
Scheme 3. Phospha-Michael Addition Reaction with Variously Substituted α,β-Unsaturated Aldehydes



aldehydes with α-substituents (**2n**,**o**) inhibited the phospha-Michael process, probably due to the challenge of forming the iminium intermediates. On the other hand, 3-methylbut-2-enal (**2p**) was smoothly converted to the corresponding tetrasubstituted phosphonate in 55% yield.

To the best of our knowledge, the undecorated secondary amine-catalyzed phospha-Michael reaction of dialkyl phosphonates or trialkyl phosphites on the enone systems for the synthesis of γ-ketophosphonate derivatives has remained largely underdeveloped.[2f−k,12] With the potential of strong hydrogen-bond activation of ketone groups with a thiourea motif for the iminium formation, we wanted to demonstrate the possibility of phospha-Michael addition reaction of enones utilizing the multifunctional NHP-thioureas. Gratifyingly, a moderate yield of the product was obtained when (*E*)-4-phenylbut-3-en-2-one (**2q**) was employed as a Micheal acceptor in our catalytic system (Scheme 4, **3q**). The reaction is compatible with both electron-donating and electron-withdrawing groups on the enones (**2r**−**t**). The reactivities of cyclohex-2-enone (**2u**) and 3-methyl-cyclohexenone (**2v**) were also investigated under the optimized reaction conditions, and the corresponding products (**3u**,**v**) were obtained in moderate yields, affording a tetrasubstituted phosphonate (**3v**) as a racemate.

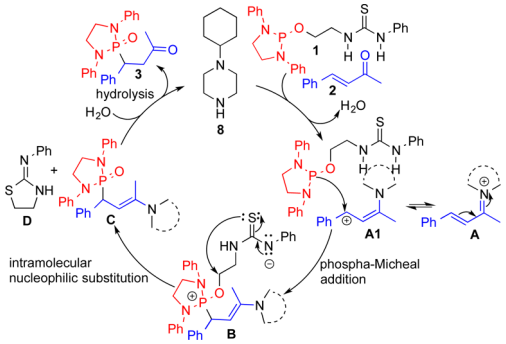
Scheme 4. Scope of α,β-Unsaturated Ketones for Phospha-Michael Addition Reaction[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), H_2O (1.5 mmol), and **8** (20 mol %) in CH_2Cl_2 (0.5 mL) at 50 °C for 96 h. [b]Isolated yield.

On the basis of the observed experimental results and related previous works,[8] a plausible mechanism is depicted in Scheme 5.

Scheme 5. Proposed Mechanism

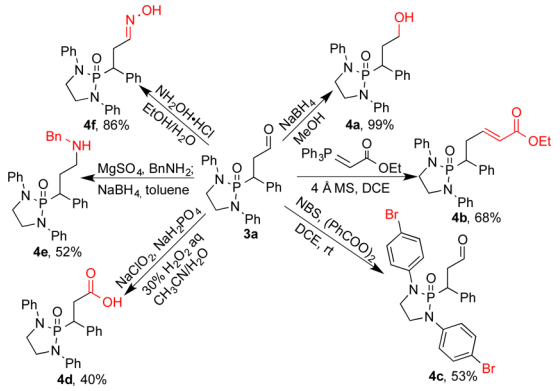


With a hydrogen-bond activation of the α,β-unsaturated ketone **2** by NHP-thiourea **1**, amine **8** can effectively form an iminium intermediate **A**. **A** would be in equilibrium with a transient benzylic carbocation-stabilized enamine intermediate **A1** also characterized as a stable allylic carbocation to increase their chemoselectivity through a hydrogen bond between the enamine intermediate and the thiourea group. **A1** subsequently undergoes a nucleophilic addition with the NHP **1** to form a C−P bond and enamine intermediate **B**. A sequential deprotonation/intramolecular nucleophilic substitution reaction provided a phosphonate intermediate **C** and thiazolidine byproduct **D**.[8] After hydrolysis of **C**, the corresponding product **3** is generated.

Next, synthetic manipulations of **3a** were carried out (Scheme 6). A reduction of aldehyde **3a** to an alcohol **4a** was achieved with $NaHB_4$ in 99% yield. Wittig reaction of **3a** afforded β-vinyl diazaphosphonate **4b** in 68% yield. Bromination of **3a** using NBS and benzoyl peroxide produced only *N*-aryl-brominated product **4c**. Additionally, oxidation of the aldehyde **3a** to the corresponding carboxylic acid **4d** was achieved with $NaClO_2$/H_2O_2 conditions.[13] Moreover, considering a significant application of the P−N ligands to the bidentate ligands,[14] reductive amination of **3a** with $BnNH_2$/$NaBH_4$ was carried out to afford the corresponding product **4e** in 52% overall yield.

DOI: 10.1021/acs.orglett.6b02121
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Synthetic Utility of Phospha-Michael Adduct 3a



Finally, treatment of **3a** with $NH_2OH{\cdot}HCl$ provided *β*-oximephosphonate **4f** in high yield (86%).

In summary, we have developed a new catalytic phospha-Michael addition protocol for the synthesis of *γ*-ketodiazaphosphonates by NHP-promoted pathway under nucleophilic additive-free reaction conditions. This method tolerated a wide range of functional groups on *α,β*-unsaturated aldehydes and was compatible with various *α,β*-unsaturated ketones. This study, for the first time, demonstrated the multiplex and critical roles of Brønsted acid motif in the phospha-Michael addition reaction, such as an internal nucleophile promoting the transformation of P(III) to P(V), a directing group achieving a complete chemoselectivity (1,4-addition), and an activator enabling *α,β*-unsaturated ketones to form iminium intermediates for direct phosphonylation. Moreover, synthetic utility of this phospha-Michael adduct was demonstrated. Further studies to find more efficient C−P bond formation based on the NHP-mediated systems 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.6b02121.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by University of Nevada Las Vegas (Faculty Opportunity Awards). Dr. Karimulla Mulla (Emory University) is acknowledged for his early, related work. Dr. Katarzyna Lorenc-Kukula (SCAAC) is acknowledged for mass spectra data.

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(10) For the full optimized reaction conditions, see the Supporting Information.

(11) Thiazolidine byproduct **D** was isolated in 82% yield.

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DOI: 10.1021/acs.orglett.6b02121
Org. Lett. XXXX, XXX, XXX−XXX