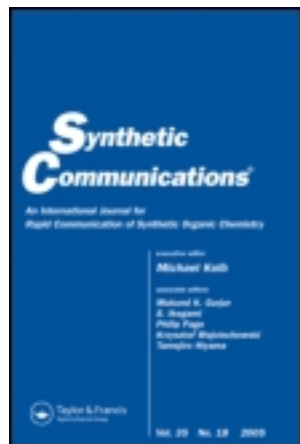


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## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

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### New and Efficient Synthesis of 1,3-Dienylphosphonates by Palladium-Catalyzed Substitution of Propargylic Esters to Diethyl Phosphite

Xiao-Ning Liu <sup>a</sup>, Wei-Lei Guo <sup>a b</sup>, Chuan-Jin Hou <sup>a</sup> & Xiang-Ping Hu <sup>b</sup>

<sup>a</sup> School of Light Industry and Chemical Engineering, Dalian Polytechnic University, Dalian, China

<sup>b</sup> Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China

Published online: 26 Jun 2013.

To cite this article: Xiao-Ning Liu, Wei-Lei Guo, Chuan-Jin Hou & Xiang-Ping Hu (2013) New and Efficient Synthesis of 1,3-Dienylphosphonates by Palladium-Catalyzed Substitution of Propargylic Esters to Diethyl Phosphite, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 43:19, 2622-2626, DOI: [10.1080/00397911.2012.725795](https://doi.org/10.1080/00397911.2012.725795)

To link to this article: <http://dx.doi.org/10.1080/00397911.2012.725795>

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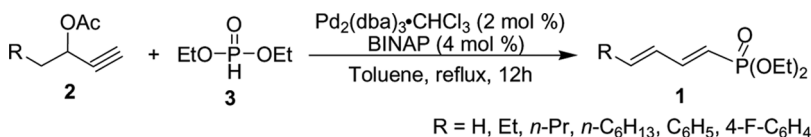
## NEW AND EFFICIENT SYNTHESIS OF 1,3-DIENYLPHOSPHONATES BY PALLADIUM-CATALYZED SUBSTITUTION OF PROPARGYLIC ESTERS TO DIETHYL PHOSPHITE

Xiao-Ning Liu,<sup>1</sup> Wei-Lei Guo,<sup>1,2</sup> Chuan-Jin Hou,<sup>1</sup> and Xiang-Ping Hu<sup>2</sup>

<sup>1</sup>School of Light Industry and Chemical Engineering, Dalian Polytechnic University, Dalian, China

<sup>2</sup>Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China

### GRAPHICAL ABSTRACT



**Abstract** An efficient route to the synthesis of 1,3-dienylphosphonates (**1**) has been developed for the first time by the substitution of propargylic esters (**2**) to the diethyl phosphite (**3**) nucleophile in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2 mol %) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (4 mol %). Both the alkyl and aryl 1,3-dienylphosphonates can be prepared from this transformation.

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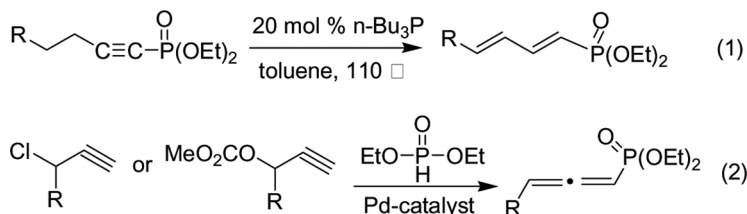
**Keywords** 1,3-Dienylphosphonates; diethyl phosphite; Pd-catalyzed; propargylic substitution

## INTRODUCTION

Phosphonates are important natural and synthetic compounds because of their biological and medical properties.<sup>[1]</sup> A special class of phosphonates containing conjugate ene moiety, 1,3-dienylphosphonates have received much consideration in recent decades because of their widespread usefulness in organic synthesis and have been employed in [2 + 2] cycloaddition,<sup>[2]</sup> [4 + 2] cycloaddition,<sup>[3]</sup> 1,3-dipolar cycloaddition,<sup>[4]</sup> 1,4-addition,<sup>[5]</sup> and enolate alkylation<sup>[6]</sup> reactions. They have also

Received April 5, 2012.

Address correspondence to Chuan-Jin Hou, School of Light Industry and Chemical Engineering, Dalian Polytechnic University, Dalian, 116034, China. E-mail: houcj@dpu.edu.cn; Xiang-Ping Hu, Dalian Institute of Chemical Physics, China Academy of Sciences, Dalian 116023, China. E-mail: xiangping@dicp.ac.cn



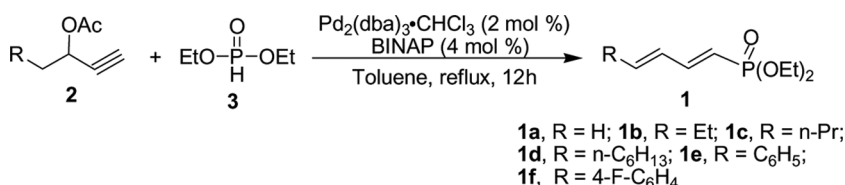
**Scheme 1.** Pd-catalyzed synthesis of 1,3-dienylphosphonates and allenylphosphonates.

been reported in the synthesis of biologically active products such as AP6 analogs<sup>[7]</sup> and *Fusarium* toxin equisetin.<sup>[8]</sup> However, methods for the synthesis of 1,3-dienylphosphonates are still rare. The need for the development of an efficient method for the synthesis of 1,3-dienylphosphonates is, therefore, of great interest.

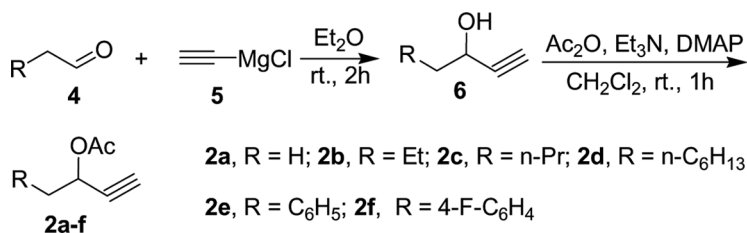
There are several reported methods for the synthesis of 1,3-dienylphosphonates including the reaction of unsaturated phosphonates with *N*-tolsylsufonylimines,<sup>[9]</sup> the titanium-mediated Knoevenagel condensation of conjugated aldehydes with diethyl malonate,<sup>[2]</sup> the Pd-catalyzed coupling reaction of unsaturated phosphonates with alkenes,<sup>[10]</sup> the Ni-catalyzed addition of P(O)-H bonds to propargyl alcohols,<sup>[11]</sup> and the alkyne insertion into zirocoacycloprenes.<sup>[12]</sup> Notably, Ma et al.<sup>[13]</sup> and Azab et al.<sup>[14]</sup> reported the Pd-catalyzed isomerization of alkynylphosphonate to 1,3-dienylphosphonates [Scheme 1, Eq. (1)]. However, the catalyst was less efficient and high catalyst loading was required (10–20 mol%). Recently, Kalek et al.<sup>[15]</sup> reported the Pd-catalyzed propargylic substitution with phosphorus nucleophiles to the synthesis of allenylphosphonates [Scheme 1, Eq. (2)]. Inspired by the isomerization of alkynylphosphonates to allenylphosphonates,<sup>[16]</sup> we report the first synthesis of 1,3-dienylphosphonates (**1**) by direct Pd-catalyzed propargylic substitution of propargylic esters (**2**) to diethyl phosphite (**3**) nucleophile (Scheme 2). Both the alkyl and aryl 1,3-dienylphosphonates can be prepared from this transformation. To the best of our knowledge, it is the first time that the 1,3-dienylphosphonates were synthesized by direct propargylic substitution.

## RESULTS AND DISCUSSION

First, the propargylic ester substrates were synthesized from related commercially available aldehydes (Scheme 3). Thus the aldehydes (**4**) were allowed to react with ethynyl magnesium chloride (**5**) in diethyl ether to give the corresponding propargylic alcohol (**6**), which can be used without further purification. Esterification of the resultant propargylic alcohol (**6**) with acetic anhydride in the presence



**Scheme 2.** Pd-catalyzed propargylic substitution to the synthesis of 1,3-dienylphosphonates.



**Scheme 3.** Synthesis of propargylic ester substrates.

**Table 1.** Pd-catalyzed propargylic substitution of a variety of propargylic esters

Entry	Substrate	Product	Isolated yield (%)
1	<b>2a</b>	<b>1a</b>	87
2	<b>2b</b>	<b>1b</b>	74
3	<b>2c</b>	<b>1c</b>	75
4	<b>2d</b>	<b>1d</b>	72
5	<b>2e</b>	<b>1e</b>	82
6	<b>2f</b>	<b>1f</b>	71

of triethylamine (TEA) and 4-dimethylaminopyridine (DMAP) gave the required propargylic esters **2a–2f**.

We then examined the propargylic substitution of hex-1-yn-3-yl acetate (**2b**) with diethyl phosphite (**3**) using palladium catalyst generated in situ from Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2 mol%) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (4 mol %) in reflux toluene. Fortunately, the reaction proceeded smoothly and the related diethyl (*1E,3E*)-hexa-1,3-dienylphosphonate was isolated in modest yield (Table 1, entry 2). The stereochemistry of **2b** was assigned as *E,E* configuration for the double bonds which was determined by NMR compared to reported data.<sup>[12,14]</sup> Attempts to improve the reactivity by variation of solvents and ligands seemed unsuccessful. Either no reaction occurred or a complicated reaction mixture was obtained when other solvents or ligands used.

Encouraged by the promising result obtained in the reaction of **2b**, the scope of propargylic substitution was then investigated under the present catalytic system, and the results are summarized in Table 1. The results suggested that a wide variety of propargylic esters react with diethyl phosphite (**3**) to give the corresponding 1,3-dienylphosphonate **1a–1f** in modest to good yield. Short- and long-alkyl chain substrates proceeded in satisfactory yield (entries 1–4). Good results were also obtained when aryl-substituted propargylic esters were tested (entries 5 and 6). The fluoridated substrate was also tolerant (entry 6). The results indicated the present catalytic system was efficient for the BINAP/palladium-catalyzed propargylic substitution in the synthesis of 1,3-dienylphosphonates.

## CONCLUSION

In conclusion, we have developed a new and efficient route to the synthesis of 1,3-dienylphosphonates. The propargylic esters reacted with diethyl phosphite to

give the corresponding 1,3-dienylphosphonates in the presence of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (2 mol %) and BINAP (4 mol%). Both of the alkyl and aryl 1,3-dienylphosphonates can be prepared in modest to good yields. To the best of our knowledge, it is the first time the 1,3-dienylphosphonates were synthesized by the direct propargylic substitution. Further study of the reaction mechanism is in progress.

## EXPERIMENTAL

### General Procedure for Synthesis of Propargylic Ester Substrates 2a–2f

To a stirred solution of aldehyde (30 mmol) in dry THF (60 mL) under  $\text{N}_2$  atmosphere was added ethynylmagnesium chloride (50 mL, 0.6 M in THF) dropwise at room temperature. The mixture was stirred for 2 h and then quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with  $\text{Et}_2\text{O}$ , washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to give the crude propargylic alcohol, which was used directly.

The crude propargylic alcohol was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (40 mL), and  $\text{Et}_3\text{N}$  (30 mmol) and DMAP (3 mmol) were added. Then  $\text{Ac}_2\text{O}$  (30 mmol) was added dropwise, and the mixture was stirred for 2 h. The reaction was quenched with water, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The product was purified by chromatography on silica gel.

Compound **2b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95 (t,  $J = 7.6$  Hz, 3H), 1.45–1.51 (m, 2H), 1.73–1.79 (m, 2H), 2.09 (s, 3H), 2.45 (s, 1H), 5.36 (t,  $J = 6.8$  Hz, 1H).

### General Procedure for Synthesis of 1,3-Dienylphosphonates 1a–1f

$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (10.4 mg, 0.010 mmol) and BINAP (12.4 mg, 0.020 mmol) were added into an oven-dried Schlenk tube. Then, dry toluene (2 mL) added, and the mixture was stirred for 30 min at room temperature. Propargylic ester substrates **2** (0.5 mmol), diethyl phosphine (62.1 mg, 0.55 mmol), and  $\text{Et}_3\text{N}$  (80  $\mu\text{L}$ , 0.5 mmol) were added successively. The reaction was refluxed for 12 h and cooled to room temperature. The solvent was removed under reduced pressure, and the product was purified by chromatography on silica gel.

Compound **1b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.04 (t,  $J = 7.6$  Hz, 3H), 1.33 (t,  $J = 7.2$  Hz, 6H), 2.15–2.22 (m, 2H), 4.04–4.11 (m, 4H), 5.57 (dd,  $^3J_{\text{H,H}} = 17.2$  Hz,  $^2J_{\text{H,P}} = 19.2$  Hz, 1H), 6.08–6.18 (m, 2H), 7.08 (ddd,  $^3J_{\text{H,H}} = 16.8$  Hz,  $^3J_{\text{H,P}} = 20.8$  Hz, 1H);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.91.

Complete experimental and spectral details are available online in the Supplemental Material.

## ACKNOWLEDGMENTS

The authors are grateful for the financial support from the Scientific Research Project of the Department of Education of Liaoning Province of China (L2010048) and the Planned Science and Technology Project of Dalian (2011J21DW010).

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