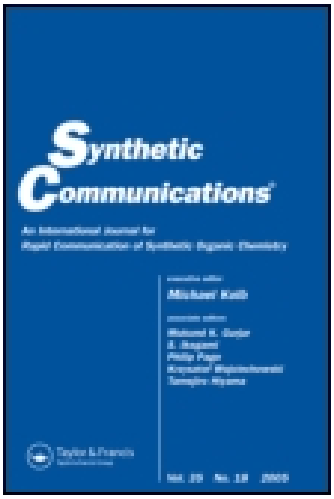

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Xiao-Ning Liu [a] , Wei-Lei Guo [a b] , Chuan-Jin Hou [a] & Xiang-Ping Hu [b]
[a] School of Light Industry and Chemical Enginerring, Dalian Polytechnic University , Dalian , China
[b] Dalian Institute of Chemical Physics, Chinese Academy of Sciences , Dalian , China
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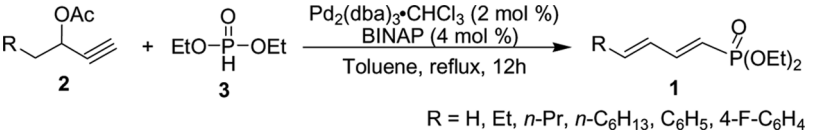
NEW AND EFFICIENT SYNTHESIS OF 1,3-DIENYLPHOSPHONATES BY PALLADIUM-CATALYZED SUBSTITUTION OF PROPARGYLIC ESTERS TO DIETHYL PHOSPHITE

Xiao-Ning Liu,[1] Wei-Lei Guo,[1,2] Chuan-Jin Hou,[1] and Xiang-Ping Hu[2]

[1]*School of Light Industry and Chemical Enginerring, Dalian Polytechnic University, Dalian, China*
[2]*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 $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %) and 2,2′-bis(diphenyl phosphino)-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.[1] 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,[2] [4 + 2] cycloaddition,[3] 1,3-dipolar cycloaddition,[4] 1,4-addition,[5] and enolate alkylation[6] reactions. They have also

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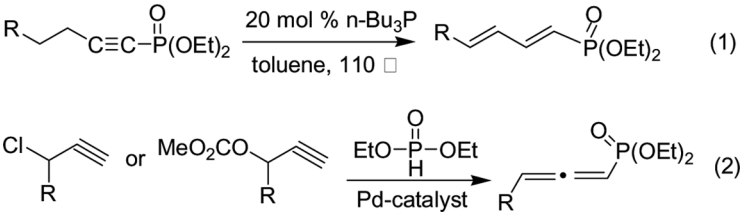
Address correspondence to Chuan-Jin Hou, School of Light Industry and Chemical Engineering, Dalian Polytechnic UniversityDalian, 116034, China. E-mail: houcj@dlpu.edu.cn; Xiang-Ping Hu, Dalian Institute of Chemical Physics, China Academy of Sciences, Dalian 116023, China. E-mail: xiangping@dicp.ac.cn



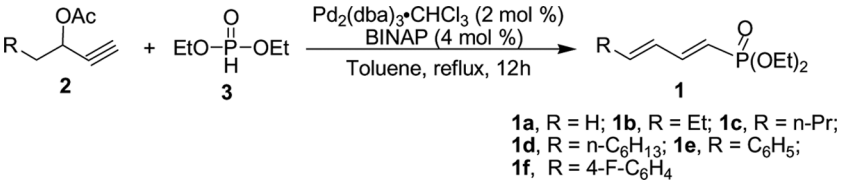
Scheme 1. Pd-catalyzed synthesis of 1,3-dienylphosphonates and allenylphosphonates.

been reported in the synthesis of biologically active products such as AP6 analogs[7] and *Fusarium* toxin equisetin.[8] 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.

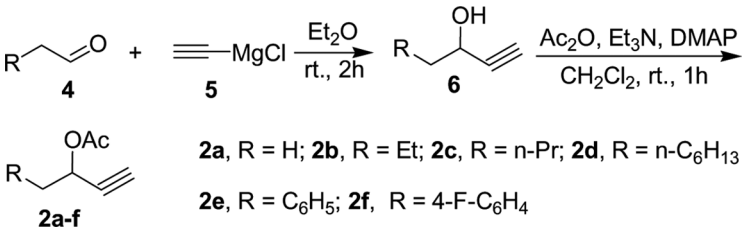
There are several reported methods for the synthesis of 1,3-dienylphosphonates including the reaction of unsaturated phosphonates with N-tolsylsufonylimines,[9] the titanium-mediated Knoevenagel condensation of conjugated aldehydes with diethyl malonate,[2] the Pd-catalyzed coupling reaction of unsaturated phosphonates with alkenes,[10] the Ni-catalyzed addition of P(O)-H bonds to propargyl alcohols,[11] and the alkyne insertion into zirocoacyclopropenes.[12] Notably, Ma et al.[13] and Azab et al.[14] 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.[15] 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,[16] 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	**2a**	**1a**	87
2	**2b**	**1b**	74
3	**2c**	**1c**	75
4	**2d**	**1d**	72
5	**2e**	**1e**	82
6	**2f**	**1f**	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 $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol%) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (4 mol %) in reflux toluene. Fortunately, the reaction proceed 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.[12,14] 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 $Pd_2(dba)_3 \cdot CHCl_3$ (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 N_2 atmosphere was added ethynylmagnesium chloride (50 mL, 0.6 M in THF) dropwise at room temeperature. The mixture was stirred for 2 h and then quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated to give the crude propargylic alcohol, which was used directly.

The crude propargylic alcohol was dissolved in dry CH_2Cl_2 (40 mL), and Et_3N (30 mmol) and DMAP (3 mmol) were added. Then Ac_2O (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 Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by chromatography on silica gel.

Compound **2b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 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

$Pd_2(dba)_3 \cdot CHCl_3$ (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 Et_3N (80 μL, 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}H NMR (400 MHz, $CDCl_3$): δ 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, $^3J_{H,H} = 17.2$ Hz, $^2J_{H,P} = 19.2$ Hz, 1H), 6.08–6.18 (m, 2H), 7.08 (ddd, $^3J_{H,H} = 16.8$ Hz, $^3J_{H,P} = 20.8$ Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.91.

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

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