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Catalyst-free synthesis of cycloalkenyl phosphonates†

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The reactions described provide a facile and efficient access to cycloalkenyl phosphonates with good to excellent yields *via* Diels–Alder cycloadditions between alkynyl phosphonates and 1,3-dienes under catalyst-free conditions.

Introduction

Among the compounds containing C–P bonds, vinyl phosphonates have attracted considerable attention as they are significant compounds in medicinal chemistry, flame retardants, agriculture, and as reagents in organic synthesis.[1] Cycloalkenyl phosphonates can be easily converted into arylphosphonates. In particular, the biaryl monophosphonates have evolved into highly efficient catalysts for C–N as well as C–C and C–O bond formation.[2] In principle, the Diels–Alder cycloaddition is the most valuable reaction for the construction of cycloalkenyl phosphonates.[3] Because of the low reactivity of alkynyl phosphonates, the synthesis of vinyl phosphonates by Diels–Alder reactions is rare.[4]

Recently, Tam's group had developed the ruthenium-catalyzed [2 + 2] and [2 + 2 + 2] cycloadditions between alkynyl phosphonates and bicyclic alkenes to obtain cycloalkenyl phosphonates in good yield.[4,5] The reaction required high temperature and long time. In 2008 Tverdomed's group reported the Diels–Alder [2 + 4] reaction of classical alka-1,3-diene with tetraethyl acetylene bisphosphonate.[6] The reaction was conducted in a sealed ampoule with diene as a solvent and 1,4-hydroquinone as a polymerization inhibitor at 140–145 °C under nitrogen for 5 h. In the same year, they developed a new methodology for synthesis 1,2-perfluoroalkyl vinylphosphonates, based on the Diels–Alder reactions of perfluoroacetylenephosphonates with different dienes.[7] However, these synthetic methods have limited scope. Our continued interest in the reactivity of alkynyl phosphonates[8] and P–C bond formations[9] recently prompted us to explore a more atom-economical and functional group tolerance method for the synthesis of cycloalkenyl phosphonates.

Results and discussion

At the beginning of this study, the alkynyl phosphonates were synthesized. There are various methods for the synthesis of alkynyl phosphonates.[10] It was found that the method developed by Gao and co-workers was the simplest and most applicable.[11] However, some of the alkynyl phosphonates can not be synthesized by this method. Diphenyl alkynyl phosphonates were synthesized by the method developed by Oh and co-workers.[12]

After the alkynyl phosphonates were synthesized, a series of catalysts and temperatures were screened for their ability to promote the Diels–Alder cycloaddition (Table 1). Diethyl (phenylethynyl)phosphonate (**1a**), and cyclopenta-1,3-diene (**2a**) were used as the substrates in these studies. The yield of cycloalkenyl phosphonates **3a** was determined based on the ^{31}P NMR signal-integration method. Recently, the Pb and Cu catalysis of Diels–Alder reactions has received much attention.[13,14] When we added $Pd(OAc)_2$, $PdCl_2$, CuI, $Cu(OTf)_2$, or I_2, as catalysts, there was no evidence of any reaction observed (entries 1–5). However, when a mixture of **1a** (0.5 mmol) and **2a** (1.0 mL) was heated in a sealed tube (15 mL) without any catalysts at 110 °C, **3a** was obtained in 48% yield (^{31}P NMR: δ = 17.6 ppm). When the temperature was raised to 120 °C, the reaction gave **3a** in 96% yield (entry 7). However, when the temperature was raised to 140 °C, the yield of product **3a** decreased greatly because of the polymerization. Two common Lewis acids, $AlCl_3$ and CuCl, were less effective for the Diels–Alder cycloaddition (entries 9 and 10).

As demonstrated in Table 2, a variety of substrates were surveyed to explore the scope and limitations of the reaction. First, phosphonates containing different functional groups were investigated. Diethyl, dimethyl, diisopropyl, dibutyl, and dibenzyl alkynyl phosphonate all could be used as substrates, generating

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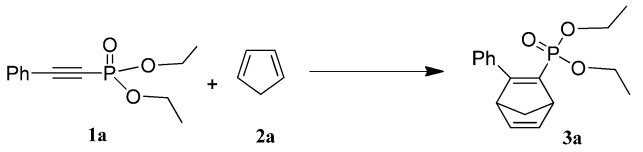
Table 1 Reaction conditions optimization[a]



Entry	Catalyst	Solvent	T/°C	Yield[b] (%)
1	$Pd(OAc)_2$	Cp	Reflux	0
2	$PdCl_2$	Cp	Reflux	0
3	$Cu(OTf)_2$	Cp	Reflux	0
4	CuI	Cp	Reflux	0
5	I_2	Cp	Reflux	0
6[c]		Cp	110	50
7[c]		Cp	120	96
8[c]		Cp	140	67
9[c]	$AlCl_3$	Cp	120	30
10[c]	CuCl	Cp	120	32

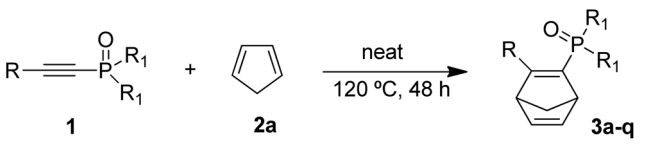
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mL), catalyst (0.05 mmol), 48 h, Ar atmosphere in a 5 mL round-bottom flask equipped with an Allihn condenser. [b] Yields were determined by ^{31}P NMR. [c] Heated in a sealed tube.

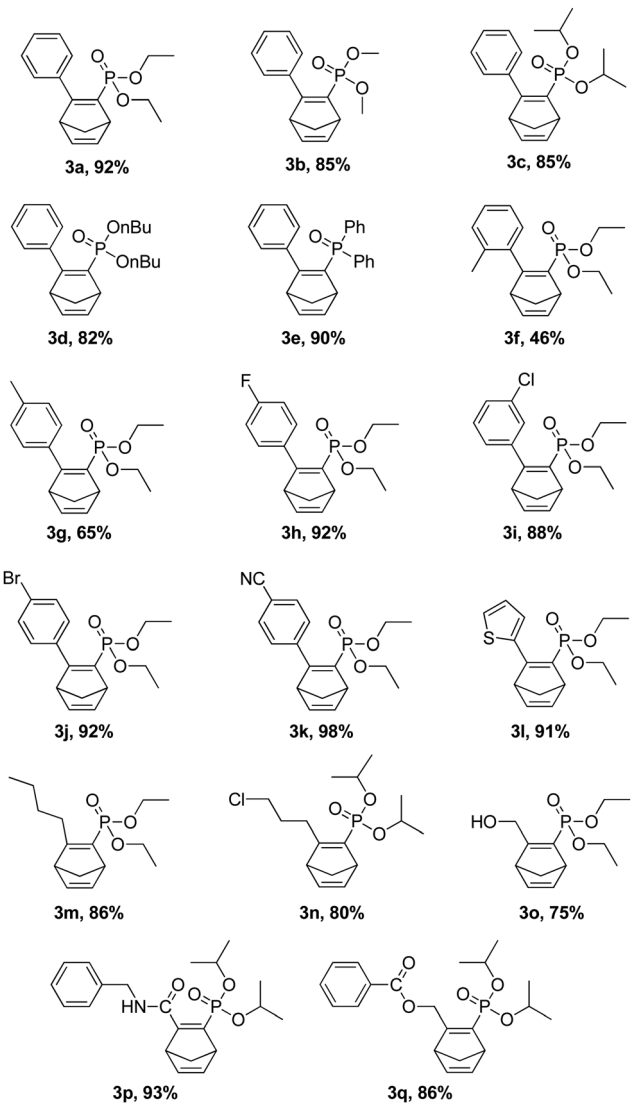
the corresponding products (**3a–3e**) in 92%, 85%, 85%, 82% and 90%. When comparing the substitutions of a methyl group in either the *ortho* or *para* positions on the phenyl ring, we discovered that steric hindrance reduce reactivity of the alkyne. Substitution the *para* position produced **3g** in 65% yield, and an *ortho* methyl group yielded only 46% isolated product **3f**. In addition, this reaction is also compatible with halogen substituents on the aromatic ring of phenylethynyl phosphonate. Thus 4-fluoro-, 3-chloro-, and 4-bromo phenylethynyl phosphonate reacted with cyclopenta-1,3-diene to give products **3h–3j** in 92%, 88% and 92% yields, respectively. Excellent yield of 98% was achieved with 4-cyano-substituted phenylethynyl phosphonate (**3k**). It seems that the electron-withdrawing group has a better reactivity than the electron-donating group. This view was confirmed that the electron-rich 2-thiophene moiety **3l** gave the high yield in the cycloaddition reaction and 4-methoxy phenylethynyl phosphonate did not work. With a number of aromatic substituted alkynyl phosphonates found to be compatible with the optimized reaction conditions, a variety of aliphatic substrates with chloro, hydroxyl, ester, amide group were investigated to further expand the scope of the reaction; relative products (**3m–3q**) were obtained in good to high yields (75–93%).

We next turned to the scope of diene used for the Diels–Alder cycloaddition reaction (Scheme 1). Interesting, when phenylethynyl phosphonate reacted with cyclohexa-1,3-diene, we acquired the product **3r** (85%) with ethylene elimination and formation of the aromatic compound. To our satisfaction, Acyclic diene such as 2,3-dimethylbuta-1,3-diene, is also suitable substrates for this cycloaddition. The Diels–Alder cycloadduct **3s** was obtained in 78% yield. Furan and thiophene were also examined. Unfortunately, no products have been obtained.

To probe the utility of the synthesis of cycloalkenyl phosphonates method further, the experimental for multigram-scale

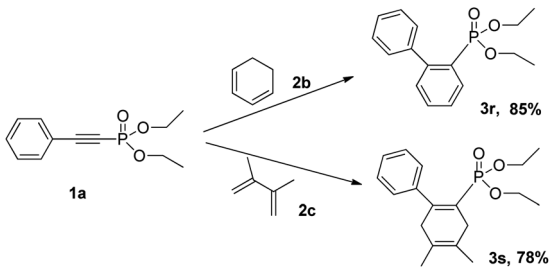
Table 2 Preparation of cycloalkenyl phosphonates from alkynyl phosphonates and cyclopenta-1,3-diene[a]





[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mL), 120 °C, 48 h in a sealed tube. [b] Isolated yields.

reaction of diethyl (phenylethynyl)phosphonate (**1a**) and cyclopenta-1,3-diene (**2a**) was carried out. A mixture of 10 mmol of diethyl (phenylethynyl)phosphonate (**1a**), 15 mL of cyclopenta-1,3-diene (**2a**) in 50 mL sealed Schlenk tube was stirred under an atmosphere of argon at 120 °C for 48 h. After the reaction completed, the reaction solution was monitored by ^{31}P NMR as shown in Fig. 1.[15] The peak at 15.7 ppm represents the product **3a** (89%, yields determined by ^{31}P NMR spectrocopy). The byproduct **3aa** at 15.4 ppm was formed from the reaction of **3a**



Scheme 1 Cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene were used for the Diels–Alder cycloaddition reaction.

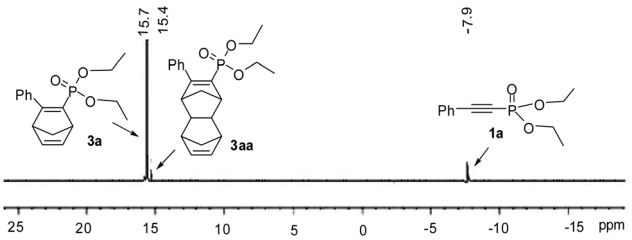


Fig. 1 ^{31}P NMR spectra for the reaction of cyclohexa-1,3-diene with diethyl (phenylethynyl)phosphonate (10 mmol).

with the excess cyclopenta-1,3-diene in 3% yield, which was proved by ESI-MS (see ESI†). The raw material diethyl (phenylethynyl)phosphonate (**1a**) at −7.9 ppm, only 8% left. The unreacted cyclopenta-1,3-diene (**2a**) could be removed by distillation at atmospheric pressure, and product cycloalkenyl phosphonates **3a** was obtained in 79% yield by distillation under reduced pressure (b.p. 113–117 °C, 6 mmHg).

Conclusions

In summary, we have successfully developed a simple and highly efficient method for the synthesis of cycloalkenyl phosphonates by the cycloaddition of alkynyl phosphonates to dienes in the absence of catalyst. Moreover, the alkynyl phosphonates used are readily available from terminal alkynes and P(O)H compounds. The high atom-economy, the remarkable functional group tolerance and operational simplicity of the procedure mean that this reaction will find wide applications in various fields.

Experimental

All reactions were carried out under an atmosphere of dry argon. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR (160 MHz) spectra were measured on Bruker 400M spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the ^1H spectrum as 0.00 ppm and $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (J values) were reported in Hertz (Hz). Chemical shifts of common trace ^1H NMR impurities (ppm): H_2O: 1.56, $CHCl_3$: 7.26. Chemical shifts for ^{31}P NMR spectra are reported in parts per million (ppm) from phosphoric acid with trimethylphosphite as the external standard (trimethylphosphite: $\delta = 141.0$ ppm). Column chromatography was performed on basic alumina gel 200–300 mesh using petroleum ether and ethyl acetate as the eluent.

General procedure for the synthesis of 3a

An oven-dried Schlenk tube was evacuated and purged with argon three times. A mixture of 0.5 mmol of diethyl (phenylethynyl)phosphonate (**1a**), 1.0 mL of cyclopenta-1,3-diene (**2a**) were sequentially added at room temperature. The reaction mixture was heated with stirring at 120 °C for 48 h.

The reaction mixture was allowed to cool to ambient temperature, and then transferred to a round-bottom flask. Silica gel (2.0 g) was added, and cyclopenta-1,3-diene left was removed under reduced pressure to afford a free-flowing powder. This powder was then dry-loaded onto a silica gel column and purified by flash chromatography using petroleum–AcOEt (2 : 1, v/v) as the eluent to give **3a**. A number of products were synthesized according to this procedure.

Acknowledgements

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