JOC The Journal of Organic Chemistry

Article

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Base-Free Direct Synthesis of Alkynylphosphonates from Alkynes and *H*-Phosphonates Catalyzed by Cu_2O

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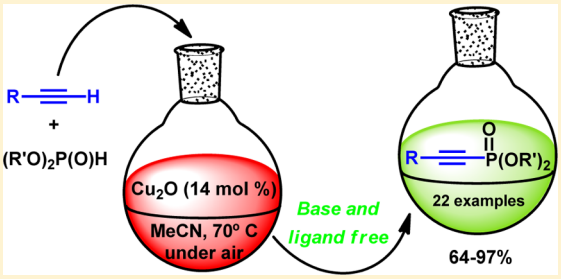
Supporting Information

ABSTRACT: A simple and mild methodology for the direct synthesis of alkynylphosphonates is presented. The reaction of a variety of terminal alkynes with dialkyl phosphites in the presence Cu_2O (14 mol %) led to the formation of the corresponding alkynylphosphonates in good to excellent yields. Reactions are performed under air, in acetonitrile as solvent, and in the absence of base or ligand additives. This new methodology is compatible with the presence of a wide variety of functional groups on the starting alkynes and can be scaled up to a gram scale.



INTRODUCTION

Alkynylphosphonates are one of the most valuable phosphorus derivatives in synthetic organic chemistry. The increasing interest in these compounds is mainly related to the wide presence of the phosphonic functionality (acid or ester) in many natural or synthetic bioactive compounds.[1] On the other hand, the carbon−carbon triple bond provides great synthetic versatility to these phosphorus derivatives, allowing a variety of subsequent structural modifications such as addition or cycloaddition reactions,[2] including "click" reactions for the synthesis of triazolyl-functionalized phosphonates with distinct biological activity.[3]

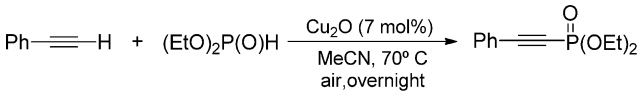
Traditional synthesis of alkynylphosphonates, by reacting $(RO)_2P(O)Cl$ as phosphorus electrophiles with Li or Mg acetylides,[4] suffers from several drawbacks such as the use of air- and humidity-sensitive chemicals, and lack of functional group tolerance. Consequently, alternative methods have been developed in recent years, most of them based on the use of transition-metal catalysts. Many of the reported methodologies require the use of functionalized starting alkenes or alkynes, including 1,1-dibromoalkenes,[5] propiolic acids,[6] metal acetylides,[7] alkynyl sulfones,[8] trialkylsilyl alkynes,[9] and 4-aryl-2-methyl-3-butyn-2-ols.[10] For technical and economic reasons, the direct synthesis of alkynylphosphonates from commercial or readily available starting alkynes is the most attractive way for the synthesis of these phosphorus compounds. In this regard, only two general direct synthetic methods have been published so far. In 2009, Han et al.[11] reported an efficient procedure based on copper-catalyzed oxidative coupling of terminal alkynes and dialkyl phosphites, by using CuI as copper source and DMSO as solvent, under dry air. It is noteworthy that the use of MeCN, THF, dioxane, CH_2Cl_2, or toluene as solvent only produced trace amounts of the desired product. The proposed reaction mechanism involves the formation of copper acetylide species, so the use of a base is mandatory for the deprotonation of the starting alkyne. In 2011, Wang and co-workers[12] reported the direct synthesis of alkynylphosphonates by using a silica-supported carbene-Cu(II) catalyst. Even though the synthesis of the catalyst is not straightforward, the process is base-free, but the catalyst could be recovered and reused. Here again, the choice of the reaction solvent was crucial for the cross-coupling to take place. Thus, the use of solvents different from DMSO (DMF, THF, toluene, CH_3OH) gave no reaction product. Very recently, the group of Han reported a Pd(II)/Ag(I)-mediated method for the dehydrogenative coupling of terminal alkynes with different P(O)-H compounds,[13] but only one example for the synthesis of an alkynyl phosphonate was reported.

Owing to our recent interest in phosphorus chemistry,[14] we have recently reported our findings on the direct synthesis of β-ketophosphonates and vinylphosphonates from alkynes or alkenes catalyzed by copper nanoparticles supported on ZnO.[14c] In the course of further studies aimed at exploring other synthetically useful applications of this methodology, we found that commercial Cu_2O was able to catalyze the direct cross-coupling between phenylacetylene and $HP(O)(OEt)_2$, leading to the corresponding alkynylphosphonate product in good yield, together with minor amounts of 1,4-diphenyl-1,3-butadiyne coming from the homocoupling of the starting alkyne (Glaser dimerization). The reaction was performed in the presence of 7 mol % of Cu_2O, in MeCN as solvent, under air, and in the absence of any base additive or ligand (Scheme 1).

Received: November 3, 2015
Published: February 3, 2016

DOI: 10.1021/acs.joc.5b02528
J. Org. Chem. 2016, 81, 1813−1818

Scheme 1. Cu_2O-Catalyzed Cross-Coupling of Phenylacetylene with Diethyl Phosphite

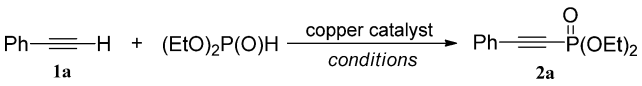


We want to present herein a new simple and mild protocol for the direct synthesis of alkynylphosphonates from terminal alkynes and dialkyl phosphites catalyzed by copper(I) oxide.

RESULTS AND DISCUSSION

We started our study by optimizing the reaction conditions, using phenylacetylene (**1a**) as model substrate. Thus, the alkyne (0.5 mmol) was added to a brownish-red suspension of $HP(O)(OEt)_2$ (0.7 mmol) and Cu_2O (5 mg, 0.035 mmol) in MeCN (2 mL), and the mixture was stirred at 70 °C overnight under air. The reaction mixture turned to a clear pale-green solution and, after chromatographic purification, gave the alkynylphosphonate **2a** in 77% yield, together with 15% of 1,4-diphenyl-1,3-butadiyne and minor amounts of $(EtO)_2P(O)OH$ and $[(EtO)_2P(O)]_2O$. As shown in Table 1, the choice of the solvent demonstrated to be important for the cross-coupling reaction but not as crucial as for the methodologies previously reported by Han and Wang.[11,12] Thus, the use of polar protic solvents such as H_2O or CH_3OH gave no conversion to the desired alkynylphosphonate, whereas the use of DMSO or THF led to the corresponding cross-coupling product (Table 1, entries 2–5), albeit in significantly lower yield compared to that obtained by using MeCN as solvent.

Table 1. Screening of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]
1	Cu_2O	MeCN	77 (86)[c]
2	Cu_2O	H_2O	
3	Cu_2O	CH_3OH	
4	Cu_2O	DMSO	53
5	Cu_2O	THF	32
6	Cu_2O	MeCN	55[d]
7	CuCl	MeCN	
8	$CuCl_2$	MeCN	
9	CuI	MeCN	
10	CuO	MeCN	38

[a]Standard reaction conditions: phenylacetylene (0.5 mmol) added to a suspension of diethyl phosphite (0.7 mmol) and the copper catalyst (7 mol %, referred to the starting alkyne) in 2 mL of solvent, stirred overnight at 70 °C, under an air atmosphere. [b]Determined by GC using internal standard. [c]Reaction performed using 14 mol % Cu_2O. [d]Reaction performed under a N_2 atmosphere.

As expected, the reaction carried out under a nitrogen atmosphere allowed us to minimize the formation of the diyne byproduct, but the conversion to the desired alkynylphosphonate was lower than that obtained by working under air (Table 1, entry 6). Different copper sources were then tested as catalysts. As shown in Table 1 (entries 7–10), CuCl, $CuCl_2$, and CuI failed in catalyzing the cross-coupling reaction, whereas CuO gave only 38% of conversion into the alkynylphosphonate product. We then optimized the catalyst loading and found that, by doubling the amount of Cu_2O (10 mg, 14 mol %), the reaction yield was increased from 77% to 86% (Table 1, entry 1). A further increase in the amount of Cu_2O did not improve the reaction yield. Then, the influence of the order of addition of reactants was studied. Thus, when the synthesis of **2a** was carried out by adding diethyl phosphite to a suspension of **1a** and Cu_2O in MeCN, only 57% conversion into **2a** was obtained.

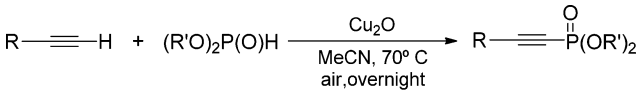
With the optimized conditions in hand, we then studied the substrate scope of our methodology by reacting a wide range of alkynes bearing different functional groups. As shown in Table 2, the Cu_2O-catalyzed cross-coupling reaction proved to be compatible with the presence of a great variety of functional groups in the starting alkyne. Aromatic substrates gave the corresponding alkynylphosphonate products in good to excellent yields, irrespective of the electronic properties of the substituents attached to the aromatic ring (Table 2, entries 2–7). Aliphatic alkynes, including those substituted with other functional groups (halogen, nitrile, hydroxyl, ketal, imide), also gave the desired alkynylphosphonate products in good yields (Table 2, entries 8–13, 19). It is worth noting that the reaction of 1,8-nonadiyne with an excess of $HP(O)(OEt)_2$ gave 68% of the corresponding monophosphonated product (Table 2, entry 14). Except for alkynes containing carboxylic acids or primary amino groups, which gave no coupling products, our methodology could be also applied to ynones, propiolates, and enynes (Table 2, entries 15–18). Interestingly, ethynylestradiol could be converted into its alkynylphosphonate analogue in good yield (Table 2, entry 20). On the other hand, dibutyl and dimethyl phosphite could also be used as starting *H*-phosphonates, giving the corresponding alkynylphosphonates in good yield (Table 2, entry 1). Unfortunately, the methodology could not be extended to the synthesis of other alkynyl phosphorus derivatives such as alkynylphosphine oxides and alkynylphosphonites. The reaction of diphenylphosphine oxide with phenylacetylene under the optimized conditions led to a low conversion of the starting alkyne (30%), giving minor amounts of the corresponding alkynylphosphine oxide (8%), together with a mixture of diphenylvinylphosphine oxide products, probably coming from the hydrophosphorylation of phenylacetylene. On the other hand, the reaction of dibutylphosphonite with phenylacetylene gave no conversion of the starting alkyne.

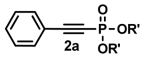
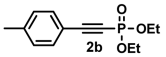
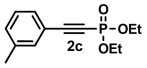
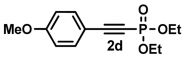
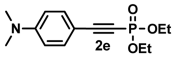
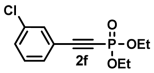
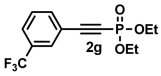
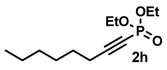
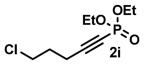
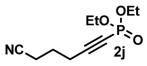
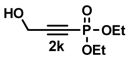
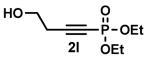
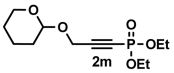
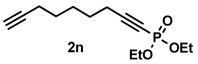
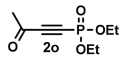
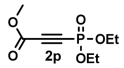
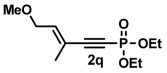
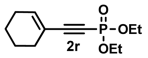
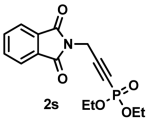
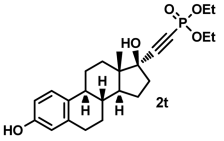
Taking into account that gram-scale synthesis of alkynylphosphonates could surely be of interest in various fields of application, we decided to study whether our methodology could be scaled up. Thus, the synthesis of alkynylphosphonate **2a** (R′ = Et) was carried out by using a 12-fold amount of the reactants, giving the corresponding cross-coupling product in 75% yield (1.07 g) after 24 h of reaction time (Table 2, entry 1, footnote *c*).

Although the exact mechanistic pathway is difficult to ascertain at this stage, the fact that the cross-coupling reaction takes place in the absence of any added base led us to think about a plausible reaction mechanism different from that proposed by Han et al.;[11] i.e., copper acetylide species should not be the main reaction intermediates under our reaction conditions. Moreover, it is striking to note that Han and coworkers also tested Cu_2O as catalyst, and a conversion of only 7% to the cross-coupling product was observed. This could indicate that the formation of a copper acetylide is negligible in the presence of Cu_2O and DMSO as solvent, even when K_2CO_3 is being used as base.

DOI: 10.1021/acs.joc.5b02528
J. Org. Chem. 2016, 81, 1813–1818

Table 2. Cu_2O-Catalyzed Direct Synthesis of Alkynylphosphonates[a]



Entry	Product	Yield (%)[b]
1		R' = Et: 86[c] R' = Me: 90 R' = Bu: 83
2		89
3		70
4		88
5		90
6		94
7		84
8		92
9		97
10		80
11		64
12		72
13		79
14		68
15		95
16		97
17		95
18		93
19		88
20		79

[a]Reaction conditions: alkyne (0.5 mmol) added to a suspension of *H*-phosphonate (0.7 mmol) and Cu_2O (14 mol %) in MeCN (2 mL), stirred overnight at 70 °C under air. [b]Isolated yield after column chromatography. [c]Scaled up synthesis of **2a** (R = Et): phenylacetylene (6 mmol), $(EtO)_2P(O)H$ (8.4 mmol), Cu_2O (14 mol %) in MeCN (20 mL), 24 h, 75% yield.

To confirm our assumptions, we carried out some additional experiments. Initially, the reaction by using copper phenylacetylide as starting material, in both the presence or the absence of Cu_2O, gave no conversion into the alkynylphosphonate **2a**. In another experiment, when 1-octyne was reacted with diethyl phosphite under the optimized conditions, in the presence of K_2CO_3 or Et_3N as base, a notably lower conversion to the alkynyl phosphonate **2h** was obtained (25% and 40%, respectively) compared to that of the reaction performed in the absence of any added base (92%, Table 2, entry 8). Finally, the synthesis of **2a** (R′ = Et) under the optimized conditions was not affected by the addition of TEMPO as radical scavenger.

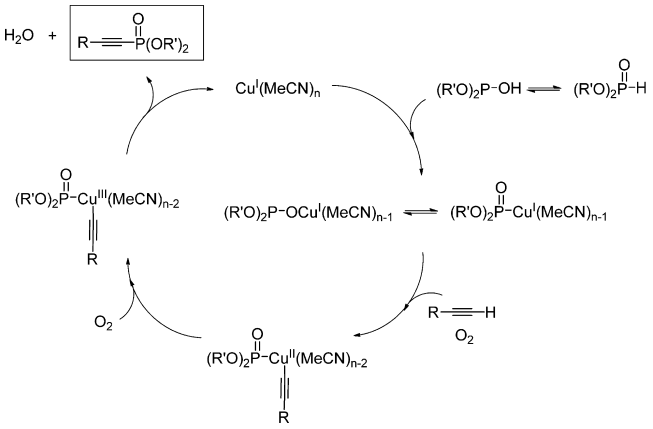
In the light of our experimental results, and those previously reported by Han and co-workers,[11] it could be inferred that the cross-coupling reaction might take place through different pathways depending on both the source of copper and the solvent used. Moreover, the experimental results observed when using different solvents for the coupling reaction (Table 1) could be related to the ability of the solvent to act as a ligand for copper, thus possibly favoring an oxidative addition−reductive elimination process under our reaction conditions. Even though the specific oxidation states and structures of the copper intermediates remain unclear, we speculate that a Cu(I)/Cu(III) redox couple is required since the efficiency of the reaction decreased in the absence of oxygen.[15] On the basis of these premises, a reaction mechanism has been proposed including (a) copper activation by the solvent to form MeCN-Cu(I) species, (b) reaction of Cu(I) with the dialkyl phosphite leading to copper(I) dialkyl phosphite, (c) reaction of the latter with the terminal alkyne in the presence of oxygen to provide a Cu(II) intermediate, (d) oxidation of copper(II) to copper(III), and (e) subsequent reductive elimination[16] to produce the alkynyl phosphonate with the concomitant regeneration of copper(I) (Scheme 2).

■ CONCLUSION

In conclusion, we have described a one-pot methodology for the base-free direct synthesis of alkynylphosphonates from commercial or readily available terminal alkynes, catalyzed by Cu_2O under an air atmosphere. The new methodology showed

DOI: 10.1021/acs.joc.5b02528
J. Org. Chem. 2016, 81, 1813−1818

Scheme 2. Proposed Reaction Pathway



to be compatible with a wide variety of functional groups in the starting alkynes and could be scaled up to a gram scale. Although the exact mechanistic pathway remained to be studied more in detail, based on our experimental observations and previous results reported by other authors, we assume that an oxidative addition−reductive elimination process could take place under our reaction conditions. This new methodology is simple and efficient and allows the direct synthesis of alkynylphosphonates with high atom economy. Further mechanistic studies, including computational analysis using DFT, are now in progress.

EXPERIMENTAL SECTION

General. All starting materials were of the best available grade and were used without further purification. Column chromatography was performed using silica gel 60 (0.040−0.063 μm, 240−400 mesh). Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% $KMnO_4$ in water.

Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR, and 121 MHz for ^{31}P MNR, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; brs = broad signal). Coupling constants (J) were reported in Hz.

Mass spectra (EI) were obtained at 70 eV on a GC/MS instrument equipped with a selective mass detector. Infrared (FT-IR) spectra were obtained on a spectrophotometer equipped with an ATR component. Melting points are uncorrected. The purity of volatile compounds and the chromatographic analyses (GC) were determined with an instrument equipped with a flame-ionization detector and a 30 m column (0.25 mm, 0.25 μm), using nitrogen as carrier gas. High-resolution mass spectra were recorded on a spectrometer equipped with an Orbitrap XL mass analyzer, (for EI) and a MAT 95 (for ESI).

General Procedure for the Synthesis of Alkynylphosphonates 2. The dialkyl phosphite (0.7 mmol) was added to a brownish-red suspension suspension of Cu_2O (10 mg, 0.07 mmol) in acetonitrile (2 mL). Then, the corresponding alkyne (0.5 mmol) was added and the reaction mixture was warmed to 70 °C and stirred overnight under air. The reaction mixture turned a pale-green clear solution. The solvent was evaporated in vacuo, and the crude product was purified by flash column chromatography (silica gel, hexane/AcOEt).

Gram-Scale Synthesis of Diethyl (Phenylethynyl)-phosphonate. Diethyl phosphite (8.4 mmol, 1082 μL) was added to a suspension of the Cu_2O (60 mg, 14 mol %) in MeCN (20 mL). Then, phenylacetylene (6.0 mmol, 660 μL) was added and the reaction mixture was warmed to 70 °C overnight under an air atmosphere. The solvent was removed in vacuo, and the product was purified by flash column chromatography (hexane−EtOAc, 4:6) to give diethyl (phenylethynyl)phosphonate in 75% yield (1.07 g).

Compound Characterization Data. All known compounds were characterized by comparison of their physical and spectroscopic data with those described in the literature. For new compounds, copies of ^{1}H, ^{13}C, and ^{31}P NMR graphical spectra are also provided (see the Supporting Information).

*Diethyl (Phenylethynyl)phosphonate (**2a**, R = Et).*[17] Yellow oil. 102.4 mg, 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.53 (m, 2H), 7.49−7.33 (m, 3H), 4.31−4.17 (m, 4H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7 (d, J = 2.5 Hz), 130.8, 128.7, 119.7 (d, J = 5.7 Hz), 99.2 (d, J = 53.0 Hz), 78.5 (d, J = 300.0 Hz), 63.4 (d, J = 5.5 Hz), 16.2 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.9 ppm.

*Dimethyl (Phenylethynyl)phosphonate (**2a**, R = Me).*[18] Colorless oil. 87.2 mg, 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.48 (m, 2H), 7.44−7.28 (m, 3H), 3.79 (d, J = 12.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8 (d, J = 2.5 Hz), 131.0, 128.7, 119.4 (d, J = 5.7 Hz), 100.2 (d, J = 53.4 Hz), 76.9 (d, J = 303.3 Hz), 53.6 (d, J = 5.5 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −2.7 ppm.

*Dibutyl (Phenylethynyl)phosphonate (**2a**, R = Bu).*[19] Colorless oil. 132.4 mg, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.53 (m, 2H), 7.50−7.42 (m, 1H), 7.40−7.34 (m, 2H), 4.21−4.12 (m, 4H), 1.79−1.67 (m, 4H), 1.53−1.39 (m, 4H), 0.95 (d, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8 (d, J = 2.5 Hz), 130.8, 128.7, 119.8 (d, J = 5.6 Hz), 99.2 (d, J = 52.7 Hz), 78.5 (d, J = 299.5 Hz), 67.1 (d, J = 5.9 Hz), 32.4 (d, J = 7.1 Hz), 18.9, 13.7. ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.56 ppm.

*Diethyl (p-Methylphenyl)ethynyl Phosphonate (**2b**).*[17] Pale yellow oil. 112.2 mg, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 4.26−4.16 (m, 4H), 2.36 (s, 3H), 1.39 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 132.5 (d, J = 2.5 Hz), 129.3, 116.4 (d, J = 5.6 Hz), 99.6 (d, J = 53.3 Hz), 77.7 (d, J = 301.1 Hz), 63.2 (d, J = 5.5 Hz), 21.6, 16.1 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5,7 ppm.

*Diethyl (m-Tolylethynyl)phosphonate (**2c**).*[20] Yellow oil. 88.2 mg, 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.33 (m, 2H), 7.30−7.22 (m, 2H), 4.30−4.17 (m, 4H), 2.35 (s, 3H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 133.2 (d, J = 2.5 Hz), 131.7, 129.9 (d, J = 2.5 Hz), 128.6, 119.4 (d, J = 5.6 Hz), 99.6 (d, J = 53.1 Hz), 78.0 (d, J = 300.7 Hz), 63.4 (d, J = 5.5 Hz), 21.2, 16.2 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.9 ppm.

*Diethyl (4-Methoxyphenyl)ethynylphosphonate (**2d**).*[17] Yellow oil. 118.0 mg, 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 4.22−4.09 (m, 4H), 3.77 (s, 3H), 1.34 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 134.4 (d, J = 2.5 Hz), 114.3, 111.3 (d, J = 5.7 Hz), 99.8 (d, J = 53.9 Hz), 77.1 (d, J = 302.3 Hz), 63.1 (d, J = 5.5 Hz), 55.4, 16.1 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.5 ppm.

*Diethyl (4-Dimethylaminophenyl)ethynylphosphonate (**2e**).*[17] Maroon oil. 126.5 mg, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.9 Hz, 2H), 4.20−4.07 (m, 4H), 2.94 (s, 6H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 134.2 (d, J = 2.5 Hz), 111.5, 105.3 (d, J = 5.9 Hz), 102.3 (d, J = 54.7 Hz), 76.4 (d, J = 305.1 Hz), 63.0 (d, J = 5.4 Hz), 40.1, 16.3 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.5 ppm.

*Diethyl (3-Chlorophenyl)ethynylphosphonate (**2f**).* Pale yellow oil. 127.9 mg, 94% yield. IR (neat): 2990, 2933, 2904, 2197, 1564, 1474, 1274, 1021, 976, 902, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.47−7.37 (m, 2H), 7.35−7.26 (m, 1H), 4.26−4.16 (m, 4H), 1.39 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 132.4 (d, J = 2.6 Hz), 131.1, 130.8 (d, J = 2.4 Hz), 130.0, 121.4 (d, J = 5.7 Hz), 97.1 (d, J = 52.5 Hz), 79.7 (d, J = 298.0 Hz), 63.5 (d, J = 5.6 Hz), 16.2 (d, J = 6.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.7 ppm. MS: m/z = 272 (M^+, 5%), 244 (11), 229 (12), 216 (15), 209 (10), 201 (11), 199 (25), 165 (14), 164 (13), 163 (27), 162 (28), 155 (10), 154 (11), 145 (13), 139 (18), 138 (40), 137 (15), 136 (100), 129 (11),

DOI: 10.1021/acs.joc.5b02528
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128 (12), 123 (19), 107 (12), 101 (13), 89 (14), 75 (11). HRMS (EI) calcd for $C_{12}H_{14}ClO_3P$ 272.0369, found 272.0374.

*Diethyl (3-Trifluoromethylphenyl)ethynylphosphonate (**2g**).* Pale yellow oil. 128.5 mg, 84% yield. IR (neat): 2990, 2937, 2908, 2197, 1319, 1270, 1139, 1029, 874, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74−7.64 (m, 2H), 7.58−7.49 (m, 2H), 4.29−4.13 (m, 4H), 1.37 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2 (d, J = 2.7 Hz), 132.7 (qd, J = 31.1, 1.7 Hz), 131.8, 130.6, 126.2 (q, J = 5.0 Hz), 123.1 (q, J = 273.6 Hz), 117.9−117.7 (m), 94.1 (d, J = 51.8 Hz), 83.8 (d, J = 293.0 Hz), 63.6 (d, J = 5.7 Hz), 16.1 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −7.3 ppm. MS: m/z = 306 (M^+, 3%), 286 (14), 279 (11), 278 (18), 277 (11), 250 (26), 248 (17), 239 (10), 238 (34), 237 (10), 233 (12), 214 (10), 213 (33), 211 (35), 210 (13), 209 (17), 197 (25), 196 (16), 186 (16), 185 (51), 177 (39), 174 (11), 171 (11), 170 (100), 169 (45), 159 (10), 158(12), 157 (38), 155(17), 151 (45), 138 (35), 137 (11), 128 (13), 120 (10), 119 (10), 116 (13), 99 (10), 88 (10). HRMS (EI) calcd for $C_{13}H_{14}F_3O_3P$ 306.0633, found 306.0638.

*Diethyl Oct-1-yn-1-ylphosphonate (**2h**).*[21] Yellow oil. 113.2 mg, 92% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.21−4.08 (m, 4H), 2.34 (td, J = 7.1, 4.4 Hz, 2H), 1.65−1.52 (m, 2H), 1.43−1.25 (m, 6H), 1.37 (t, J = 7.1 Hz, 6H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.4 (d, J = 53.2 Hz), 70.5 (d, J = 303.9 Hz), 63.0 (d, J = 5.5 Hz), 31.2, 28.5, 27.5 (d, J = 2.2 Hz), 22.5, 19.3 (d, J = 4.5 Hz), 16.1 (d, J = 7.1 Hz), 14.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.1 ppm.

*Diethyl (5-Chloropent-1-yn-1-yl)phosphonate (**2i**).* Colorless oil. 115.5 mg, 97% yield. IR (neat): 2986, 2929, 2904, 2206, 1262, 1160, 1029, 972, 800, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.24−4.07 (m, 4H), 3.65 (t, J = 6.2 Hz, 2H), 2.57 (td, J = 6.9, 4.4 Hz, 2H), 2.10−2.02 (m, 2H), 1.37 (t, J = 7.1 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 100.9 (d, J = 53.0 Hz), 71.6 (d, J = 302.4 Hz), 63.2 (d, J = 5.5 Hz), 43.2, 30.2 (d, J = 2.3 Hz), 16.7 (d, J = 4.6 Hz), 16.1 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.7 ppm. MS: m/z = 238 (M^+, 1%), 185 (10), 183 (33), 176 (33), 175 (23), 165 (10), 161 (10), 149 (12), 148 (100), 147 (46), 133 (10), 129 (16), 120 (14), 93 (21), 91 (10), 83 (10), 81 (11), 66 (11), 65 (45). HRMS (EI) calcd for $C_9H_{16}ClO_3P$ 238.0526, found 238.0531.

*Diethyl (5-Cyanopent-1-yn-1-yl)phosphonate (**2j**).* Pale yellow oil. 91.6 mg, 80% yield. IR (neat): 2978, 2929, 2896, 2242, 2210, 1254, 1041, 967 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.19−4.06 (m, 4H), 2.57−2.42 (m, 4H), 1.99−1.86 (m, 2H), 1.34 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.5, 99.5 (d, J = 52.7 Hz), 72.6 (d, J = 301.5 Hz), 63.3 (d, J = 5.6 Hz), 23.5 (d, J = 2.4 Hz), 18.3 (d, J = 4.5 Hz), 16.2 (d, J = 7.2 Hz), 16.1 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −7.1 ppm. MS: m/z = 229 (M^+, 1%), 185 (11), 183 (100), 157 (14), 156 (36), 155 (21), 144 (47), 143 (98), 142 (30), 131 (17), 130 (52), 129 (21), 128 (20), 127 (21), 118 (16), 117 (62), 116 (60), 115 (99), 104 (55), 103 (76), 102 (24), 91 (53), 90 (19), 89 (63), 78 (27), 77 (68), 76 (21), 75 (21), 74 (18), 65 (15), 64 (13), 63 (48), 62 (14), 51 (24), 50 (16). HRMS (EI) calcd for $C_{10}H_{16}NO_3P$ 229.0868, found 229.0875.

*Diethyl (3-Hydroxyprop-1-yn-1-yl)phosphonate (**2k**).*[22] Pale yellow oil. 61.5 mg, 64% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.34 (d, J = 3.8 Hz, 2H), 4.20−4.10 (m, 4H), 1.35 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.4 (d, J = 50.6 Hz), 74.1 (d, J = 298.7 Hz), 63.6 (d, J = 5.6 Hz), 50.6 (d, J = 4.4 Hz), 16.1 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.8 ppm.

*Diethyl (4-Hydroxybut-1-yn-1-yl)phosphonate (**2l**).* Yellow oil. 74.2 mg, 72% yield. IR (neat): 3399, 2986, 2933, 2908, 2210, 1245, 1164, 1029, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.22−4.07 (m, 4H), 3.79 (t, J = 6.5 Hz, 2H), 2.61 (td, J = 6.4, 4.6 Hz, 2H), 1.37 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.1 (d, J = 53.2 Hz), 71.4 (d, J = 302.8 Hz), 63.3 (d, J = 5.5 Hz), 59.8 (d, J = 2.5 Hz), 23.6 (d, J = 4.5 Hz), 16.1 (d, J = 7.1 Hz).^{31}P NMR (121 MHz, $CDCl_3$) δ −6.3 ppm. MS: m/z = 206 (M^+, 1%), 176 (53), 148 (45), 147 (25), 133 (23), 121 (13), 120 (100), 115 (12), 102 (21), 81 (10), 65 (13). HRMS (EI) calcd for $C_8H_{15}O_4P$ 206.0708, found 206.0711.

*Diethyl 3-(Tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-ylphosphonate (**2m**).* Pale yellow oil. 109.1 mg, 79% yield. IR (neat): 2949, 2210, 1270, 1123, 1033, 976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (t, J = 2.8 Hz, 1H), 4.36 (d, J = 3.8 Hz, 2H), 4.21−4.12 (m, 4H), 3.86−3.76 (m, 1H), 3.58−3.49 (m, 1H), 1.81−1.51 (m, 6H), 1.37 (t, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.4, 96.9 (d, J = 50.3 Hz), 75.8 (d, J = 295.5 Hz), 63.4 (d, J = 5.5 Hz), 62.2, 54.0 (d, J = 4.4 Hz), 30.2, 25.4, 18.9, 16.2 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −7.3 ppm. MS: m/z = 276 (M^+, 1%), 275 (12), 221 (81), 203 (18), 193 (52), 192 (20), 191 (28), 177 (15), 165 (100), 163 (18), 162 (12), 149 (11), 148 (48), 147 (43), 146 (25), 137 (21), 136 (16), 135 (26), 134 (13), 121 (13), 120 (43), 119 (29), 107 (10), 103 (37), 102 (18), 85 (18), 84 (15), 83 (14), 82 (10), 81 (14), 65 (18), 56 (10), 55 (44). HRMS (EI) calcd for $C_{12}H_{21}O_5P$ 276.1127, found 276.1130.

*Diethyl Nona-1,8-diyn-1-ylphosphonate (**2n**).* Colorless oil. 87.1 mg, 68% yield. IR (neat): 3301, 2990, 2937, 2855, 2206, 1258, 1045, 967 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.22−4.06 (m, 4H), 2.42−2.32 (m, 2H), 2.26−2.15 (m, 2H), 1.96 (t, J = 2.6 Hz, 1H), 1.66−1.50 (m, 6H), 1.37 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.0 (d, J = 53.3 Hz), 84.1, 70.5 (d, J = 304.1 Hz), 68.6, 63.1 (d, J = 5.5 Hz), 27.9, 27.8, 27.0 (d, J = 2.2 Hz), 19.2 (d, J = 4.5 Hz), 18.2, 16.1 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.3 ppm. MS: m/z = 256 (M^+, 1%), 207 (10), 200 (31), 199 (32), 185 (12), 172 (24), 171 (10), 161 (12), 148 (19), 147 (21), 145 (12), 135 (10), 133 (21), 131 (24), 121 (11), 120 (39), 119 (31), 118 (60), 117 (100), 115 (20), 105 (17), 103 (12), 102 (12), 93 (10), 92 (11), 91 (57), 81 (16), 79 (30), 77 (19), 65 (21), 53 (10). HRMS (EI) calcd for $C_{13}H_{21}O_3P$ 256.1228, found 256.1231.

*Diethyl (3-Oxobut-1-yn-1-yl)phosphonate (**2o**).* Yellow oil. 96.9 mg, 95% yield. IR (neat): 2990, 2921, 2839, 1687, 1266, 1204, 1021, 980, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.29−4.15 (m, 4H), 2.43 (s, 3H), 1.40 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.5 (d, J = 4.3 Hz), 92.7 (d, J = 43.0 Hz), 77.8 (d, J = 278.1 Hz), 64.2 (d, J = 5.7 Hz), 32.5, 16.2 (d, J = 6.8 Hz).^{31}P NMR (121 MHz, $CDCl_3$) δ −9.1 ppm. MS: m/z = 204 (M^+, 1%), 189 (31), 177 (18), 175 (13), 161 (71), 159 (30), 149 (81), 148 (49), 147 (39), 135 (25), 134 (100), 133 (88), 131 (14), 131 (67), 121 (11), 117 (13), 116 (11), 115 (20), 109 (15), 107 (47), 99 (10), 96 (11), 95 (30), 93 (21), 91 (14), 89 (59), 85 (11), 81 (27), 79 (11), 78 (13), 69 (10), 65 (46), 53 (44). HRMS (EI) calcd for $C_8H_{13}O_4P$ 204.0551, found 204.0555.

*Methyl 3-(Diethoxyphosphoryl)propiolate (**2p**).* Pale yellow oil. 106.7 mg, 97% yield. IR (neat): 2990, 2962, 2132, 1732, 1433, 1282, 1164, 1045, 984, 882 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.29−4.13 (m, 4H), 3.83 (s, 3H), 1.38 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1 (d, J = 5.9 Hz), 86.5 (d, J = 46.6 Hz), 75.5 (d, J = 279.1 Hz), 64.3 (d, J = 5.7 Hz), 53.6, 16.2 (d, J = 6.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −9.8 ppm. MS: m/z = 220 (M^+, 1%), 193 (13), 189 (47), 177 (13), 175 (13), 165 (58), 162 (16), 161 (33), 160 (21), 147 (56), 135 (83), 134 (82), 133 (100), 132 (14), 118 (13), 116 (16), 115 (25), 81 (24), 80 (24), 79 (39), 69 (11), 65 (32), 53 (32). HRMS (EI) calcd for $C_8H_{13}O_5P$ 220.0501, found 220.0508.

*(E)-Diethyl (5-Methoxy-3-methylpent-3-en-1-yn-1-yl)phosphonate (**2q**).* Yellow oil. 116.9 mg, 95% yield. IR (neat): 2982, 2933, 2908, 1650, 1474, 1249, 1168, 1029, 976, 861 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (t, J = 6.2 Hz, 1H), 4.17−4.03 (m, 4H), 3.97 (d, J = 6.3 Hz, 2H), 3.28 (s, 3H), 1.78 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (d, J = 3.4 Hz), 118.4 (d, J = 5.9 Hz), 101.1 (d, J = 52.1 Hz), 76.2 (d, J = 300.3 Hz), 68.6, 63.3 (d, J = 5.5 Hz), 58.6, 16.8 (d, J = 1.8 Hz), 16.2 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.9 ppm. MS: m/z = 246 (M^+, 68%), 231 (55), 218 (16), 217 (28), 203 (38), 190 (12), 189 (29), 175 (100), 171 (20), 161 (22), 160 (11), 159 (20), 157 (96), 147 (14), 143 (12), 141 (21), 129 (17), 109 (28), 95 (34), 91 (10), 81 (14), 79 (35), 78 (17), 77 (39), 67 (19), 66 (10), 65 (30), 53 (10), 51 (15). HRMS (EI) calcd for $C_{11}H_{19}O_4P$ 246.1021, found 246.1024.

*Diethyl (Cyclohex-1-en-1-yl)ethynylphosphonate (**2r**).* Pale yellow oil. 112.6 mg, 93% yield. IR (neat): 2984, 2937, 2868, 2173, 1687, 1258, 1160, 1037, 984 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H), 4.21−4.07 (m, 4H), 2.15−2.10 (m, 4H), 1.65−1.55 (m, 4H), 1.35 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (d, J = 3.3 Hz), 118.5 (d, J = 5.9 Hz), 101.6 (d, J = 52.8 Hz), 75.7 (d, J = 302.8 Hz), 63.1 (d, J = 5.4 Hz), 28.0 (d, J = 1.6 Hz), 26.0, 21.9, 21.1,

DOI: 10.1021/acs.joc.5b02528
J. Org. Chem. 2016, 81, 1813−1818

16.2 (d, J = 7.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.2 ppm. MS: m/z = 242 (M^+, 64%), 241 (27), 214 (28), 213 (45), 207 (30), 199 (16), 197 (22), 187 (12), 186 (76), 185 (72), 171 (11), 170 (20), 169 (42), 159 (10), 158 (11), 150 (16), 149 (22), 145 (15), 135 (17), 134 (25), 133 (40), 132 (35), 131 (34), 122 (13), 121 (13), 120 (16), 119 (15), 117 (44), 107 (21), 106 (98), 105 (91), 104 (70), 103 (69), 102 (12), 93 (14), 92 (15), 91 (100), 89 (12), 81 (12), 79 (36), 78 (48), 77 (66), 65 (31), 63 (11), 55 (13), 51 (13). HRMS (EI) calcd for $C_{12}H_{19}O_3P$ 242.1072, found 242.1075.

*Diethyl (3-(1,3-Dioxoisoindolin-2-yl)prop-1-yn-1-yl)phosphonate (**2s**).* White solid; mp 76.0−78.2 °C. 141.3 mg, 88% yield. IR (KBr): 2990, 2962, 2921, 2218, 1715, 1609, 1425, 1258, 1119, 1045, 1021, 963, 726, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.86 (m, 2H), 7.80−7.74 (m, 2H), 4.58 (d, J = 3.9 Hz, 2H), 4.23−4.07 (m, 4H), 1.36 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 134.5, 131.8, 123.8, 93.5 (d, J = 50.6 Hz), 73.5 (d, J = 293.5 Hz), 63.5 (d, J = 5.5 Hz), 27.3 (d, J = 4.6 Hz), 16.1 (d, J = 7.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ −7.8 ppm. MS: m/z = 321 (M^+, 1%), 293 (11), 292 (10), 276 (13), 265 (10), 248 (19), 214 (17), 213 (100), 212 (26), 186 (11), 185 (31), 184 (66), 161 (12), 160 (40), 157 (13), 156 (11), 148 (10), 146 (34), 133 (15), 130 (71), 129 (11), 119 (11), 105 (16), 104 (42), 102 (17), 77 (13), 76 (32). HRMS (EI) calcd for $C_{15}H_{16}NO_5P$ 321.0766, found 321.0772.

*Diethyl [(8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl]ethynylphosphonate (**2t**).* Pale yellow solid; mp 79.5−82.0 °C. 170.7 mg, 79% yield. IR (KBr): 3321, 2986, 2937, 2872, 2197, 1617, 1511, 1450, 1241, 1025, 980, 816 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 8.5, 2.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 4.27−4.14 (m, 4H), 2.82−2.69 (m, 2H), 2.41−2.27 (m, 1H), 2.20−2.10 (m, 1H), 2.07−1.97 (m, 2H), 1.94−1.83 (m, 1H), 1.82−1.68 (m, 4H), 1.61−1.48 (m, 1H), 1.45−1.33 (m, 3H), 1.39 (td, J = 7.0, 2.8 Hz, 6H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 137.8, 131.5, 126.5, 115.3, 112.9, 105.3 (d, J = 49.5 Hz), 80.3 (d, J = 3.8 Hz), 75.3 (d, J = 314.0 Hz), 63.7 (dd, J = 5.5, 1.2 Hz), 50.2, 48.0, 43.3, 39.4, 38.7, 31.1, 29.7, 27.4, 26.4, 23.1, 16.3 (dd, J = 6.9, 1.2 Hz), 12.8. ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.2 ppm. (The signal corresponding to OH was not observed). MS: m/z = 432 (M^+, 1%), 271 (20), 270 (100), 214 (10), 213 (21), 186 (12), 185 (34), 172 (27), 160 (16), 159 (17), 158 (12), 157 (15), 146 (31), 145 (18), 144 (10), 133 (12), 131 (11), 115 (12). HRMS (EI) calcd for $C_{24}H_{33}O_5P$ 432.2066, found 432.2065.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02528.

Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra of all alkynylphosphonate products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was generously supported by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PIP-2011-11220100100268), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, Préstamo BID PICT-2010-0669), and Universidad Nacional del Sur (UNS, PGI 24/Q044) from Argentina. V.G. thanks the CONICET for a postdoctoral fellowship.

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DOI: 10.1021/acs.joc.5b02528
J. Org. Chem. 2016, 81, 1813−1818