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Alcoholysis of Phosphaisocoumarins and Synthesis of 2-(2-Oxoalkyl)phenylphosphonates

Ai-Yun Peng,*[a] Yu-Juan Guo,[a] Zhi-Hai Ke,[a] and Shizheng Zhu[b]

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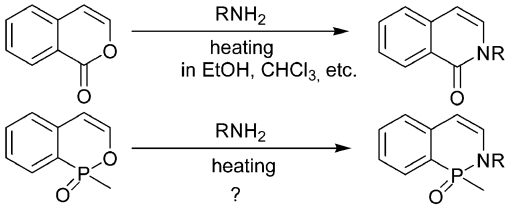
Phosphaisocoumarins do not undergo aminolysis, but instead they were found to be susceptible to alcoholysis in the presence of alcohols and primary amines. This paper examined this unexpected alcoholysis reaction and found that in the presence of Et_3N or K_2CO_3, 4-unsubstituted- and 4-chlorophosphaisocoumarins underwent the alcoholysis reaction smoothly to give a series of 2-(2-oxoalkyl)phenylphosphonates in good yields, whereas 4-iodo- and 4-bromophosphaisocoumarins underwent a dehalogenation–alcoholysis tandem reaction. The possible mechanism for the alcoholysis reaction was discussed. In addition, direct access to 2-(2-oxoalkyl)-phenylphosphonates was developed by the mercury(II)-catalyzed hydration of 2-(1-alkynly)phenylphosphonates with high regioselectivity. In a preliminary study, the obtained novel keto phosphonates showed medium inhibitory activity towards α-chymotrypsin.

Introduction

Although phosphonates are not very abundant in nature, their diverse bioactivities have attracted considerable synthetic[1] and pharmacological[2] interest. They are usually recognized as effective transition-state analogue inhibitors for a variety of enzymes including proteases and esterases.[2a–2c] They have also been developed to be used as insecticides, herbicides, fungicides, plant growth regulators, and drugs to treat bone disorders.[2d]

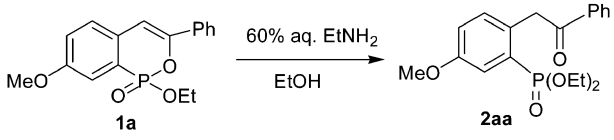
In recent years, we have synthesized novel cyclic phosphonates, that is, phosphaisocoumarins,[3] some of which preliminarily showed medium inhibitory activity towards protein tyrosine phosphatase 1B (PTP1B), medium antitumor activity, and good insecticidal activity.[4] However, the chemical properties and reactivities of phosphaisocoumarins are still not very clear.

Because isocoumarins could be converted into the corresponding isoquinolones readily by treatment with primary amines in solvent, such as alcohol and chloroform,[5] we reasoned that phosphaisoquinolones might be synthesized in a similar way (Scheme 1).



Scheme 1.

However, to our surprise, the reaction of 3-phenyl-7-methoxyphosphaisocoumarin (**1a**) with an excess amount of aqueous ethylamine in ethanol did not lead to any aminolysis product, but instead afforded alcoholysis product **2aa** whether the reaction was carried out under thermal conditions or at room temperature (Scheme 2).



Scheme 2. Reaction of **1a** with aqueous ethylamine in ethanol. Reagents and conditions for thermal reaction: **1a** (0.25 mmol), EtOH (2.5 mL), aq. $EtNH_2$ (30 equiv.), 90 °C, 6 h, yield: 45%. Reagents and conditions for room-temperature reaction: **1a** (0.25 mmol), EtOH (2.5 mL), aq. $EtNH_2$ (8 equiv.), r.t., 48 h, yield: 73%.

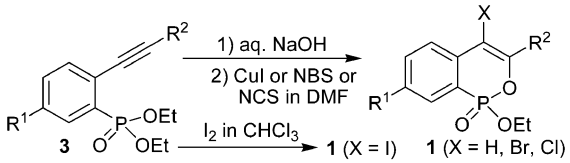
This unexpected alcoholysis reaction attracted our interests. On the one hand, in this reaction, it was the weaker nucleophile ethanol instead of ethylamine that attacked the phosphorus atom; the examination of this reaction would help us to further understand the differences between carboxylates and phosphonates. On the other hand, from the viewpoint of retrosynthesis, 2-(2-oxoalkyl)phenylphosphonates **2** might be useful intermediates for the preparation of other phosphonates. For example, the reduction of

[a] School of Chemistry & Chemical Engineering, Sun Yat-sen University,
135 Xingangxi Lu, Guangzhou 510275, China
Fax: +86-020-84112425
E-mail: cespay@mail.sysu.edu.cn
[b] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
354 Fenglin Lu, Shanghai 200032, China

2 followed by thermal condensation would afford 3,4-dihydrophosphaisocoumarins according to the synthesis of 3,4-dihydroisocoumrins.[6] However, to the best of our knowledge, there are no reports about the synthesis and applications of **2**, except that we obtained two of these phosphonates as minor products in the iodocyclization of 2-(1-alkynyl)phenylphosphonates. Thus, in this paper, we decided to investigate the alcoholysis of phosphaisocoumarins and tried to develop a general method to synthesize 2-(2-oxoalkyl)phenylphosphonates **2**.

Results and Discussion

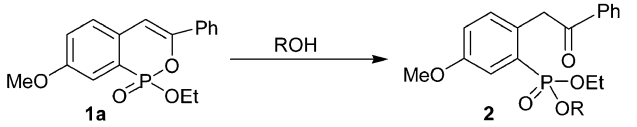
Starting materials **1** were prepared according to our previous procedure (Scheme 3).[3,7] We first examined the alcoholysis of **1a** under various conditions and the results are summarized in Table 1. The catalyst was essential, as without any catalyst **1a** was recovered unchanged (Table 1, entry 1). Similar to $EtNH_2$ mentioned in Scheme 2, nBuNH$_2$ was more effective to catalyze this reaction at room temperature than under thermal conditions (Table 1, entries 2 and 3), whereas Et_3N was more efficient at 60 °C, leading to **2aa** in 78% yield, in which an excess amount of volatile Et_3N was added so as to ensure completion of the reaction (Table 1, entries 4 and 5). The use of inorganic bases was also examined, and the results showed that NaOH only led to the hydrolysis product,[8] $NaHCO_3$ did not afford **2aa** at all, and K_2CO_3 (1.5 equiv.) at 85 °C gave **2aa** in 80% yield (Table 1, entries 7–10). In addition, although acid was used to catalyze the alcoholysis of the carboxylates,[9] it could not catalyze this reaction (Table 1, entries 11 and 12). The methanolysis of **1a** also proceeded smoothly under Et_3N-catalyzed conditions, but the isolated yield of desired product **2ab** was relatively low (Table 1, entry 13). It was found that **2ab** decomposed slowly to an unidentified compound with strong polarity upon chromatography with silica gel, probably because it was easily hydrolyzed to the monoester under weakly acidic conditions.[10] The reaction of **1a** with secondary or tertiary alcohols, such as *i*PrOH or *t*BuOH, did not proceed at all under the same conditions (Table 1, entries 14 and 15).



Scheme 3. Synthesis of all kinds of phosphaisocoumarins **1**.

To further explore the scope of this reaction, the ethanolysis of other phosphaisocoumarins **1** with various substituents was investigated in the presence of K_2CO_3 or Et_3N. As shown in Table 2, for those cases where X is hydrogen and chlorine, the corresponding 2-(2-oxoalkyl)phenylphosphonates **2** could be obtained in good-to-excellent

Table 1. Alcoholysis of **1a** under various conditions.[a]

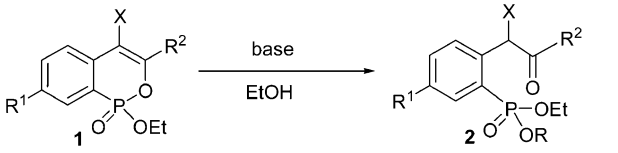


Entry	R	Catalyst (equiv.)	Temp. [°C]	Time [h]	Isolated yield [%]
1	Et	No catalyst	85	36	no reaction
2	Et	nBuNH$_2$ (4)	r.t.	48	74 (**2aa**)
3	Et	nBuNH$_2$ (4)	80	24	44 (**2aa**)
4	Et	Et_3N (15)	r.t.	24	trace
5	Et	Et_3N (15)	60	36	78 (**2aa**)
6	Et	pyridine (4)	60	36	65 (**2aa**)
7	Et	NaOH (1.5)	85	24	–[a]
8	Et	$NaHCO_3$ (1.5)	85	24	no reaction
9	Et	K_2CO_3 (1.5)	85	18	80 (**2aa**)
10	Et	K_2CO_3 (1.5)	r.t.	36	<50 (**2aa**)
11	Et	H_2SO_4 (1)	85	24	no reaction
12	Et	*p*-TsOH (1)	85	24	no reaction
13	Me	Et_3N (15)	60	24	55 (**2ab**)
14	*i*Pr	Et_3N (15)	60	24	no reaction
15	*t*Bu	Et_3N (15)	60	24	no reaction

[a] The reaction led to the hydrolysis product of **1a** (**2**, R = H).

yields by this ethanolysis reaction. Functionalities, for example, R^1 = methoxy, chlorine, hydrogen; R^2 = aryl, alkyl, cyclopropyl, were able to withstand the reaction conditions. K_2CO_3 was efficient in most cases, but for substrates **1e** and **1g**, most of the starting materials were recovered under K_2CO_3-catalyzed conditions (Table 2, entries 4 and 7). The use of Et_3N instead of K_2CO_3 afforded desired products **2e** and a racemic mixture of (±)-**2g** in good yields for **1e** and **1g**, respectively (Table 2, entries 5 and 8).

Table 2. Base-catalyzed ethanolysis of **1**.[a]



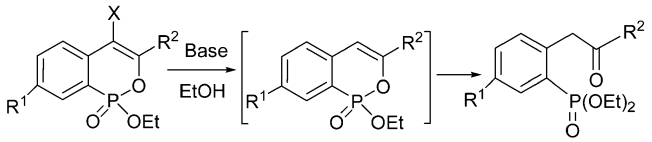
Entry	**1**			Base	Time	Isolated
	R^1	R^2	X	(equiv.)	[h]	yield [%]
1	OMe	*c*Pr	H (**1b**)	K_2CO_3 (1.5)	18	74 (**2b**)
2	H	*n*Bu	H (**1c**)	K_2CO_3 (1.5)	24	79 (**2c**)
3	H	Ph	H (**1d**)	K_2CO_3 (1.5)	24	75 (**2d**)
4	Cl	*c*Pr	H (**1e**)	K_2CO_3 (1.5)	36	**1e**+**2e**[b]
5	Cl	*c*Pr	H (**1e**)	Et_3N (15)	36	71 (**2e**)
6	Cl	Ph	H (**1f**)	K_2CO_3 (1.5)	36	65 (**2f**)
7	H	Ph	Cl(**1g**)	K_2CO_3 (1.5)	24	**1g** + (±)-**2g**[b]
8	H	Ph	Cl (**1g**)	Et_3N (15)	18	82 [(±)-**2g**]

[a] Reactions were carried out with **1**, K_2CO_3 at 85 °C or Et_3N at 60 °C in EtOH. [b] The reaction mixture was not isolated but detected by TLC.

However, when 4-iodophosphaisocoumrin **1h** was treated with ethanol and Et_3N at 60 °C for 60 h, precursor **1h** disappeared completely and iodide-free phosphaisocoumarin **1a** was obtained in 69% yield (Table 3, entry 1). A similar

result was obtained when K_2CO_3 was used as the catalyst (Table 3, entry 2). With the addition of an excess amount of Et_3N, iodide-free ethanolysis product **2a** was detected by TLC (Table 3, entry 3). In this reaction, the base was essential (Table 3, entry 4). Under similar conditions, 4-iodo- and 4-bromophosphacoumarins **1i**–**k** only gave the dehalogenation–ethanolysis products (Table 3, entries 5–7).

Table 3. Ethanolysis of 4-iodo- or 4-bromophosphaisocoumarins.[a]

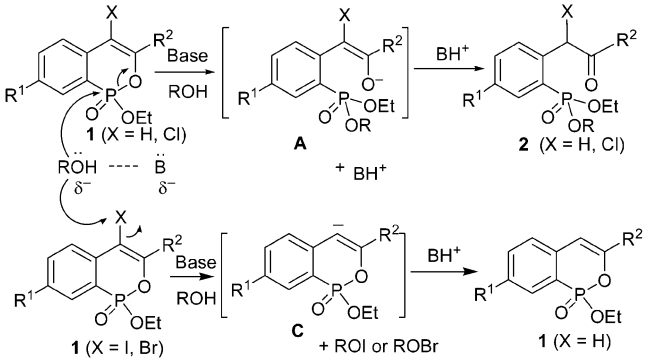


Entry	1			Base	Time	Isolated
	R^1	R^2	X	(equiv.)	[h]	yield [%]
1	OMe	Ph	I (**1h**)	Et_3N (15)	60	69 (**1a**)
2	OMe	Ph	I (**1h**)	K_2CO_3 (1.0)	4	**1i +1a**[b]
3	OMe	Ph	I (**1h**)	Et_3N (35)	36	**1a+2a**[b]
4	OMe	Ph	I (**1h**)	No base	36	no reaction
5	OMe	Ph	Br (**1i**)	Et_3N (35)	36	50 (**2a**)
6	H	Ph	I (**1j**)	Et_3N (20)	36	59 (**2d**)
7	H	Ph	Br (**1k**)	Et_3N (20)	36	60 (**2d**)

[a] Reactions were carried out with **1**, K_2CO_3 at 85 °C or Et_3N at 60 °C in EtOH. [b] The reaction mixture was not isolated but detected by TLC.

On the basis of the above results, plausible mechanisms are proposed in Scheme 4. Alcohol (ROH) is a weak nucleophile, and it alone cannot promote the alcoholysis and dehalogenation reactions (Table 1, entry 1; Table 3, entry 4). However, the base can enhance the nucleophilicity of ROH by the formation of an R–O–H···base hydrogen bond. The attack of the activated ROH on the phosphorus atom of **1** (X = H, Cl) followed by proton transfer would lead to desired products **2**. In contrast, activated ROH might also attack the positively polarized iodide or bromine atom of **1** (X = I, Br), resulting in the formation of intermediate **C** and ROI or ROBr. In 2006, Gazizov and coworkers[11] reported a similar debromoalkoxylation reaction with the formation of unstable EtOBr. Intermediate **C** would transform into phosphaisocoumarin **1** (X = H) by proton transfer, which could undergo the subsequent alcoholysis reaction. Among these, amidation of phosphaisocoumarins was not detected when a primary amine was used as the catalyst, probably because the formed P–O bond is stronger than the P–N bond, which means that the alcoholysis product is more stable than the aminolysis product.

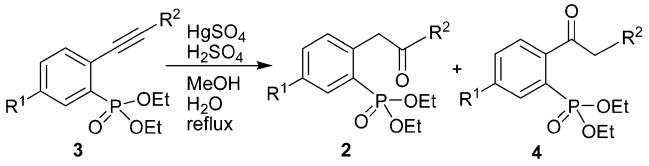
However, the above alcoholysis reaction is not a very convenient method to prepare 2-(2-oxoalkyl)phenylphosphonates **2**. Because the catalytic hydration of alkynes can provide direct access to carbonyl compounds,[12] we speculated that compounds **2** might be synthesized directly and conveniently by hydration of 2-(1-alkynyl)phenylphosphonates **3**. Although hydration reactions of internal alkynes often gives a mixture of regioisomeric ketones, the hydration of alkynes **3a**–**f** with a catalytic amount of



Scheme 4. Possible mechanisms for the alcoholysis and dehalogenation reactions.

$HgSO_4/H_2SO_4$ only yielded **2a**–**f** and regioisomers **4** were not detected (Table 4). These results are not surprising, because internal alkynes bearing a π-accepting substituent (e.g., amides, esters, phosphonates) are usually hydrated by conjugate addition to give β-keto compounds.[13] However, in most cases, the yield of the desired ketone was not very satisfactory, although the starting material has totally disappeared in each case (Table 4, entries 2–6). Some unidentified phosphonate-hydrolyzed byproducts were observed in the crude reaction mixture under these conditions, which might be the reason for the relatively low yields of the ketones.

Table 4. Hydration of 2-(1-alkynyl)phenylphosphonates **3** to synthesize **2**.[a]



Entry	R^1	R^2	Time [h]	Isolated yield [%]
1	OMe	Ph (**3a**)	3	87 (**2a**)
2	OMe	*c*Pr (**3b**)	2	40 (**2b**)
3	H	*n*Bu (**3c**)	2	35 (**2c**)
4	H	Ph (**3d**)	3	64 (**2d**)
5	Cl	*c*Pr (**3e**)	2	47 (**2e**)
6	Cl	Ph (**3f**)	2	45 (**2f**)

[a] Reactions were carried out with **3** (0.2 mmol), $HgSO_4$ (0.02 mmol), concentrated H_2SO_4 (2 drops), MeOH (10.0 mL), and H_2O (0.4 mL) at reflux for 2–3 h.

All 2-(2-oxoalkyl)phenylphosphonates **2**, except **2f**,[3b] are new compounds, and their structures were confirmed by spectroscopic methods (see Experimental Section). For example, the structure of **2a** was confirmed by the existence of two benzyl protons (δ =4.65 ppm) in the ^1H NMR spectrum, the carbonyl carbon atom (δ =197.30 ppm) in the ^{13}C NMR spectrum, and the appearance of a band at 1690 cm^{-1} in the IR spectrum. It is interesting to note that there was no benzyl proton in the ^1H NMR spectrum for the racemic

mixture of (±)-**2g**; their structures were confirmed by the existence of a positive DEPT signal at δ = 57.20 ppm in the ^{13}C NMR spectrum and the appearance of the molecular cation at m/z = 366 $[M]^+$.

In addition, we tested the obtained 2-(2-oxoalkyl)phenylphosphonates **2** preliminarily as inhibitors of α-chymotrypsin. Some of them showed medium inhibitory activity towards α-chymotrypsin. For example, the IC_{50} values of **2ab** and **2f** were 53.9 and 30.1 μM, respectively. Further biochemical evaluation of these compounds is underway.

Conclusions

In summary, the alcoholysis of phosphaisocoumarins into 2-(2-oxoalkyl)phenylphosphonates was examined for the first time. For this alcoholysis reaction, a basic catalyst was essential, and acid could not catalyze the reaction at all. 4-Iodo- and 4-bromophosphaisocoumarins were found to undergo a dehalogenation–alcoholysis tandem reaction under the reaction conditions. In addition, alternative and direct access to 2-(2-oxoalkyl)phenylphosphonates was developed by the mercury(II)-catalyzed hydration of 2-(1-alkynly)phenylphosphonates with high regioselectivity. The obtained novel keto phosphonates showed medium inhibitory activity towards α-chymotrypsin in a preliminary study and these compounds might also serve as important synthetic intermediates.

Experimental Section

General Remarks: NMR spectra were recorded with a Varian Mercury-Plus 300 instrument in $CDCl_3$ by using the residual solvent signal at δ = 7.27 (^1H) or 77.0 (^{13}C) ppm as the internal standard. ^{31}P NMR spectra used the 85% H_3PO_4 as the external reference. Elemental analyses were determined with a Vario EL Elemental Analyzer. EI mass spectra were recorded with a Thermo DSQ EI-mass spectrometer. ESI mass spectra were recorded with a LCMS-2010A Liquid Chromatograph mass spectrometer. HRMS were determined by using a Thermo MAT95XP High-Resolution mass spectrometer. IR spectra were recorded as potassium bromide pellets with a Bruker Equinox 55 FTIR spectrometer. Anhydrous ethanol and methanol were purified by distillation from magnesium. Et_3N was purified by distillation from calcium hydride. All other commercially available reagents were used as received. Column chromatography was performed on 200–300 mesh silica gel. Thin-layer chromatography was conducted on Kieselgel 60 F254 (Merck). Spots were observed under UV irradiation (254 nm). Anhydrous Na_2SO_4 were used to dry organic solutions during workup, and evaporation of the solvents was performed under vacuum with a rotary evaporator.

Starting Material 1: All precursors **1** were prepared according to our previous procedures.[3,7] Among them, **1b** and **3b** (Scheme 3) are new compounds. Procedures for their preparation and their characterization data are noted below.

Diethyl (2-Cyclopropylethynyl-5-methoxyphenyl)phosphonate (3b): To a mixture of the corresponding perfluoroalkanesulfonate (944.3 mg, 1.75 mmol), $PdCl_2(PPh_3)_2$ (36.8 mg, 0.0525 mmol), CuI (33.8 mg, 0.175 mmol), anhydrous LiCl (223 mg, 5.25 mmol), Et_3N (1.0 mL, 7.10 mmol), and DMF (5.0 mL) was added dropwise the cyclopropyl acetylene (0.45 mL, 5.31 mmol) at room temperature. After stirring at 60 °C for 5 h under an atmosphere of nitrogen, the reaction mixture was diluted with EtOAc and washed with aqueous NH_4Cl until neutral. The mixture was then washed with brine and dried (Na_2SO_4), and the solvents were evaporated in vacuo. The residue was chromatographed on silica gel [petroleum ether (b.p. 60–90 °C)/EtOAc, 5:1–2:1] to give corresponding product **3b** (361 mg, 67%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.51 (m, 2 H), 6.94–6.98 (m, 1 H), 4.06–4.25 (m, 4 H), 3.84 (s, 3 H), 1.43–1.52 (m, 1 H), 1.37 (t, J = 6.9 Hz, 6 H), 0.85–0.90 (m, 4 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 158.20 (d, $J_{C,P}$ = 18.1 Hz), 134.91 (d, $J_{C,P}$ = 15.1 Hz), 131.05 (d, $J_{C,P}$ = 185.1 Hz), 118.86 (d, $J_{C,P}$ = 11.1 Hz), 118.65 (d, $J_{C,P}$ = 7.0 Hz), 118.28 (d, $J_{C,P}$ = 3.0 Hz), 97.12, 73.73 (d, $J_{C,P}$ = 6.0 Hz), 62.17 (d, $J_{C,P}$ = 5.0 Hz), 55.49, 16.27 (d, $J_{C,P}$ = 7.0 Hz), 8.38, 0.38 ppm. IR (KBr): $\tilde{\nu}$ = 2980, 1723, 1481, 1397, 1238, 1152, 1027, 966 cm^{-1}. MS (ESI): m/z (%) = 309 (14) $[M + H]^+$, 372 (100), 331 (8). $C_{16}H_{21}O_4P$ (308.31): calcd. C 62.33, H 6.87; found C 62.35, H 6.85.

3-Cyclopropyl-1-ethoxy-7-methoxy-2,1-benzoxaphosphorin 1-Oxide (1b): Compound **3b** (308.3 mg, 1.0 mmol) and aqueous sodium hydroxide (1 M, 6.0 mL, 6.0 mmol) were combined in ethanol (5.0 mL) and heated at reflux for 2 h. The reaction mixture was evaporated in vacuo to remove the ethanol, then diluted with water (20 mL), cooled in an ice bath, neutralized with concentrated hydrochloric acid, and extracted with EtOAc. The extracts were evaporated in vacuo to give the corresponding monoester (252 mg, 90%) as a yellow oil, which was used without further purification.

A mixture of the above monoester (160.1 mg, 0.50 mmol) and CuI (9.5 mg, 0.05 mmol) was dissolved in DMF (5.0 mL). After stirring at room temperature for 24 h, the reaction mixture was then diluted with EtOAc and washed with saturated NH_4Cl and brine, and then dried (Na_2SO_4); the solvents were evaporated in vacuo. The residue was chromatographed on silica gel [petroleum ether (b.p. 60–90 °C)/EtOAc, 5:1–2:1] to give product **1b** (104 mg, 65%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.33 (m, 1 H), 7.11–7.16 (m, 2 H), 5.94 (d, J = 0.9 Hz, 1 H), 4.09–4.20 (m, 2 H), 3.86 (s, 3 H), 1.34 (t, J = 6.9 Hz, 3 H), 1.01–1.07 (m, 1 H), 0.81–0.91 (m, 4 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 158.24 (d, $J_{C,P}$ = 19.1 Hz), 152.73 (d, $J_{C,P}$ = 10.0 Hz), 131.27 (d, $J_{C,P}$ = 7.0 Hz), 127.36 (d, $J_{C,P}$ = 140.8 Hz), 120.83 (d, $J_{C,P}$ = 3.0 Hz), 120.37 (d, $J_{C,P}$ = 180.1 Hz), 112.33 (d, $J_{C,P}$ = 10.0 Hz), 102.92 (d, $J_{C,P}$ = 12.1 Hz), 62.66 (d, $J_{C,P}$ = 6.1 Hz), 55.6, 16.33 (d, $J_{C,P}$ = 7.1 Hz), 14.39 (d, $J_{C,P}$ = 6.1 Hz), 5.87, 5.12 ppm. MS (ESI): m/z (%) = 281 (5) $[M + H]^+$, 344 (100), 385 (33). IR (KBr): $\tilde{\nu}$ = 2928, 1487, 1270, 1176, 1027, 962 cm^{-1}. $C_{14}H_{17}O_4P$ (280.26): calcd. C 60.00, H 6.11; found C 60.25, H 6.14.

General Procedure for the Synthesis of 2 by the Alcoholysis of 1: To a solution of **1** (0.2 mmol) in anhydrous alcohol (2.0 mL) was added K_2CO_3 (41 mg, 0.3 mmol) or Et_3N (0.42 mL, 3.0 mmol). After stirring at 85 °C or 60 °C until material **1** was completely or mostly disappeared by TLC monitoring, the reaction mixture was concentrated. The residue was chromatographed on silica gel [petroleum ether (b.p. 60–90 °C)/EtOAc, 6:1–3:1] to give corresponding product **2**.

Diethyl [5-Methoxy-2-(2-oxo-2-phenylethyl)phenyl]phosphonate (2aa): According to the general procedure, the reaction of **1a** (70 mg, 0.22 mmol) with K_2CO_3 (46 mg, 0.33 mmol) in anhydrous EtOH (3.0 mL) at 85 °C afforded **2aa** (64 mg, 80%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 3.6 Hz, 2 H), 7.45–7.60 (m, 4 H), 7.05–7.19 (m, 2 H), 4.65 (s, 2 H), 3.94–4.14 (m, 4 H), 3.86 (s, 3 H), 1.25 (dt, J_1 = 22.8 Hz, J_2 = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 197.30, 157.80 (d, $J_{C,P}$ =

18.5 Hz), 136.70, 133.47, 133.24, 132.82, 130.03 (d, $J_{C,P}$ = 9.1 Hz), 128.16 (d, $J_{C,P}$ = 180.7 Hz), 128.25 (d, $J_{C,P}$ = 24.3 Hz), 118.77 (d, $J_{C,P}$ = 10.6 Hz), 118.25 (d, $J_{C,P}$ = 4.4 Hz), 62.10 (d, $J_{C,P}$ = 8.4 Hz), 55.42, 43.13 (d, $J_{C,P}$ = 5.1 Hz), 16.17 (d, $J_{C,P}$ = 7.2 Hz) ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 19.36 ppm. IR (film): $\tilde{\nu}$ = 2924, 1690, 1445, 1331, 1248, 1218, 1140, 1081, 1022, 964 cm^{-1}. MS (EI): *m*/*z* (%) = 362 (25) $[M]^+$, 257 (28), 105 (100), 77 (28). HRMS (EI): calcd. for $C_{19}H_{23}O_5P$ 362.1278; found 362.1279.

Ethyl Methyl [5-Methoxy-2-(2-oxo-2-phenylethyl)phenyl]phosphonate (2ab): According to the general procedure, the reaction of **1a** (63 mg, 0.20 mmol) with Et_3N (0.42 mL, 3.0 mmol) in anhydrous MeOH (3.0 mL) at 60 °C afforded **2ab** (38 mg, 55%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 3.7 Hz, 2 H), 7.47–7.62 (m, 4 H), 7.07–7.24 (m, 2 H), 4.64 (s, 2 H), 3.98–4.14 (m, 2 H), 3.87 (s, 3 H), 3.63 (d, *J* = 11.1 Hz, 3 H), 1.28 (dt, *J* = 14.4 Hz, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 197.42, 157.91 (d, $J_{C,P}$ = 19.0 Hz), 136.77, 133.68, 133.41, 132.97, 130.25 (d, $J_{C,P}$ = 9.0 Hz), 128.35 (d, $J_{C,P}$ = 30.0 Hz), 127.44 (d, $J_{C,P}$ = 173.3 Hz), 118.95 (d, $J_{C,P}$ = 9.4 Hz), 118.55 (d, $J_{C,P}$ = 4.4 Hz), 62.38 (d, $J_{C,P}$ = 3.2 Hz), 55.50, 52.58 (d, $J_{C,P}$ = 4.7 Hz), 43.25 (d, $J_{C,P}$ = 4.3 Hz), 16.28 (d, $J_{C,P}$ = 6.9 Hz) ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 20.88 ppm. IR (film): $\tilde{\nu}$ = 2963, 1686, 1408, 1261, 1021, 873 cm^{-1}. MS (EI): *m*/*z* (%) = 348 (30) $[M]^+$, 243 (24), 105 (100), 77 (19). HRMS (EI): calcd. for $C_{18}H_{21}O_5P$ 348.1121; found 348.1105.

Diethyl [2-(2-Cyclopropyl-2-oxoethyl)-5-methoxyphenyl]phosphonate (2b): According to the general procedure, the reaction of **1b** (84 mg, 0.30 mmol) with K_2CO_3 (62 mg, 0.45 mmol) in anhydrous EtOH (3.0 mL) at 85 °C afforded **2b** (73 mg, 74%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.48 (m, 1 H), 7.01–7.16 (m, 2 H), 4.18 (s, 2 H), 4.00–4.15 (m, 4 H), 3.83 (s, 3 H), 1.97–2.06 (m, 1 H), 1.31 (dt, *J* = 6.9 Hz, *J* = 0.6 Hz, 6 H), 1.03–1.08 (m, 2 H), 0.85–0.91 (m, 2 H) ppm. ^{13}C NMR (75.4 MHz): δ = 207.83, 157.78 (d, $J_{C,P}$ = 16.4 Hz), 133.17 (d, $J_{C,P}$ = 18.7 Hz), 129.90 (d, $J_{C,P}$ = 9.2 Hz), 128.15 (d, $J_{C,P}$ = 181.0 Hz), 118.68, 118.46 (d, $J_{C,P}$ = 19.5 Hz), 62.16 (d, $J_{C,P}$ = 3.8 Hz), 55.42, 50.63, 47.66, 20.25, 16.31 (d, $J_{C,P}$ = 6.4 Hz), 11.04 ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 19.43 ppm. IR (film): $\tilde{\nu}$ = 2925, 1700, 1492, 1384, 1284, 1251, 1146, 1070, 1021, 963 cm^{-1}. MS (EI): *m*/*z* (%) = 326 (48) $[M]^+$, 258 (100), 257 (35), 69 (35). HRMS (EI): calcd. for $C_{16}H_{23}O_5P$ 326.1278; found 326.1280.

Diethyl [2-(2-Oxohexyl)phenyl]phosphonate (2c): According to the general procedure, the reaction of **1c** (80 mg, 0.30 mmol) with K_2CO_3 (62 mg, 0.45 mmol) in anhydrous EtOH (3.0 mL) at 85 °C afforded **2c** (74 mg, 79%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.93 (m, 3 H), 7.19–7.23 (m, 1 H), 4.11 (s, 2 H), 3.98–4.15 (m, 4 H), 2.55 (t, *J* = 7.2 Hz, 2 H), 1.55–1.65 (m, 2 H), 1.27–1.38 (m, 8 H), 0.92 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.65, 138.37 (d, $J_{C,P}$ = 10.6 Hz), 133.78 (d, $J_{C,P}$ = 9.2 Hz), 132.32 (d, $J_{C,P}$ = 5.3 Hz), 132.08 (d, $J_{C,P}$ = 14.9 Hz), 126.58 (d, $J_{C,P}$ = 15.0 Hz), 125.93, 62.14 (d, $J_{C,P}$ = 8.1 Hz), 48.20, 42.39, 25.84, 22.40, 16.33 (d, $J_{C,P}$ = 7.8 Hz), 13.97 ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 19.82 ppm. IR (film): $\tilde{\nu}$ = 2958, 1719, 1440, 1399, 1250, 1138, 1094, 1023, 963 cm^{-1}. MS (EI): *m*/*z* (%) = 312 (1) $[M]^+$, 255 (3), 228 (100), 227 (20), 85 (2), 57 (5). HRMS (EI): calcd. for $C_{16}H_{25}O_4P$ 312.1485; found 312.1486.

Diethyl [2-(2-Oxo-2-phenylethyl)phenyl]phosphonate (2d): According to the general procedure, the reaction of **1d** (57 mg, 0.20 mmol) with K_2CO_3 (41 mg, 0.30 mmol) in anhydrous EtOH (3.0 mL) at 85 °C afforded **2d** (50 mg, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–8.06 (m, 3 H), 7.37–7.56 (m, 6 H), 4.73 (s, 2 H), 3.95–4.10 (m, 4 H), 1.22 (t, *J* = 5.7 Hz, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 196.89, 138.43 (d, *J* = 5.2 Hz), 136.70, 133.70 (d, *J* = 4.7 Hz), 132.85, 132.23 (d, $J_{C,P}$ = 1.6 Hz), 132.02, 128.42, 128.10, 127.28 (d, $J_{C,P}$ = 182.5 Hz), 126.49 (d, $J_{C,P}$ = 7.2 Hz), 62.05 (d, $J_{C,P}$ = 2.8 Hz), 44.05 (d, $J_{C,P}$ = 1.5 Hz), 16.16 (d, $J_{C,P}$ = 3.4 Hz) ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 19.32 ppm. IR (film): $\tilde{\nu}$ = 2983, 1691, 1478, 1247, 1217, 1140, 1081, 1020, 966 cm^{-1}. MS (EI): *m*/*z* (%) = 332 (10) $[M]^+$, 227 (5), 105 (100), 77 (15). HRMS (EI): calcd. for $C_{18}H_{21}O_4P$ 332.1172; found 332.1171.

Diethyl [5-Chloro-2-(2-cyclopropyl-2-oxoethyl)phenyl]phosphonate (2e): According to the general procedure, the reaction of **1e** (80 mg, 0.28 mmol) with Et_3N (0.59 mL, 4.2 mmol) in anhydrous EtOH (3.0 mL) at 60 °C afforded **2e** (66 mg, 71%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.91 (m, 1 H), 7.45–7.49 (m, 1 H), 7.15–7.20 (m, 1 H), 4.27 (s, 2 H), 4.01–4.20 (m, 4 H), 2.01–2.09 (m, 1 H), 1.32 (dt, *J* = 9.0 Hz, *J* = 6.0 Hz, 6 H), 1.07–1.12 (m, 2 H), 0.90–0.97 (m, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.17, 150.03 (d, $J_{C,P}$ = 4.8 Hz), 134.49, 133.81 (d, $J_{C,P}$ = 7.3 Hz), 133.63, 132.54, 129.79 (d, $J_{C,P}$ = 183.1 Hz), 62.77 (d, $J_{C,P}$ = 6.1 Hz), 48.19, 20.84, 16.64 (d, $J_{C,P}$ = 7.2 Hz), 11.49 ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 17.36 ppm. IR (film): $\tilde{\nu}$ = 2924, 1657, 1407, 1269, 1118, 1022, 874 cm^{-1}. MS (EI): *m*/*z* (%) = 330 (30) $[M]^+$, 262 (73), 206 (39), 69 (100). HRMS (EI): calcd. for $C_{15}H_{20}ClO_4P$ 330.0782; found 330.0782.

Diethyl [5-Chloro-2-(2-oxo-2-phenylethyl)phenyl]phosphonate (2f):[3b] According to the general procedure, the reaction of **1f** (40 mg, 0.125 mmol) with K_2CO_3 (26 mg, 0.188 mmol) in anhydrous EtOH (2.0 mL) at 85 °C afforded **2f** (30 mg, 65%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–8.10 (m, 3 H),7.46–7.62 (m, 4 H), 7.20–7.26 (m, 1 H), 4.70 (s, 2 H), 3.95–4.13 (m, 4 H), 1.25 (t, *J* = 7.2 Hz, 6 H) ppm. MS (EI): *m*/*z* (%) = 366 (6) $[M]^+$, 228 (2), 105 (100), 77 (17). HRMS (EI): calcd. for $C_{18}H_{20}ClO_4P$ 366.0782; found 366.0785.

Diethyl [2-(1-Chloro-2-oxo-2-phenylethyl)phenyl]phosphonate (±)-2g: According to the general procedure, the reaction of **1g** (60 mg, 0.187 mmol) with Et_3N (0.40 mL, 288 mg, 2.846 mmol) in anhydrous EtOH (2.0 mL) at 60 °C afforded (±)-**2g** (56 mg, 82%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–8.14 (m, 9 H), 4.05–4.30 (m, 4 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 191.43, 139.00 (d, $J_{C,P}$ = 9.3 Hz), 134.26, 133.59, 133.53, 132.90, 130.85 (d, $J_{C,P}$ = 13.1 Hz), 129.17, 128.70 (d, $J_{C,P}$ = 168.2 Hz), 128.59, 128.51, 128.10 (d, $J_{C,P}$ = 29.2 Hz), 125.18, 62.66 (m, 2 P-O*C*H$_2$), 57.20 (+, in DEPT135 spectrum), 16.31 (d, $J_{C,P}$ = 7.4 Hz, P-OCH$_2$*C*H$_3$), 16.12 (d, $J_{C,P}$ = 7.4 Hz, P-OCH$_2$*C*H$_3$) ppm. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 18.34 ppm. IR (film): $\tilde{\nu}$ = 2927, 1699, 1408, 1261, 1117, 1020, 873 cm^{-1}. MS (EI): *m*/*z* (%) = 366 (7) $[M]^+$, 105 (100), 77 (20). HRMS (EI): calcd. for $C_{18}H_{20}O_4ClP$ 366.0782; found 366.0783.

General Procedure for the Synthesis of 2 by the Hydration of 3: A solution of compound **3** (0.2 mmol) in MeOH (3 mL) was added to a mixture of $HgSO_4$ (6 mg, 0.02 mmol), MeOH (7 mL), H_2O (0.4 mL), and concentrated H_2SO_4 (2 drops), and the mixture was heated at reflux for 2–3 h. H_2O (10 mL) was added, MeOH was removed under reduced pressure, and the remaining mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and dried with Na_2SO_4, and the solvents were evaporated in vacuo. The residue was chromatographed on silica gel [petroleum ether (b.p. 60–90 °C)/EtOAc, 5:1–2:1] to give product **2**. Their structures were

confirmed by comparison of their ^{1}H NMR spectra with those of the corresponding alcoholysis products.

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