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Construction of 1*H*-pyrrol-2-ylphosphonates via [3+2] cycloaddition of phosphate azomethine ylides with ynones

Jiang Meng, Di Wu, Ying Shi, Xingxin Yu *, Wei-Ping Deng

Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

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ABSTRACT

An efficient route for the construction of 1*H*-pyrrol-2-ylphosphonates via the [3+2] cycloaddition of phosphonate azomethine ylides with ynones is described. This transformation proceeds with good functional group tolerance under mild conditions with good efficiency and selectivity. And the synthesis of 1*H*-pyrrol-2-ylphosphonates could also be achieved via the three-component reaction of benzaldehydes, aminomethyl phosphonates and ynones.

1. Introduction

Considerable attention has been paid to organophosphorus compounds[1] due to their ubiquity in biological systems[2] and their potential to serve as pharmaceuticals.[3] Recent studies have indicated that many phosphorus-containing heterocycle compounds showed interesting bioactivities.[4] For instance, nitrogen-containing bisphosphonates (N-BPs) are the only clinically validated drugs targeting hFPPS (human farnesyl pyrophosphate synthase), and also disease modifying agents induce apoptosis and down-regulation of ERK (Extracellular Regulated Kinase) phosphorylation in human multiple myeloma cell lines.[4a] Meanwhile, pyrroles[5] are privileged structural motifs in many natural products and pharmaceuticals exhibiting remarkable biological activities.[6] Because of the importance of organophosphorus compounds and pyrroles, our continuous interest in natural product-like compounds prompted us to devote our efforts for the development of efficient and rapid methods for the synthesis of phosphorus-containing pyrroles, with a hope of finding more active hits or leads for our particular biological assays.

Recently, many efforts have been made towards the development of novel and highly efficient synthetic protocols for 1*H*-pyrrol-2-ylphosphonates synthesis, such as the aromatization of phosphonate pyrrolidines,[7] the phosphorylation of pyrroles,[8] the ring-closing reaction of functionalized aminophosphorus derivatives,[9] the multi-component coupling reaction[10] and the [3+2] cycloaddition.[11] Among which, the [3+2] cycloaddition of phosphonate azomethine ylides to both activated alkenes and alkynes as dipolarophiles has arguably been one of the most ideal and powerful synthetic strategies.[12] The catalytic asymmetric [3+2] cycloaddition of azomethine ylides with ynones has been established.[13] However, phosphonate azomethine ylides have rarely been employed for the synthesis of 1*H*-pyrrol-2-ylphosphonates.[14]

Recently, we developed a direct and facile synthesis of multi-substituted pyrroles via AgOAc-catalyzed [3+2] cycloaddition of azomethine ylides with ynones, providing the corresponding adducts in moderate to high yields (up to 89%).[15] Herein, we would like to disclose our latest results for the synthesis of 1*H*-pyrrol-2-ylphosphonates via [3+2] cycloaddition of phosphonate azomethine ylides with ynones.

2. Results and discussion

Initial study was performed with phosphonate azomethine ylide **1a** and ynone **2a** in the presence of base in THF at room temperature (Table 1). To our delight, the formation of desired 1*H*-pyrrol-2-ylphosphonate **3a** was observed when *t*-BuOK was used as the base, albeit in low yield (17%, Table 1, entry 1). The yield of **3a** was further increased to 34% in the presence of NaH (Table 1, entry 2). In order to reduce the competitive byproducts, the amounts and ratios of phosphonate azomethine ylide **1a** and ynone **2a** were screened (Table 1, entries 3–5). Using 2 equiv of phosphonate azomethine

* Corresponding author. Tel./fax: +86 21 64252431; e-mail address: xxyu@ecust.edu.cn (X. Yu).

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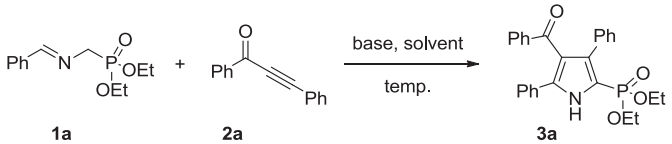
Table 1
The [3+2] cycloaddition of phosphonate azomethine ylide **1a** with ynone **2a**[a]



1a 2a 3a

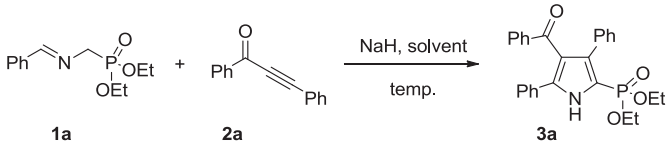
Entry	1a	2a	Base	Yield[b] (%)
1	1.2 equiv	1 equiv	*t*-BuOK/1.2 equiv	17
2	1.2 equiv	1 equiv	NaH/1.2 equiv	34
3	1.5 equiv	1 equiv	NaH/1.5 equiv	49
4	2 equiv	1 equiv	NaH/2 equiv	64
5	2.5 equiv	1 equiv	NaH/2.5 equiv	62
6	2 equiv	1 equiv	*t*-BuONa/2 equiv	43
7	2 equiv	1 equiv	*t*-BuOK/2 equiv	47
8	2 equiv	1 equiv	LDA/2 equiv	37
9	2 equiv	1 equiv	*n*-BuLi/2 equiv	—[c]
10	2 equiv	1 equiv	CH_3ONa/2 equiv	40

[a] Reaction conditions: All reactions were carried out in 0.1 M scale in 1 mL THF at room temperature. The base was added to a solution of **1a**, about 1 min later **2a** was added, and then the solution was stirred about 2 h without other statement.
[b] Isolated yield based on ynone **2a**.
[c] The reaction was complicated and no desired product was isolated.

ylide **1a** led to the generation of 1*H*-pyrrol-2-ylphosphonate **3a** with 64% yield (Table 1, entry 4). Similar yield was observed when the amount of **1a** was increased to 2.5 equiv (Table 1, entry 5). Base screening demonstrated that NaH was the best choice. Other bases such as *t*-BuONa, *t*-BuOK, LDA, *n*-BuLi, CH_3ONa gave unsatisfactory results (Table 1, entries 6–10).

Next, solvents and reaction temperatures were investigated in the presence of 2 equiv of phosphonate azomethine ylide **1a** and 2 equiv of NaH (Table 2). THF was found to be optimal for this kind of transformation (Table 2, entry 1). Carrying out the reactions at 0 °C, and then warming up to room temperature naturally had positive effect on yield.

Table 2
Screening studies of the reaction conditions[a]



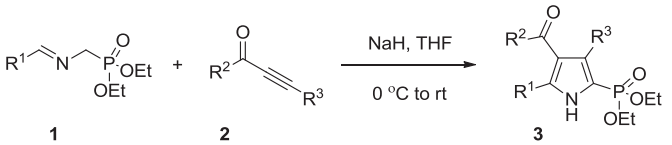
1a 2a 3a

Entry	Base	Solvent	Yield[b] (%)
1	NaH/2 equiv	THF	64
2	NaH/2 equiv	Toluene	33
3	NaH/2 equiv	2-Me-THF	38
4	NaH/2 equiv	1,4-Dioxane	29
5	NaH/2 equiv	CPME	44
6	NaH/2 equiv	CH_3CN	25
7	NaH/2 equiv	DMF	23
8	NaH/2 equiv	DCM	30
9	C_2H_5ONa/2 equiv	C_2H_5OH	0
10	NaH/2 equiv	THF	54[c]

[a] Reaction conditions: All reactions were carried out with 0.2 mmol of **1a** and 0.1 mmol of **2a** in 1 mL of solvent at 0 °C, once **2a** added the temperature was allowed to rise to room temperature without other statement.
[b] Isolated yield based on ynone **2a**.
[c] Carried out at −10 °C, 3 h.

The above optimization led to **1a**/**2a**=2:1, 2 equiv of NaH, THF, 0 °C to room temperature as the optimal reaction conditions for this [3+2] cycloaddition. The scope and generality of substrates were then examined and the results are summarized in Table 3. A wide array of ynones **2** with electron-neutral, electron-deficient or electron-rich substituents on the aromatic ring, reacted smoothly

Table 3
Substrate scope of the [3+2] cycloaddition of phosphonate azomethine ylide **1** with ynone **2**[a]



1 2 3

Entry	R^1	R^2/R^3	Yield[b] (%)
1	C_6H_5 (**1a**)	C_6H_5/C_6H_5 (**2a**)	60 (**3a**)
2	C_6H_5 (**1a**)	3-ClC_6H_4/C_6H_5 (**2b**)	65 (**3b**)
3	C_6H_5 (**1a**)	4-ClC_6H_4/C_6H_5 (**2c**)	67 (**3c**)
4	C_6H_5 (**1a**)	4-BrC_6H_4/C_6H_5 (**2d**)	62 (**3d**)
5	C_6H_5 (**1a**)	4-$MeOC_6H_4/C_6H_5$ (**2e**)	43 (**3e**)
6	C_6H_5 (**1a**)	2-Naphthyl/C_6H_5 (**2f**)	54 (**3f**)
7	C_6H_5 (**1a**)	C_6H_5/4-MeC_6H_4 (**2g**)	60 (**3g**)
8	C_6H_5 (**1a**)	C_6H_5/*n*-C_4H_9 (**2h**)	57 (**3h**)
9	C_6H_5 (**1a**)	C_6H_5/Cyclopropyl (**2i**)	48 (**3i**)
10	4-FC_6H_4 (**1b**)	C_6H_5/C_6H_5 (**2a**)	51 (**3j**)
11	4-ClC_6H_4 (**1c**)	C_6H_5/C_6H_5 (**2a**)	63 (**3k**)
12	4-ClC_6H_4 (**1c**)	4-ClC_6H_4/C_6H_5 (**2c**)	66 (**3l**)
13	4-ClC_6H_4 (**1c**)	4-$MeOC_6H_4/C_6H_5$ (**2e**)	48 (**3m**)[c]
14	4-BrC_6H_4 (**1d**)	C_6H_5/C_6H_5 (**2a**)	63 (**3n**)
15	4-$NO_2C_6H_4$ (**1e**)	C_6H_5/C_6H_5 (**2a**)	69 (**3o**)
16	4-MeC_6H_4 (**1f**)	C_6H_5/C_6H_5 (**2a**)	55 (**3p**)
17	Isopropyl (**1g**)	C_6H_5/C_6H_5 (**2a**)	—[d]
18	C_6H_5 (**1a**)	Methyl/C_6H_5 (**2j**)	—[d]
19	C_6H_5 (**1a**)	Methoxy/C_6H_5 (**2k**)	—[d]

[a] Reaction conditions: All reactions were carried out with **1** (0.4 mmol), **2** (0.2 mmol); NaH (0.4 mmol) in 2 mL THF at 0 °C, once **2** added the temperature was allowed to rise to room temperature without other statement.
[b] Isolated yield based on ynone **2**.
[c] 14% Dihydropyrrole **4m** was isolated.
[d] No desired product.

with phosphonate azomethine ylide **1a** to afford the corresponding 1*H*-pyrrol-2-ylphosphonates **3** in moderate to good yields (Table 3, entries 1–7). For instance, reaction of phosphonate azomethine ylide **1a** and ynone **2c** generated the expected product **3c** in 67% yield (Table 3, entry 3). Notably, 2-naphthyl substrate **2f** was also tolerated in this reaction (Table 3, entry 6). In addition to the aromatic ring attached to the carbon carbon triple bond, *n*-butyl and cyclopropyl groups were found suitable as well to afford the desired 1*H*-pyrrol-2-ylphosphonates **3** in moderate yields (Table 3, entries 7–9). This [3+2] cycloaddition was found to be workable for phosphonate azomethine ylides **1b**–**1f** with electron-withdrawing and -donating substituents on the aromatic backbone, and proceeded smoothly leading to the desired 1*H*-pyrrol-2-ylphosphonates **3** in moderate yields (Table 3, entries 10–16). The structure of compound **3k** was verified by X-ray diffraction analysis (Fig. 1, CCDC 1040194). Unfortunately, When R^1 was replaced with alkyl group like isopropyl, the reaction did not give the desired product (Table 3, entry 17). When R^2 was replaced with methyl or

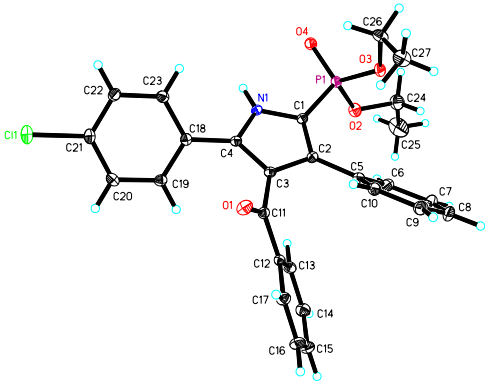
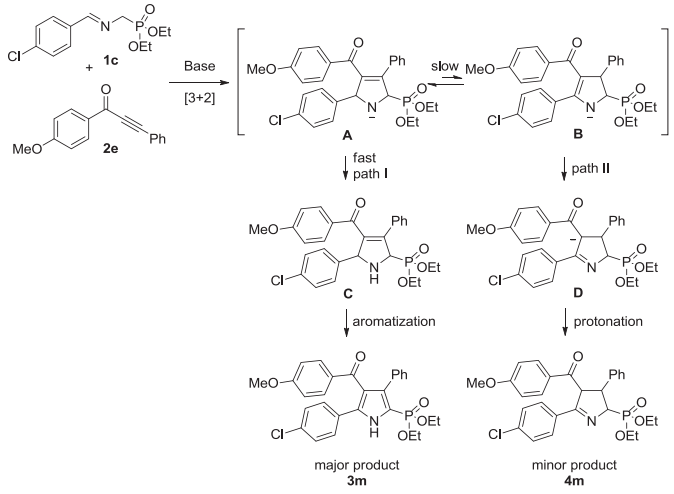


Fig. 1. X-ray ORTEP illustration of compound **3k**.

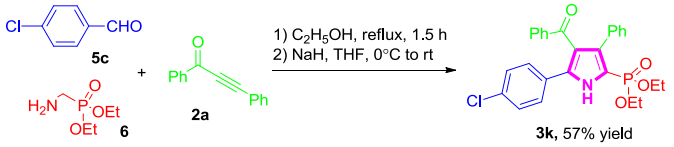
methoxy, the reactions also did not take place under the optimal reaction conditions (Table 3, entries 18 and 19).

Due to 14% dihydropyrrole **4m** was isolated in the reaction of phosphonate azomethine ylide **1c** and ynone **2e** (Table 3, entry 13), we reason that dihydropyrrole intermediate **A** was formed first via the [3+2] cycloaddition in the presence of base (Scheme 1). Intermediate **A** underwent a fast protonation and aromatization[16] process to generate the major product 1*H*-pyrrol-2-ylphosphonates **3m** (path I). Meanwhile, the slow rearrangement would occur to generate intermediate **B**. Subsequent tautomerism and protonation would give rise to the minor product **4m** (path II).



Scheme 1. A plausible route for the [3+2] cycloaddition.

The three-component reaction of 4-chlorobenzaldehyde **5c**, aminomethyl phosphonate **6** and ynone **2a** has been explored. To our delight, the transformation proceeded smoothly affording the desired 1*H*-pyrrol-2-ylphosphonate **3k** in 57% yield (Scheme 2).



Scheme 2. Synthesis of 1*H*-pyrrol-2-ylphosphonate **3k** via the three-component reaction of 4-chlorobenzaldehyde **5c**, aminomethyl phosphonate **6** and ynone **2a**.

3. Conclusion

In conclusion, we have developed an efficient route for the construction of 1*H*-pyrrol-2-ylphosphonates via the [3+2] cycloaddition of phosphonate azomethine ylides with ynones. This transformation proceeded with good functional group tolerance under mild conditions with good efficiency and selectivity. A plausible reaction pathway was proposed, and the synthesis of 1*H*-pyrrol-2-ylphosphonates could also be achieved via the three-component reaction of benzaldehydes, aminomethyl phosphonates and ynones. Currently, the related library construction and biological activity screening of these pyrrole compounds are still ongoing, and the results will be reported in due course.

4. Experimental section

4.1. General

All reagents and starting materials were obtained commercially and used as received unless otherwise stated. All reactions were carried out with dry solvents. Anhydrous tetrahydrofuran (THF), 2-Me-THF, CPME, toluene and ethanol were dried with sodium (Na). Anhydrous dichloromethane (DCM) and *N*,*N*-dimethylformamide (DMF) were dealt with CaH_2. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.20–0.30 mm silica gel plates (GF254, Qingdao, China) using UV light as the visualizing agent. Silica gel (200–300 mesh, Qingdao, China) was used for flash column chromatography. NMR spectra were recorded on Bruker AVANCE III 400 M instrument and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 accurate-Mass Q-TOF LC/MS system (1200-6520/Agilent). Melting points were obtained in open capillary tubes using a micro melting point apparatus.

4.2. General procedure for the preparation of compounds 3 via the [3+2] cycloaddition of phosphonate azomethine ylides with ynones

To a solution of phosphonate azomethine ylide (0.4 mmol) in 1.5 mL dry THF at 0 °C was added 0.4 mmol NaH (16 mg, 60%) in batches. About 1 min later, a solution of ynone (0.2 mmol) in 0.5 mL dry THF was dropped to the reaction solution. And then the reaction was allowed to rise to room temperature and monitored with TLC. The reaction was quenched with saturated NH_4Cl when completed (about 2 h). The mixture was extracted with EtOAc, the combined organic phases were washed with brine and concentrated by reduced pressure to get the crude product, which was purified by column chromatography on silica gel using PE/EA (5:1–1:1).

4.3. Procedure for the preparation of compounds 3k via the three-component reaction

To a solution of aminomethyl phosphonate **6** (735.3 mg, 4.4 mmol) in 20 mL anhydrous ethanol was added 4-chlorobenzaldehyde **5c** (562.3 mg, 4 mmol), and the mixture was heated at reflux for 1.5 h. Evaporation of the solvent under reduced pressure afforded phosphonate azomethine ylide **1c**. And then NaH (160 mg, 4 mmol, 60%) and ynone **2a** (412.4 mg, 2 mmol) were added, respectively, in 25 mL dry THF at 0 °C. The reaction was allowed to rise to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl when completed, and extracted with EtOAc. The mixture was extracted with EtOAc, the combined organic phases were washed with brine and concentrated by reduced pressure to get the crude product, which was purified by column chromatography on silica gel using PE/EA (5:1–1:1) affording the desired 1*H*-pyrrol-2-ylphosphonate **3k** (560 mg, 57% yield).

4.4. Characterization data of compounds 3

*4.4.1. Diethyl (4-benzoyl-3,5-diphenyl-1H-pyrrol-2-yl)phosphonate (**3a**).* Yellow solid, 56 mg, 60% yield. Mp: 165–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.67 (d, J=7.7 Hz, 2H), 7.47 (d, J=7.4 Hz, 2H), 7.32 (d, J=7.5 Hz, 2H), 7.29–7.24 (m, 4H), 7.19–7.13 (m, 5H), 4.03–3.93 (m, 2H), 3.91–3.81 (m, 2H), 1.10 (t, J=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 138.8 (d, $^3J_{CP}$=12 Hz), 138.4, 134.9 (d, $^2J_{CP}$=16 Hz), 133.5, 132.4, 130.9, 130.0, 129.9, 128.5, 128.3, 128.2, 127.8, 127.5, 127.1, 122.5 (d, $^3J_{CP}$=12 Hz), 115.4 (d, $^1J_{CP}$=226 Hz), 62.3, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3121, 3081, 2977, 2861, 1649, 1596, 1549, 1491, 1463, 1395, 1286, 1245, 1220, 1050, 1020, 977,

904, 783, 733, 696 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{26}NO_4P$ $[M]^+$ 459.1599, found 459.1597.

*4.4.2. Diethyl (4-(3-chlorobenzoyl)-3,5-diphenyl-1H-pyrrol-2-yl) phosphonate (**3b**).* Yellow solid, 64 mg, 65% yield. Mp: 173–175 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.60 (s, 1H), 7.52–7.47 (m, 3H), 7.31–7.27 (m, 5H), 7.24–7.17 (m, 4H), 7.04–7.08 (m, 1H), 3.99–3.93 (m, 2H), 3.88–3.82 (m, 2H), 1.10 (t, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 138.9, 138.4 (d, $^3J_{CP}$=12 Hz), 134.0 (d, $^2J_{CP}$=16 Hz), 132.9, 132.3, 131.1, 129.7, 128.9, 128.8, 128.1, 127.7, 127.4, 127.3, 126.8, 126.5, 126.2, 120.8 (d, $^3J_{CP}$=12 Hz), 114.7 (d, $^1J_{CP}$=227 Hz), 61.3, 14.9; IR (KBr): $\tilde{\nu}$=3422, 3122, 3083, 2985, 2924, 1652, 1570, 1549, 1491, 1463, 1242, 1218, 1159, 1049, 1021, 979, 789, 749, 696, 591 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}ClNO_4P$ $[M]^+$ 493.1210, found 493.1201.

*4.4.3. Diethyl (4-(4-chlorobenzoyl)-3,5-diphenyl-1H-pyrrol-2-yl) phosphonate (**3c**).* Yellow solid, 66 mg, 67% yield. Mp: 195–198 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.60 (d, J=8.5 Hz, 2H), 7.51–7.48 (m, 2H), 7.29–7.31 (m, 2H), 7.26–7.21 (m, 3H), 7.21–7.16 (m, 3H), 7.10 (d, J=8.5 Hz, 2H), 3.97–3.87 (m, 2H), 3.85–3.75 (m, 2H), 1.06 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 139.0 (d, $^3J_{CP}$=12 Hz), 138.8, 136.9, 135.0 (d, $^2J_{CP}$=16 Hz), 133.4, 131.3, 130.8, 130.1, 128.6, 128.5, 128.4, 128.2, 127.7, 127.4, 122.2 (d, $^3J_{CP}$=12 Hz), 115.6 (d, $^1J_{CP}$=227 Hz), 62.5, 16.0; IR (KBr): $\tilde{\nu}$=3422, 3124, 3085, 2978, 2923, 2854, 1656, 1584, 1492, 1463, 1399, 1245, 1219, 1159, 1090, 1055, 1018, 904, 793, 697 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}ClNO_4P$ $[M]^+$ 493.1210, found 493.1201.

*4.4.4. Diethyl (4-(4-bromobenzoyl)-3,5-diphenyl-1H-pyrrol-2-yl) phosphonate (**3d**).* Yellow solid, 67 mg, 62% yield. Mp: 180–183 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.53–7.48 (m, 4H), 7.36–7.23 (m, 7H), 7.21–7.14 (m, 3H), 3.96–3.86 (m, 2H), 3.84–3.74 (m, 2H), 1.09 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 139.0 (d, $^3J_{CP}$=12 Hz), 137.2, 135.0 (d, $^2J_{CP}$=16 Hz), 133.4, 131.4, 131.2, 130.8, 130.1, 128.6, 128.5, 128.4, 127.7, 127.6, 127.4, 122.1 (d, $^3J_{CP}$=12 Hz), 115.6 (d, $^1J_{CP}$=227 Hz), 62.5, 16.0; IR (KBr): $\tilde{\nu}$=3422, 3126, 3089, 2980, 2924, 2864, 1656, 1582, 1491, 1464, 1396, 1245, 1222, 1169, 1054, 1021, 975, 906, 792, 757, 697, 523 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}BrNO_4P$ $[M]^+$ 537.0705, found 537.0706.

*4.4.5. Diethyl (4-(4-methoxybenzoyl)-3,5-diphenyl-1H-pyrrol-2-yl) phosphonate (**3e**).* Yellow solid, 42 mg, 43% yield. Mp: 195–190 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.69 (d, J=8.8 Hz, 2H), 7.48–7.46 (m, 2H), 7.36–7.34 (m, 2H), 7.29–7.23 (m, 4H), 7.21–7.15 (m, 2H), 6.66 (d, J=8.8 Hz, 2H), 4.04–3.94 (m, 2H), 3.92–3.82 (m, 2H), 3.74 (s, 3H), 1.11 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 163.1, 137.8 (d, $^3J_{CP}$=12 Hz), 134.6 (d, $^2J_{CP}$=16 Hz), 133.5, 132.3, 131.3, 130.9, 129.9, 128.4, 128.2, 128.1, 127.6, 127.1, 122.7 (d, $^3J_{CP}$=12 Hz), 115.1 (d, $^1J_{CP}$=226 Hz), 113.2, 62.3, 55.3, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3161, 3085, 2962, 2851, 1639, 1598, 1573, 1490, 1462, 1391, 1262, 1221, 1152, 1026, 904, 797, 696, 648, 593 cm^{-1}; HRMS (EI-TOF): calcd for $C_{28}H_{28}NO_5P$ $[M]^+$ 489.1705, found 489.1700.

*4.4.6. Diethyl (4-(2-naphthoyl)-3,5-diphenyl-1H-pyrrol-2-yl)phosphonate (**3f**).* Yellow solid, 55 mg, 54% yield. Mp: 197–199 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.15 (s, 1H), 7.84 (d, J=8.5 Hz, 1H), 7.72 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.6 Hz, 1H), 7.50–7.48 (m, 3H), 7.42 (d, J=7.6 Hz, 1H), 7.37 (d, J=7.5 Hz, 2H), 7.26–7.19 (m, 3H), 7.14–7.10 (m, 2H), 7.09–7.02 (m, 1H), 4.08–4.98 (m, 2H), 3.97–3.87 (m, 2H), 1.14 (t, J=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 138.3 (d, $^3J_{CP}$=12 Hz), 135.6, 135.3, 134.9 (d, $^2J_{CP}$=16 Hz), 133.4, 132.5, 132.2, 130.8, 129.8, 129.4, 128.5, 128.3, 128.2, 128.2, 127.8, 127.6, 127.6, 127.2, 126.3, 125.1, 122.7 (d, $^2J_{CP}$=12 Hz), 115.4 (d, $^1J_{CP}$=226 Hz), 62.4, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3114, 3058, 2974, 2920, 1641, 1626, 1550, 1491, 1463, 1437, 1393, 1294, 1246, 1221, 1149, 1119, 1057, 1017, 976, 906, 840, 799, 766, 697, 528 cm^{-1}; HRMS (EI-TOF): calcd for $C_{31}H_{28}NO_4P$ $[M]^+$ 509.1756, found 509.1753.

*4.4.7. Diethyl (4-benzoyl-5-phenyl-3-(p-tolyl)-1H-pyrrol-2-yl)phosphonate (**3g**).* Yellow solid, 57 mg, 60% yield. Mp: 200–202 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.68 (d, J=7.3 Hz, 2H), 7.45 (dd, J=7.5, 1.6 Hz, 2H), 7.29 (t, J=7.4 Hz, 1H), 7.31–7.28 (m, 5H), 7.15 (t, J=7.7 Hz, 2H), 6.99 (d, J=7.9 Hz, 2H), 4.03–3.93 (m, 2H), 3.91–3.81 (m, 2H), 2.25 (s, 3H), 1.11 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 138.3 (d, $^3J_{CP}$=12 Hz), 138.3, 136.8, 135.1 (d, $^2J_{CP}$=16 Hz), 132.4, 130.8, 130.3, 129.9, 129.8, 128.4, 128.3, 128.3, 128.2, 127.8, 122.5 (d, $^3J_{CP}$=12 Hz), 115.3 (d, $^1J_{CP}$=226 Hz), 62.4, 21.2, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3125, 3080, 2985, 2921, 1654, 1596, 1531, 1492, 1464, 1411, 1391, 1280, 1242, 1222, 1188, 1169, 1057, 1034, 974, 912, 777, 744, 694, 604 cm^{-1}; HRMS (EI-TOF): calcd for $C_{28}H_{28}NO_4P$ $[M]^+$ 473.1756, found 473.1754.

*4.4.8. Diethyl (4-benzoyl-3-butyl-5-phenyl-1H-pyrrol-2-yl)phosphonate (**3h**).* Yellow solid, 50 mg, 57% yield. Mp: 120–122 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.66 (d, J=7.5 Hz, 2H), 7.32 (t, J=7.2 Hz, 1H), 7.30–7.24 (m, 2H), 7.19 (t, J=7.4 Hz, 2H), 7.15–7.10 (m, 3H), 4.09–4.01 (m, 4H), 2.74–2.70 (m, 2H), 1.45–1.43 (m, 2H), 1.35–1.25 (m, 8H), 0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 138.6 (d, $^3J_{CP}$=12 Hz), 137.9, 135.8 (d, $^2J_{CP}$=17 Hz), 131.2, 130.1, 128.7, 127.6, 127.5, 127.0, 126.8, 120.8 (d, $^2J_{CP}$=12 Hz), 114.2 (d, $^1J_{CP}$=228 Hz), 61.2, 32.8, 24.1, 21.9, 15.2, 12.8; IR (KBr): $\tilde{\nu}$=3422, 3132, 3087, 2958, 2929, 2868, 1641, 1596, 1554, 1462, 1431, 1242, 1217, 1169, 1110, 1048, 1022, 965, 908, 772, 740, 694, 658, 602 cm^{-1}; HRMS (EI-TOF): calcd for $C_{25}H_{30}NO_4P$ $[M]^+$ 439.1912, found 439.1910.

*4.4.9. Diethyl (4-benzoyl-3-cyclopropyl-5-phenyl-1H-pyrrol-2-yl) phosphonate (**3i**).* Yellow solid, 41 mg, 48% yield. Mp: 138–140 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.76 (d, J=7.2 Hz, 2H), 7.41 (t, J=6.8 Hz, 1H), 7.34–7.27 (m, 4H), 7.24–7.13 (m, 3H), 4.14–4.07 (m, 4H), 1.82–1.73 (m, 1H), 1.35–1.24 (m, 6H), 0.65–0.60 (m, 4H); ^{13}C NMR (100 MHz, CDCl3) δ 194.9, 138.9, 137.8 (d, $^3J_{CP}$=12.0 Hz), 135.9 (d, $^2J_{CP}$=16 Hz), 132.6, 130.9, 129.8, 128.3, 128.2, 128.1, 128.0, 123.2 (d, $^3J_{CP}$=13 Hz), 116.6 (d, $^1J_{CP}$=227 Hz), 62.3, 16.3, 7.9, 7.1; IR (KBr): $\tilde{\nu}$=3422, 3145, 3092, 2985, 2928, 2870, 1646, 1595, 1578, 1465, 1435, 1407, 1319, 1235, 1217, 1168, 1057, 1025, 977, 924, 907, 831, 773, 740, 694, 637, 618 cm^{-1}; HRMS (EI-TOF): calcd for $C_{24}H_{26}NO_4P$ $[M]^+$ 423.1599, found 423.1596.

*4.4.10. Diethyl (4-benzoyl-5-(4-fluorophenyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3j**).* Yellow solid, 49 mg, 51% yield. Mp: 178–182 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 7.64 (d, J=7.4 Hz, 2H), 7.52 (dd, J=8.6, 5.4 Hz, 2H), 7.31–7.26 (m, 3H), 7.18–7.13 (m, 5H), 6.92 (t, J=8.6 Hz, 2H), 3.96–3.87 (m, 2H), 3.84–3.76 (m, 2H), 1.06 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 162.6 (d, $^1J_{CF}$=248 Hz), 138.3, 137.9 (d, $^3J_{CP}$=12 Hz), 135.1 (d, $^3J_{CP}$=16 Hz), 133.4, 132.5, 130.5 (d, $^3J_{CF}$=8 Hz), 130.0, 129.8, 127.9, 127.5, 127.2, 127.1, 122.5 (d, $^3J_{CP}$=12 Hz), 115.2 (d, $^2J_{CF}$=22 Hz), 115.2 (d, $^1J_{CP}$=227 Hz), 62.4, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3126, 3083, 2985, 2934, 2867, 1651, 1596, 1500, 1456, 1398, 1242, 1221, 1161, 1052, 1018, 978, 909, 846, 788, 751, 697, 592, 530 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}FNO_4P$ $[M]^+$ 477.1505, found 477.1504.

*4.4.11. Diethyl (4-benzoyl-5-(4-chlorophenyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3k**).* Yellow solid, 62 mg, 63% yield. Mp: 206–210 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 7.66–7.64 (m, 2H), 7.46 (d, J=8.6 Hz, 2H), 7.33–7.28 (m, 3H), 7.23–7.21 (m, 2H), 7.18–7.13 (m, 5H), 3.99–3.89 (m, 2H), 3.87–3.77 (m, 2H), 1.08 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 138.13, 137.4 (d, $^3J_{CP}$=12 Hz), 134.9 (d, $^2J_{CP}$=16 Hz), 134.2, 133.2, 132.6, 129.9, 129.8, 129.8, 129.3, 128.5, 127.9, 127.6, 127.2, 122.8 (d, $^3J_{CP}$=12 Hz), 115.6 (d,

$^{1}J_{CP}$=226 Hz), 62.4, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3134, 3086, 2979, 2927, 2862, 1657, 1596, 1578, 1490, 1462, 1394, 1314, 1242, 1223, 1158, 1092, 1050, 1027, 975, 901, 785, 742, 698, 588 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}ClNO_4P$ $[M]^+$ 493.1210, found 493.1194.

*4.4.12. Diethyl (4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3l**).* Yellow solid, 70 mg, 66% yield. Mp: 198–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.58 (d, *J*=7.8 Hz, 2H), 7.46 (d, *J*=8.0 Hz, 2H), 7.27–7.25 (m, 4H), 7.16–7.12 (m, 5H), 4.00–3.90 (m, 2H), 3.88–3.78 (m, 2H), 1.09 (t, *J*=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 138.95, 137.5 (d, $^{3}J_{CP}$=12 Hz), 136.5, 134.8 (d, $^{2}J_{CP}$=16 Hz), 134.5, 133.1, 131.2, 129.9, 129.8, 129.2, 128.6, 128.2, 127.7, 127.4, 122.3 (d, $^{3}J_{CP}$=12 Hz), 115.7 (d, $^{1}J_{CP}$=226 Hz), 62.5, 15.9; IR (KBr): $\tilde{\nu}$=3448, 3125, 3074, 2980, 2936, 1646, 1585, 1545, 1488, 1460, 1438, 1390, 1286, 1243, 1219, 1166, 1086, 1056, 1012, 902, 826, 792, 742, 695, 589, 535 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{24}Cl_2NO_4P$ $[M]^+$ 527.0820, found 527.0796.

*4.4.13. Diethyl (5-(4-chlorophenyl)-4-(4-methoxybenzoyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3m**).* Yellow solid, 50 mg, 48% yield. Mp: 202–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 7.66 (d, *J*=8.0 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 7.32 (d, *J*=6.7 Hz, 2H), 7.26–7.22 (m, 3H), 7.18–7.16 (m, 2H), 6.66 (d, *J*=8.1 Hz, 2H), 4.01–3.91 (m, 2H), 3.89–3.79 (m, 2H), 3.75 (s, 3H), 1.09 (t, *J*=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 162.2, 135.6 (d, $^{3}J_{CP}$=12 Hz), 133.6 (d, $^{2}J_{CP}$=16 Hz), 132.9, 132.3, 131.2, 130.1, 128.8, 128.6, 128.4, 127.4, 126.5, 126.2, 121.9 (d, $^{3}J_{CP}$=12 Hz), 114.3 (d, $^{1}J_{CP}$=226 Hz), 112.2, 61.3, 54.3, 14.9; IR (KBr): $\tilde{\nu}$=3422, 3141, 3085, 2980, 2928, 2861, 1645, 1594, 1508, 1491, 1462, 1395, 1314, 1261, 1221, 1154, 1052, 1021, 976, 908, 831, 802, 698, 630, 518 cm^{-1}; HRMS (EI-TOF): calcd for $C_{28}H_{27}ClNO_5P$ $[M]^+$ 523.1315, found 523.1311.

*4.4.14. Diethyl (4-benzoyl-5-(4-bromophenyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3n**).* Yellow solid, 68 mg, 63% yield. Mp: 193–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 7.65 (d, *J*=7.3 Hz, 2H), 7.41–7.36 (m, 4H), 7.33–7.29 (m, 3H), 7.14–7.13 (m, 5H), 4.00–3.91 (m, 2H), 3.89–3.79 (m, 2H), 1.09 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 138.2, 137.5 (d, $^{3}J_{CP}$=12 Hz), 135.0 (d, $^{2}J_{CP}$=16 Hz), 133.3, 132.6, 132.6, 131.4, 130.1, 129.9, 129.8, 127.9, 127.5, 127.2, 122.8 (d, $^{3}J_{CP}$=12 Hz), 122.4, 115.6 (d, $^{1}J_{CP}$=227 Hz), 62.4, 15.9; IR (KBr): $\tilde{\nu}$=3422, 3129, 3084, 2976, 2926, 2860, 1656, 1595, 1488, 1462, 1393, 1314, 1260, 1241, 1223, 1157, 1049, 1027, 974, 900, 815, 783, 744, 697, 588 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}BrNO_4P$ $[M]^+$ 537.0705, found 537.0708.

*4.4.15. Diethyl (4-benzoyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrrol-2-yl)phosphonate (**3o**).* Brown orange solid, 70 mg, 69% yield. Mp: 202–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.09 (d, *J*=8.8 Hz, 2H), 7.76 (d, *J*=8.8 Hz, 2H), 7.66 (d, *J*=7.5 Hz, 2H), 7.33 (t, *J*=7.4 Hz, 1H), 7.29–7.26 (m, 2H), 7.20–7.11 (m, 5H), 3.97–3.88 (m, 2H), 3.86–3.78 (m, 2H), 1.07 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 146.9, 137.9, 137.1, 135.8 (d, $^{3}J_{CP}$=12 Hz), 135.3 (d, $^{2}J_{CP}$=16 Hz), 132.9, 132.9, 129.9, 129.8, 129.1, 128.1, 127.6, 127.5, 124.2 (d, $^{3}J_{CP}$=12 Hz), 123.4, 117.0 (d, $^{1}J_{CP}$=226 Hz), 62.6, 15.9; IR (KBr): $\tilde{\nu}$=3423, 3123, 3086, 2979, 2929, 2862, 1656, 1597, 1550, 1518, 1461, 1393, 1337, 1244, 1223, 1156, 1051, 1029, 978, 901, 852, 784, 736, 696, 587 cm^{-1}; HRMS (EI-TOF): calcd for $C_{27}H_{25}N_2O_6P$ $[M]^+$ 504.1450, found 504.1453.

*4.4.16. Diethyl (4-benzoyl-3-phenyl-5-(p-tolyl)-1H-pyrrol-2-yl) phosphonate (**3p**).* Yellow solid, 55 mg, 55% yield. Mp: 155–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.67 (d, *J*=7.5 Hz, 2H), 7.38 (d, *J*=7.1 Hz, 2H), 7.32–7.27 (m, 3H), 7.17–7.15 (m, 5H), 7.05 (d, *J*=7.0 Hz, 2H), 3.98–3.96 (m, 2H), 3.86–3.84 (m, 2H), 2.27 (s, 3H), 1.08 (t, *J*=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 137.9 (d, $^{3}J_{CP}$=12 Hz), 137.3, 137.1, 133.9 (d, $^{2}J_{CP}$=16 Hz), 132.5, 131.3, 128.9, 128.8, 127.9, 127.3, 126.9, 126.8, 126.5, 126.1, 121.2 (d, $^{3}J_{CP}$=12 Hz), 113.8 (d, $^{1}J_{CP}$=226 Hz), 61.3, 20.2, 14.9; IR (KBr): $\tilde{\nu}$=3422, 3127, 3101, 2978, 2926, 2859, 1650, 1596, 1503, 1462, 1395, 1242, 1225, 1157, 1049, 1025, 973, 902, 816, 777, 743, 699, 585 cm^{-1}; HRMS (EI-TOF): calcd for $C_{28}H_{28}NO_4P$ $[M]^+$ 473.1756, found 473.1754.

4.5. Characterization data of compound 4m

*4.5.1. Diethyl (5-(4-chlorophenyl)-4-(4-methoxybenzoyl)-3-phenyl-3,4-dihydro-2H-pyrrol-2-yl)-phosphonate (**4m**).* Light yellow oil, 15 mg, 14% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.69 (m, 4H), 7.36–7.30 (m, 5H), 7.21 (d, *J*=7.0 Hz, 2H), 6.84 (d, *J*=8.0 Hz, 2H), 5.18–5.16 (m, 1H), 4.75 (dd, *J*=21.0, 4.8 Hz, 1H), 4.22–4.09 (m, 4H), 3.91–3.82 (m, 1H), 3.85 (s, 3H), 1.31 (t, *J*=7.1 Hz, 3H), 1.23 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 170.8, 163.1, 141.9, 135.9, 130.7, 130.3, 128.5, 128.3, 127.8, 127.3, 126.6, 126.2, 112.9, 78.5 (d, $^{1}J_{CP}$=157 Hz), 64.9, 62.2, 61.7, 54.5, 50.2, 15.5, 15.3; IR (KBr): $\tilde{\nu}$=3225, 3062, 2963, 2927, 2853, 1708, 1666, 1598, 1572, 1510, 1492, 1456, 1400, 1311, 1257, 1172, 1092, 1026, 972, 836, 799, 748, 699, 595 cm^{-1}; LRMS (EI-TOF): calcd for $C_{28}H_{29}ClNO_5P$ $[M]^+$ 525.1, found 526.1 $[M+H]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.091.

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