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Selective Synthesis of Substituted Pyrrole-2-phosphine Oxides and -phosphonates from 2*H*-Azirines and Enolates from Acetyl Acetates and Malonates

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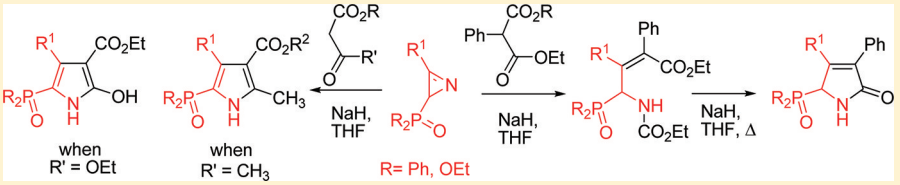
Supporting Information

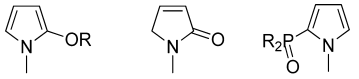


ABSTRACT: A simple and efficient selective synthesis of 1*H*-pyrrole-2-phosphine oxides **3** and -phosphonates **7** by addition of enolates derived from acetyl acetates to 2*H*-azirinylphosphine oxide **1** and -phosphonate **6** is reported. Nucleophilic addition of enolates derived from diethyl malonate to 2*H*-azirines **1** and **6** led to the formation of functionalized 2-hydroxy-1*H*-pyrrole-5-phosphine oxide **9** and -phosphonate **10**, while vinylogous α-aminoalkylphosphine oxides **14** and -phosphonate **15** may be obtained from azirines and the enolate derived from diethyl 2-phenylmalonate. Ring closure of vinylogous derivatives **14** and **15** in the presence of base led to the formation of 1,5-dihydro-3-pyrrolin-2-ones containing a phosphine oxide **17** or a phosphonate group **18**.

INTRODUCTION

2*H*-Azirine ring systems represent an important class of compounds because of their high reactivity.[1] They can be used as key intermediates in organic synthesis in the preparation of heterocycles[2a−e] and acyclic functionalized amino derivatives,[2f−h] since any of the three bonds of the azirine ring can be cleaved, depending on the experimental conditions used. On the other hand, pyrroles[3] are important heterocycles broadly used in material science[4] and not only can be found in naturally occurring and biologically important molecules[5] but also are important intermediates in the synthesis of natural products;[6] some of the recently isolated pyrroles have been found to exhibit considerable cytotoxicity and function in multidrug resistant (MDR) reversal[7a] and antimycobacterial activity.[7b] In this context, 2-silyloxypyrroles **I** (Scheme 1, R = SiR_3) and α,β-unsaturated γ-butyrolactams or 1,5-dihydro-3-pyrrolin-2-ones **II** (Scheme 1) demonstrated in the last years a wide use as efficient donors in diastereoselective and in enantioselective aldol reactions and related processes such as Mannich and Michael reactions.[8,9] For these reasons, although many methods have been devised for their preparation[10] the design and development of new methods of synthesis of substituted pyrroles continues to be a challenge.[11]

Scheme 1



The importance of azaheterocyclic phosphonates in synthetic, agrochemical, and medicinal chemistry has been well-documented[12] because it is known that phosphorus substituents regulate important biological functions[13] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting because they can be useful substrates for the preparation of biologically active compounds. However, very little information is reported about the properties of phosphonopyrroles[12] **III** (Scheme 1) undoubtedly due to the fact that there is no general method for their preparation. Only a few examples have been reported for the synthesis of 2-phosphonopyrroles (**III**) as shown in Scheme 2 involving either the use of heterocyclic precursors such as the aromatization of 3-oxo-2-phosphonate pyrrolidines (**IV**)[14] and the phosphorylation of pyrroles (**V**)[12a] or the use of acyclic substrates such as the [3 + 2] cycloaddition of iminomethylphosphonates (**VI**) with acetylenic compounds[15] or the ring-closing metathesis of functionalized aminophosphorus derivatives (**VII**).[16]

We describe new methods for the preparation of phosphorus-substituted nitrogen heterocycles[17] including *N*-hydroxypyrrole derivatives[17d] from functionalized phosphine oxides and phosphonates and the synthetic uses of aminophosphorus derivatives as starting materials for the synthesis of

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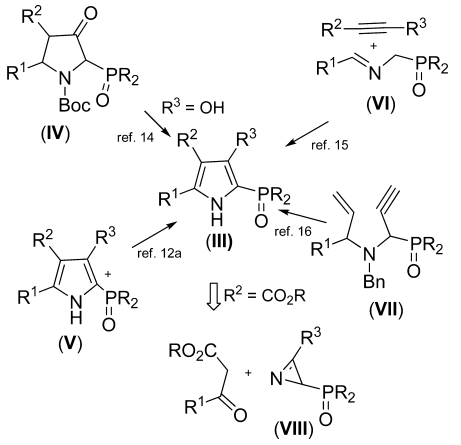
Scheme 2



acyclic compounds[18] and phosphorus-containing heterocycles.[19] Likewise, we reported the preparation of 2*H*-azirinylphosphine oxides **VIII** (R = Ph) and -phosphonates **VIII** (R = OEt, Scheme 2) through base-mediated Neber reaction of *β*-ketoxime tosylates[20] and their use for the synthesis of aminophosphorus derivatives,[21] and phosphorylated pyrazines,[22a] oxazoles,[22b,c] or aziridines.[22d] Continuing with our interest in the chemistry of small strained nitrogen heterocycles, we report here a new strategy for the preparation of functionalized pyrroles (**III**) containing phosphorus substituents such as a phosphine oxide (**III**, R = Ph) or a phosphonate group (**III**, R = OEt) by the selective addition of enolates derived from acetylacetates and malonates to phosphorylated azirines **VIII** (Scheme 2).

RESULTS AND DISCUSSION

Selective Addition of Enolates Derived from Acetylacetates to 2*H*-Azirines. Because of the strain of the three-membered ring, the electrophilic character of the C−N double bond is higher than in a normal imine, and azirines react with nucleophiles at the N−C3 double bond to produce aziridines.[1] Reaction of 2*H*-azirinylphosphine oxide **1a** (R = Ph, R^1 = CH_3) with methyl 2-oxobutanoate **2a** (R^2 = CH_3) and NaH in THF led to the formation of 4-methoxycarbonyl-3,5-dimethyl-1*H*-pyrrol-2-ylphosphine oxide **3a** (R = Ph, R^1 = R^2 = CH_3; Scheme 3, Table 1, entry 1). In the ^{31}P NMR spectrum the

Scheme 3

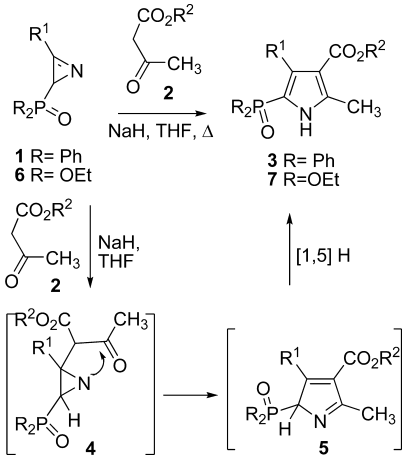


Table 1. Substituted Pyrroles 3 and 7

entry	compd	R	R^1	R^2	yield[a] (%)
1	**3a**	Ph	CH_3	CH_3	60
2	**3b**	Ph	CH_3	C_2H_5	60
3	**3c**	Ph	C_2H_5	CH_3	75
4	**7a**	OEt	CH_3	CH_3	60
5	**7b**	OEt	Ph	CH_3	95

[a]Yield of isolated purified compounds **3** and **7** from azirines **1** or **6**.

phosphine oxide group of this substituted pyrrole **3a** resonated at δ_P = 21.9 ppm, while singlets at δ_H = 1.89 ($^4J_{PH}$ = 1.5 Hz) and 2.42 ppm for both methyl groups in the ^1H NMR were observed. The formation of pyrrole **3a** suggests the approach of the enolate derived from acetyl acetate **2** to the C=N double bond of the azirine followed by ring-opening of the three membered heterocycle **4**, cyclization to the 5*H*-pyrrole **5**, and subsequent prototropic rearrangement to aromatic pyrrole **3**.

Similarly, pyrrole-phosphine oxides **3b,c** were obtained (Scheme 2, Table 1, entries 2 and 3) when the reaction of azirine **1a** (R = Ph, R^1 = CH_3) was performed with the enolate derived from ethyl 2-oxobutanoate **2b** (R^2 = C_2H_5) in the presence of NaH in THF or by the reaction of azirine **1b** (R = Ph, R^1 = C_2H_5) with the enolate derived from methyl 2-oxobutanoate **2a** (R^2 = CH_3). This process could also be extended to 2*H*-azirines derived from phosphonates **6**. Treatment of 3-methyl- (**6a**) (R = OEt, R^1 = CH_3) and 3-phenyl-2*H*-azirine (**6b**) (R = OEt, R^1 = Ph) with the enolate derived from methyl 2-oxobutanoate **2a** gave 1*H*-pyrrol-2-yl phosphonates **7a,b** (Scheme 2, Table 1, entries 4 and 5). Pyrrole derivatives[3] have been also obtained by ring expansion of 3-vinyl 2*H*-azirines[23] or by reaction of azirines with dimethyl acetylenedicarboxylate.[24] However, our strategy describes, as far as we know, the first synthesis of 1*H*-pyrrole-2-phosphonates and -phosphine oxides from azirines.

Selective Addition of Enolates Derived from Diethyl Malonates to 2*H*-Azirines. Reaction of enolates derived from *β*-diesters to 2*H*-azirines was also studied in order to test if these nucleophiles could give a new entry to substituted phosphorylated pyrrole derivatives. For this reason, we explored the reaction of 2*H*-azirinylphosphine oxides **1** and -phosphonates **6** with the enolates derived from malonates. Treatment of 3-methyl-2*H*-azirin-2-yldiphenylphosphine oxide **1a** (R = Ph, R^1 = CH_3) and 3-ethyl-2*H*-azirin-2-ylphosphonate **6b** (R = OEt, R^1 = C_2H_5) with enolate derived from diethyl malonate **8a** (R^3 = H) and NaH at 0 °C led exclusively to the formation of 2-hydroxy-1*H*-pyrroles with a phosphine oxide **9** (R = Ph) (Scheme 4, Table 2, entries 1 and 2) or a phosphonate in the 5 position **10** (R = OEt) (Scheme 4, Table 2, entry 3).

The formation of these hydroxypyrrole derivatives **9** and **10** may be explained by nucleophilic addition of the enolate from diethyl malonate to the imine bond of the azirines (Scheme 4) followed by ring-opening of the aziridine intermediate **11** (R^3 = H) and [1,3] hydrogen rearrangement from the carbon to the nitrogen atom with formation of intermediate **12**, intramolecular cyclization of which may give 1,5-dihydro-3-pyrrolin-2-one **13**. The aromatization of these heterocycles **13** may give the corresponding pyrrole derivatives **9** and **10**, favored by the presence of an ethoxycarbonyl group in position 3. A procedure for the synthesis of 3-hydroxypyrrole-phosphonates **III** (see Scheme 2, vide supra) by the aromatization of 3-oxo-2-phosphonate pyrrolidines (**IV**) has

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Scheme 4

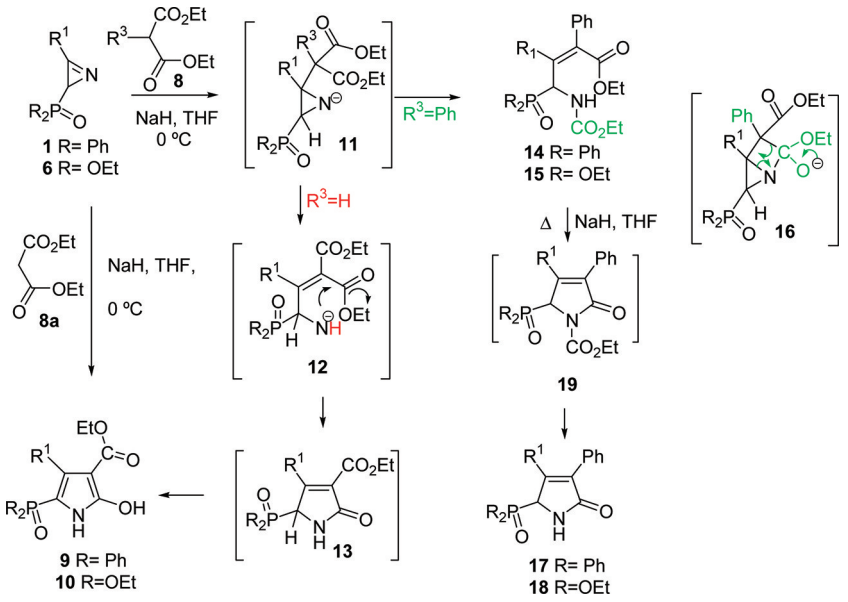

Table 2. Heterocycles Obtained from Azirines and Enolates Derived from Malonates

entry	compd	R	R^1	yield[a] (%)
1	**9a**	Ph	CH_3	60[b]
2	**9b**	Ph	C_2H_5	72[b]
3	**10**	OEt	C_2H_5	65[b]
4	**14a**	Ph	CH_3	50[b]
5	**14b**	Ph	C_2H_5	60[b]
6	**15**	OEt	CH_3	45[b]
7	**17a**	Ph	CH_3	83[c]
8	**17b**	Ph	C_2H_5	70[c]
9	**18**	OEt	CH_3	94[c]

[a]Yield of isolated purified compounds **9**, **10**, **14**, **15**, **17**, and **18**. [b]From azirines **1** and **6**. [c]From vinylogous derivatives **14** and **15**.

been reported.[14] However, this process reported here describes, as far as we know, the first the synthesis of 2-hydroxy-pyrroles with a phosphine oxide **9** or a phosphonate in the 5 position **10**.

However, a different behavior was observed by the reaction of 2*H*-azirinylphosphine oxides **1** and - phosphonates **6** with the enolate derived from a 2-substituted malonate. Treatment of 2*H*-azirin-2-yldiphenylphosphine oxide **1a,b** (R = Ph) and 2*H*-azirin-2-ylphosphonate **6a** (R = OEt) with enolate derived from diethyl 2-phenylmalonate **8b** (R^3 = Ph) and NaH at 0 °C led exclusively to the formation of vinylogous α-amino-alkylphosphine oxides **14** (R = Ph) (Scheme 4, Table 2, entries 4 and 5) or -phosphonate **15** (R = OEt) (Scheme 4, Table 2, entry 6). The selective nucleophilic addition of the enolate of 2-phenyl diethyl malonate to the imine bond of the azirines may explain the formation of adduct **11**. Ring-opening of the aziridine intermediate **11** with concomitant [1,5] rearrangemnent of the carboxylate group to the nitrogen atom may give the corresponding vinylogous α-amino-alkylphosphine oxides **14** and -phosphonate **15**.[25] Vinylogous α-aminophosphorus derivatives[26] **14** and **15** are isosteres of biologically active α-vinylglycines.[27]

Thermal treatment of vinylogous α-aminoalkylphosphine oxides **14** and -phosphonate **15** with NaH in reflux THF led to the formation of 1,5-dihydro-3-pyrrolin-2-ones or 1*H*-pyrrol-2(5*H*)-ones with a phosphine oxide **17** (R = Ph) (Scheme 4, Table 2, entries 7 and 8) or a phosphonate in the 5 position **18** (R = OEt) (Scheme 4, Table 2, entry 9). The formation of these pyrrole derivatives **17** and **18** may be explained by cyclocondensation of vinylogous derivatives **14** and **15** in the presence of NaH, formation of *N*-protected 1,5-dihydro-3-pyrrolin-2-ones **19**, and deprotection of these heterocycles **19** (Scheme 4). This process describes the first synthesis of 1,5-dihydro-3-pyrrolin-2-ones or 1*H*-pyrrol-2(5*H*)-ones **17** and **18** with a phosphorus-containing functional group.

CONCLUSION

In conclusion, this account describes a simple, mild, and convenient strategy for the selective synthesis of 1*H*-pyrroles **3** and **7** containing in the 2 position a phosphine oxide or a phosphonate group by addition of enolates derived from β-keto esters to 2*H*-azirinylphosphine oxide **1** and -phosphonate **6**, while the addition of enolates derived from diethyl malonate to 2*H*-azirines **1** and **6** led to the formation of functionalized 2-hydroxy-1*H*-pyrrole-5-phosphine oxide **9** and -phosphonate **10**. However, vinylogous α-aminoalkylphosphine oxides **14** and -phosphonate **15** may be obtained from azirines and the enolate derived from diethyl 2-phenylmalonate. Vinylogous α-amino-phosphorus derivatives are scarcely studied and prepared[26] and are isosteres of biologically active α-vinylglycines.[27] Basic cyclocondensation in the presence of a base (NaH) of these substrates **14** and **15** gives 1,5-dihydro-3-pyrrolin-2-ones **17** and **18** with a phosphine oxide or a phosphonate group in 5 position. Substituted pyrroles are important building blocks in organic synthesis,[3−7] and in recent years, some specific pyrrole derivatives such as oxypyrroles **I** or 1,5-dihydro-3-pyrrolin-2-ones **II** (Scheme 1) gained great relevance in diastereoselective and enantioselective preparative organic synthesis,[8−11] while phosphorus substituents regulate important biological functions,[13] and then molecular modifications involving the introduction of organophosphorus functionalities in pyrrole derivatives could be interesting because these new substituted five membered heterocycles may be useful substrates for the

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preparation of biologically active compounds of interest in medicinal chemistry.[12]

EXPERIMENTAL SECTION

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. IR-FT spectra were obtained as solids in KBr or as neat oils in NaCl. Mass spectra (MS) were made by electron impact (EI) at an ionizing voltage of 70 eV or by chemical ionization (CI) and high-resolution mass spectra (HRMS) was measured by the EI method. ^{1}H (300, 400 MHz), ^{13}C (75, 100 MHz), and ^{31}P NMR (120,160 MHz) spectra were recorded on 300 or 400 MHz spectrometers, respectively, in $CDCl_3$, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$, as internal standard in a broad band decoupled mode. The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet. Flash-column chromatography was carried out using commercial grades of silica gel finer than 230 mesh. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates, and spot visualization wasaccomplished by UV light (254 nm) or $KMnO_4$ solution. Azirines **1** and **6** were prepared according to literature procedure.[20b]

General Procedure for the Synthesis of Substituted Pyrrole 3 or 7. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of alkyl 2-oxobutanoate **2** (5.5 mmol). The mixture was stirred at room temperature for 1 h. A solution of 2*H*-azirinylphosphine oxides **1** (R = Ph) or -phosphonates **6** (R = OEt) (5.0 mmol) in dry THF (6 mL) was added slowly under nitrogen atmosphere. The mixture was stirred under reflux in THF for 2 or 5 h until TLC showed the disappearance of azirine. The NaH remainder was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction was dissolved with CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate) to yield the compounds **3** or **7** as white solid or as yellow oil.

Methyl 5-Diphenylphosphoryl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (3a). Compound **3a** was obtained as a white solid from 2*H*-azirine **1a** using the general procedure (1059 mg, 60%): mp 236−237 °C; ^{1}H NMR (CD_3OD) δ 1.89 (d, $^4J_{PH}$ = 1.5 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 7.36−7.69 (m, 10H, H-arom), 10.41 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 12.8, 13.9, 50.6, 113.3 (d, $^3J_{PC}$ = 11.1 Hz), 115.4 (d, $^1J_{PC}$ = 133.0 Hz), 128.4−133.2, 130.7 (d, $^2J_{PC}$ = 14.6 Hz), 141.0 (d, $^4J_{PC}$ = 8.1 Hz) 166.1; ^{31}P NMR (CD_3OD) δ 21.9; IR (NaCl) ν_{max} 3154, 3081, 3037, 2958, 1698, 1438, 1169, 1125 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}NO_3P$ [M$^+$ + H] 354.1254, found 354.1253.

Ethyl 5-Diphenylphosphoryl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (3b). Compound **3b** was obtained as a white solid from 2*H*-azirine **1b** using the general procedure (1101 mg, 60%): mp 241−242 °C; ^{1}H NMR (CD_3OD) δ 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.21 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 7.22−7.67 (m, 10H, CH-Arom), 10.44 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 12.8, 14.2, 14.4, 59.3, 113.6 (d, $^3J_{PC}$ = 11.6 Hz), 115.4 (d, $^1J_{PC}$ = 133.0 Hz), 128.5−133.3, 130.7 (d, $^2J_{PC}$ = 14.6 Hz), 140.9 (d, $^4J_{PC}$ = 8.1 Hz), 165.9; ^{31}P NMR (CD_3OD) δ 21.9; IR (NaCl) ν_{max} 3136, 3087, 3029, 2980, 1699, 1436, 1160, 1116 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}NO_3P$ [M$^+$ + H] 368.1416, found 368.1425.

Methyl 5-Diphenylphosphoryl-4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylate (3c). Compound **3c** was obtained as a white solid from 2*H*-azirine **1c** using the general procedure (1376 mg, 75%): mp 245−246 °C; ^{1}H NMR (CD_3OD) δ 0.57 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3), 2.37 (q, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.40−7.68 (m, 10H, CH-arom), 11.21 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 14.2, 14.6, 19.9, 50.5, 112.1 (d, $^3J_{PC}$ = 11.1 Hz), 114.5 (d, $^1J_{PC}$ = 133.0 Hz), 128.4−133.5, 137.2 (d, $^2J_{PC}$ = 15.1 Hz), 141.7 (d, $^4J_{PC}$ = 8.6 Hz), 168.8; ^{31}P NMR (CD_3OD) δ 22.5; IR (NaCl) ν_{max} 3155, 3082, 2958, 1698, 1169, 1127 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}NO_3P$ [M$^+$ + H] 368.1416, found 368.1418.

Methyl 5-Diethoxyphosphoryl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (7a). Compound **7a** was obtained as a yellow oil from 2*H*-azirine **6a** using the general procedure (867 mg, 60%): R_f 0.30 (ethyl acetate); ^{1}H NMR (CD_3OD) δ 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 2.30 (d, $^4J_{PH}$ = 1.8 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.91−4.06 (m, 4H, OCH_2) 10.36 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 11.9 (d, $^4J_{PC}$ = 3.0 Hz), 13.9 (d, $^2J_{PC}$ = 6.6 Hz), 16.2, 50.6 (d, $^6J_{PC}$ = 1.5 Hz), 62.1, 112.7 (d, $^1J_{PC}$= 228.6 Hz), 113.1 (d, $^3J_{PC}$= 15.1 Hz), 132.0 (d, $^2J_{PC}$= 17.1 Hz), 140.7 (d, $^4J_{PC}$ = 11.1 Hz) 166.0 (d, $^4J_{PC}$ = 2.5 Hz); ^{31}P NMR (CD_3OD) δ 11.7; IR (NaCl) ν_{max} 3181, 3110, 2980, 2918, 1694, 1018 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{21}NO_5P$ [M$^+$ + H] 290.1157, found 290.1160.

Methyl 5-Diethoxyphosphoryl-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (7b). Compound **7b** was obtained as a white solid from 2*H*-azirine **1b** using the general procedure (1668 mg, 95%): mp 157−158 °C; ^{1}H NMR (CD_3OD) δ 1.11 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3), 3.09 (d, $^5J_{PH}$ = 4.6 Hz, 3H, CH_3), 3.60 (s, 3H OCH_3), 3.83 (dq, $^3J_{PH}$ = 28.5 Hz, $^3J_{HH}$ = 7.2 Hz, 4H, OCH_2), 7.33 (s, 5H, H-arom), 11.40 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 13.7, 15.9, 50.5, 62.1, 112.8 (d, $^3J_{PC}$ = 14.1 Hz), 113.6 (d, $^1J_{PC}$ = 228.6 Hz), 126.9−134.6, 135.5 (d, $^2J_{PC}$ = 16.6 Hz), 140.6 (d, $^3J_{PC}$ = 11.1 Hz) 165.4 (d, $^4J_{PC}$ = 2.5 Hz); ^{31}P NMR (CD_3OD) δ 10.3; IR (NaCl) ν_{max} 3155, 3101, 2980, 1698, 1204, 1014 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $NaC_{17}H_{22}NO_5P$ [M$^+$ + Na] 374.1133, found 374.1137.

General Procedure for the Synthesis of Substituted Pyrrole 9 and 10. To a solution of NaH (5.5 mmol) in dry THF (15 mL) at 0 °C under nitrogen atmosphere was added a solution of diethyl malonate **8a** (5.5 mmol). The mixture was stirred at the same temperature for 1 h. A solution of 2*H*-azirinylphosphine oxides **1** (R = Ph) or -phosphonates **6** (R = OEt_2) (5 mmol) in dry THF (6 mL) was slowly added at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 2 or 5 h until TLC showed the disappearance of azirine. The NaH remainder was neutralized with a saturated solution of NH_4Cl. The crude reaction was extracted with CH_2Cl_2 (3 × 10 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by crystallization from CH_2Cl_2/hexane 1/1 or chromatography using silica gel hexane/ethyl acetate 1/1 to yield the compound **9** or **10** as a brown solid or as a colorless oil.

Methyl 5-Diphenylphosphoryl-2-hydroxy-4-methyl-1*H*-pyrrole-3-carboxylate (9a). Compound **9a** was obtained as a brown solid from 2*H*-azirine **1a** as described in the general procedure (1236 mg, 67%): mp 225−226 °C; ^{1}H NMR (CD_3OD) δ 1.32 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.98 (d, $^4J_{PH}$ = 1.9 Hz, 3H, CH_3) 4.30 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 7.41−7.70 (m, 10H, CH-arom), 9.60 (s, 1H, OH), 9.92 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 12.5, 14.4, 60.1, 95.1 (d, $^3J_{PC}$ = 10.6 Hz), 108.7 (d, $^1J_{PC}$ = 136.5 Hz), 128.3 (d, $^2J_{PC}$ = 13.1 Hz), 128.5−133.3, 156.3 (d, $^4J_{PC}$ = 10.6 Hz), 168.4; ^{31}P NMR (CD_3OD) δ 20.9; IR (NaCl) ν_{max} 3279, 3056, 2923, 2762, 1717, 1650, 1192, 1120 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $NaC_{20}H_{20}NO_4P$ [M$^+$ + Na] 392.1028, found 392.1024.

Ethyl 5-Diphenylphosphoryl-4-ethyl-2-hydroxy-1*H*-pyrrole-3-carboxylate 9b. Compound **9b** was obtained as a brown solid from 2*H*-azirine **1b** as described in the general procedure (1379 mg, 72%) as a brown solid: mp 231−232 °C; ^{1}H NMR (CD_3OD) δ 0.71 (t, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3), 1.32, (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 2.35 (q, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2), 4.30 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 7.27−7.80 (m, CH-Arom), 9.64 (s, 1H, OH), 10.04 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 14.2, 14.8, 19.8, 60.0, 94.0 (d, $^3J_{PC}$ = 10.6 Hz), 107.6 (d, $^1J_{PC}$ = 136.0 Hz), 128.4−132.0, 133.5, 134.9 (d, $^2J_{PC}$ = 13.6 Hz), 156.7 (d, $^3J_{PC}$ = 11.1 Hz), 168.1; ^{31}P NMR (CD_3OD) δ 21.4; IR (NaCl) ν_{max} 3292, 3136, 2980, 2900, 1654, 1200, 1120 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}NO_4P$ [M$^+$ + H] 384.1365, found 384.1366.

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Ethyl 5-Diethoxyphosphoryl-4-ethyl-2-hydroxy-1*H*-pyrrole-3-carboxylate (10). Compound **10** was obtained as a colorless oil from 2*H*-azirine **6a** as described in the general procedure (1037 mg, 65%): R_f 0.44 (ethyl acetate); ^{1}H NMR (CD_3OD) δ 1.08 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3), 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 1.28 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3), 2.67 (q, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2), 4.02 (dq, $^3J_{PH}$ = 23.8 Hz, $^3J_{HH}$ = 7.3 Hz, 4H, OCH_2), 4.27 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2) 9.62 (s, 1H, OH), 9.89 (s, 1H, NH); ^{13}C NMR (CD_3OD) δ 14.5, 15.7, 16.4, 19.8, 60.3, 62.3, 94.1 (d, $^2J_{PC}$ = 14.1 Hz), 104.7 (d, $^1J_{PC}$ = 235.2 Hz), 135.7 (d, $^3J_{PC}$ = 16.6 Hz), 156.4 (d, $^4J_{PC}$ = 15.1 Hz), 168.5; ^{31}P NMR (CD_3OD) δ 12.1; IR (NaCl) ν_{max} 3279, 3074, 2980, 1721, 1663, 1232, 1014 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{23}NO_6P$ [M$^+$ + H] 320.1258, found 320.1253.

General Procedure for the Synthesis of α-Aminoalkylphosphine Oxides 14 and -phosphonate 15. To a solution of NaH (5.5 mmol) in dry THF (15 mL) at 0 °C under nitrogen atmosphere was added a solution of diethyl 2-phenylmalonate **8** (5.5 mmol). The mixture was stirred at the same temperature for 1 h. A solution of 2*H*-azirinylphosphine oxides **1** (R = Ph) or -phosphonates **6** (R = OEt) (5 mmol) in dry THF (6 mL) was added slowly at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 2 or 5 h until TLC showed the disappearance of azirine. The NaH remainder was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction was dissolved with CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate) to yield the compounds **14** or **15** as a white solid.

Ethyl 4-(Diphenylphosphoryl)-4-((ethoxycarbonyl)amino)-3-methyl-2-phenylbut-2-enoate (14a). Compound **14a** was obtained as a white solid from 2*H*-azirine **1a** as described in the general procedure (1227 mg, 50%): mp 93−94 °C; ^{1}H NMR (CD_3OD) δ 1.07−1.26 (m, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3), 2.27 (s, 3H, CH_3), 3.97−4.21 (m, $^3J_{HH}$ = 7.2 Hz, 4H, OCH_2), 5.58 (t, $^2J_{PH}$ = 9.2 Hz, 1H, CH-P), 6.30 (d, $^3J_{HH}$ = 3.8 Hz, 1H, NH), 6.81−7.91 (m, 15H, CH-Arom); ^{13}C NMR (CD_3OD) δ 13.8, 13.9, 17.1, 52.3 (d, $^1J_{PC}$ = 73.0 Hz), 60.5, 61.1, 127.4−132.6, 134.8, 135.8, 155.6 (d, $^3J_{PC}$ = 7.6 Hz), 167.9; ^{31}P NMR (CD_3OD) δ 35.1; IR (NaCl) ν_{max} 3203, 3056, 2976, 1708, 1534, 1249, 1196 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{31}NO_5P$ [M$^+$ + H] 492.1934, found 492.1934.

Ethyl 3-((Diphenylphosphoryl)((ethoxycarbonyl)amino)-methyl)-2-phenylpent-2-enoate (14b). Compound **14b** was obtained as a white solid from 2*H*-azirine **1b** as described in the general procedure (1515 mg, 60%): mp 122−123 °C; ^{1}H NMR (CD_3OD) δ 1.08−1.22 (m, $^3J_{HH}$ = 7.0 Hz, 9H, CH_3), 2.76 (dq, $^4J_{PH}$ = 36.8 Hz, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 3.99−4.21 (m, $^3J_{HH}$ = 7.0 Hz, 4H, OCH_2), 5.57 (t, $^2J_{PH}$ = 9.5 Hz, 1H, CH-P), 6.18 (s, 1H, NH), 6.74−7.95 (m, 15H, CH-Arom); ^{13}C NMR (CD_3OD) δ 13.8, 14.2, 14.8, 23.9, 52.6 (d, $^1J_{PC}$ = 73.0 Hz), 60.4−61.5, 127.5−131.9, 135.1, 141.3, 155.6 (d, $^2J_{PC}$ = 9.1 Hz), 167.7; ^{31}P NMR (CD_3OD) δ 35.4; IR (NaCl) ν_{max} 3430, 3061, 2967, 2927, 1472, 1436, 1196, 1120 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{33}NO_5P$ [M$^+$ + H] 506.2096, found 506.2106.

Ethyl 4-(Diethoxyphosphoryl)-4-((ethoxycarbonyl)amino)-3-methyl-2-phenylbut-2-enoate (15). Compound **15** was obtained as a white solid from 2*H*-azirine **6a** as described in the general procedure (961 mg, 45%): mp 80−81 °C; ^{1}H NMR (CD_3OD) δ 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3), 1.29 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 2.11 (d, $^4J_{PH}$ = 3.2 Hz, 3H, CH_3), 3.88−4.31 (m, 8H, OCH_2), 4.90 (dd, $^2J_{PH}$ = 22.8 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, CH-P), 5.66 (s, 1H, NH), 7.28−7.56 (m, 5H, CH-Arom); ^{13}C NMR (CD_3OD) δ 14.0, 14.4, 16.0, 16.2 (d, $^3J_{PC}$ = 12.6 Hz), 50.8 (d, $^1J_{PC}$ = 150.6 Hz), 60.7−66.7, 127.7−129.5, 135.0 (d, $^2J_{PC}$ = 12.1 Hz), 135.7, 136.9, 155.3 (d, $^3J_{PC}$ = 11.1 Hz), 168.0 (d, $^4J_{PC}$ = 1.5 Hz); ^{31}P NMR (CD_3OD) δ 21.1; IR (NaCl) ν_{max} 3244, 2985, 1708, 1530, 1499, 1218, 1022 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}NO_7P$ [M$^+$+H] 428.1838, found 428.1840.

General Procedure for the Synthesis of Substituted Pyrroles 17 and 18. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of substituted phenylmalonate **8** (5 mmol). The mixture was stirred with reflux in THF for 1−2 h until TLC showed the disappearance of compound **14** or **15**. The NaH remainder was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction was disolved with CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel hexane/ethyl acetate 1/1 to yield the compounds **17** or **18** as a colorless or a pale yellow oil.

5-(Diphenylphosphoryl)-3-methyl-4-phenyl-1*H*-pyrrol-2-(5*H*)-one (17a). Compound **17a** was obtained as a colorless oil from **14a** as described in the general procedure (1548 mg, 83%): R_f = 0.20 (ethyl acetate); ^{1}H NMR (CD_3OD) δ 2.19 (d, $^4J_{PH}$ = 2.2 Hz, 3H, CH_3), 5.19 (d, $^2J_{PH}$ = 14.2 Hz, 1H, CH-P), 6.41 (s, 1H, NH), 6.99−7.92 (m, 15H, CH-Arom); ^{13}C NMR (CD_3OD) δ 14.8, 61.3 (d, $^1J_{PC}$ = 72.0 Hz), 125.3−133.0, 134.3 (d, $^2J_{PC}$ = 6.0 Hz), 150.5 (d, $^3J_{PC}$ = 5.0 Hz), 172.9; ^{31}P NMR (CD_3OD) δ 29.9; IR (NaCl) ν_{max} 3176, 3065, 1721, 1690, 1441, 1178 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{21}NO_2P$ [M$^+$ + H] 374.1310, found 374.1311.

5-(Diphenylphosphoryl)-3-ethyl-4-phenyl-1*H*-pyrrol-2-(5*H*)-one (17b). Compound **17b** was obtained as a pale yellow oil from **14b** as described in the general procedure: (1355 mg, 70%): Rf 0.22 (ethyl acetate); ^{1}H NMR (CD_3OD) δ 1.16 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH_3), 2.62 (q, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2), 5.26 (d, $^2J_{PH}$ = 14.5 Hz, 1H, CH-P), 6.91−7.86 (m, 15H, CH-Arom); ^{13}C NMR (CD_3OD) δ 13.7, 21,4, 58.7 (d, $^1J_{PC}$ = 72.5 Hz), 125.4−132.8, 133.8 (d, $^2J_{PC}$ = 5.5 Hz), 156.3 (d, $^4J_{PC}$ = 4.5 Hz), 173.2; ^{31}P NMR (CD_3OD) δ 30.1; IR (NaCl) ν_{max} 3176, 3065, 2967, 2932, 2869, 1677, 1432, 1196 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}NO_2P$ [M$^+$+H] 388.1466, found 388.1474.

5-(diethoxyphosphoryl)-3-methyl-4-phenyl-1*H*-pyrrol-2-(5*H*)-one 18. Compound **18** was obtained as a pale yellow oil from **15** as described in the general procedure (1.452 g, 94%): R_f 0.16 (ethyl acetate); ^{1}H NMR (CD_3OD) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 2.28 (d, $^4J_{PH}$ = 2.4 Hz, 3H, CH_3), 4.40 (q, $^3J_{HH}$ = 7.0 Hz, 4H, OCH_2), 5.45 (d, $^2J_{PH}$ = 18.6 Hz, 1H, CH-P), 7.25- 7.69 (m, 6H, H-Arom y NH); ^{13}C NMR (CD_3OD) δ 14.5, 16.4 (d, $^3J_{PC}$ = 4.0 Hz), 58.5 (d, $^1J_{PC}$ = 152.1 Hz), 63.5, 128.1−129.4, 130.8 (d, $^4J_{PC}$ = 2.0 Hz), 133.9 (d, $^2J_{PC}$ = 8.1 Hz), 148.0 (d, $^3J_{PC}$ = 7.6 Hz), 173.1 (d, $^3J_{PC}$ = 2.0 Hz); ^{31}P NMR (CD_3OD) δ 18.1; IR (NaCl) ν_{max} 3199, 3065, 2980, 1686, 1245, 1009, 729 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}NO_4P$ [M$^+$ + H] 310.1203, found 310.1208.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR for compounds **3a−c**, **7a,b**, **9a,b**, **10**, **14a,b**, **15**, **17a,b**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org/

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