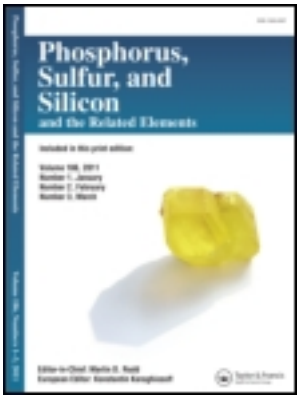

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Synthesis of Phosphorylated Enaminoketones and Their Application in the Preparation of Trifluoromethyl-Functionalized 2-Phosphonopyrroles

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SYNTHESIS OF PHOSPHORYLATED ENAMINOKETONES AND THEIR APPLICATION IN THE PREPARATION OF TRIFLUOROMETHYL-FUNCTIONALIZED 2-PHOSPHONOPYRROLES

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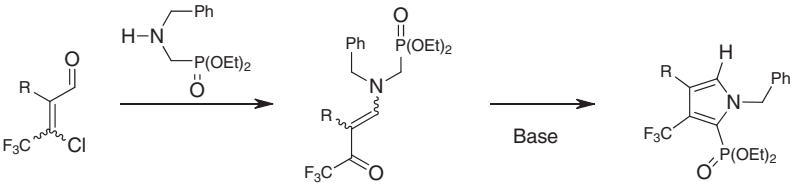
GRAPHICAL ABSTRACT



Abstract *New trifluoromethyl-functionalized 2-phosphonopyrroles were obtained by 5-exotrig cyclization of trifluoromethyl and phosphonyl functionalized enaminoketones.*

Keywords 2-Phosphonopyrroles; trifluoromethyl pyrroles; 5-exotrig cyclization trifluoromethyl enaminoketones; β-enaminoesters

INTRODUCTION

Heterocycles bearing a trifluoromethyl group have attracted much attention in pharmaceutical sciences because the introduction of fluorine into an organic compound can cause important changes in the physical, chemical, and biological properties such as enhanced hydrophobic binding and increased stability.[1] It has been also shown that the presence of a phosphonyl group can influence the biological functions of heterocyclic systems.[2] Some synthetic approaches to 2-phosphonopyrroles have already been reported[3]: (1) 1,3-dipolar cycloaddtion of nitrile ylides or carbanions derived from isocyanomethylphosphonate or *N*-phosphonomethylimines to alkynes or alkenes containing a suitable leaving group,[4] (2) direct phosphonylation of pyrrole salts with chlorophosphates,[2,5] (3) phosphonylation of pyrrole with dimethyl phosphite and $Mn(OAc)_3 \cdot 2\ H_2O$ as coupling agent,[6] (4) thermolysis of cyclic phosphonates in *N*-methylpyrrole,[7] (5) aromatization of the corresponding

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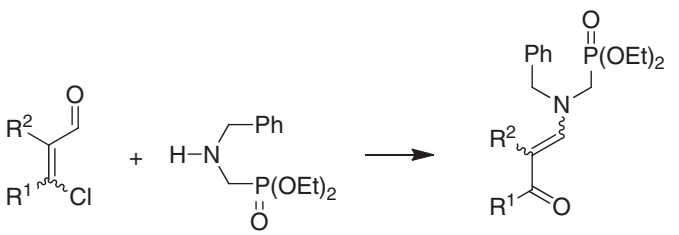
2-phosphonate NH-pyrrolidines using air,[8] and (6) an excellent procedure, in which the key step involves a ring-closing metathesis/oxidation sequence of dienes or enynes bearing an amino and a phosphonyl function.[9]

RESULTS AND DISCUSSION

3-Chloro-4,4,4-trifluoro-2-phenylbutenal (**1a**), easily available (as a 40:60 *E*/*Z* mixture) from the Vilsmeier reaction of 1,1,1-trifluoro-3-phenylacetone,[10] is known to be a versatile building block for the synthesis of both acyclic and cyclic trifluoromethyl-functionalized compounds.[11] This acroleine can be converted into enaminoketone by reaction with *N*-benzylglycine ethyl ester. The resulting enaminoketone was cyclized to the corresponding pyrrole containing trifluoromethyl and carboxylic group.[12] In our present work, we first make use of this acrolein and the phosphorus analogue of *N*-benzylglycinate to prepare the enaminoketone **2a**. Similarly enaminoketones **2b**,**c** were prepared (Scheme 1, Table 1).



1a: $R^1 = CF_3$; R^2 = Ph
b: $R^1 = CF_3$; $R^2 = CO_2Et$
c: $R^1 = CH_3$; R^2 = Ph

2a–c

Scheme 1

The enaminoketone **2a** exists in the form of one diastereomer (only one signal observed in both ^{31}P and ^{19}F NMR spectrum); its configuration (*E* or *Z*) was not determined, however.

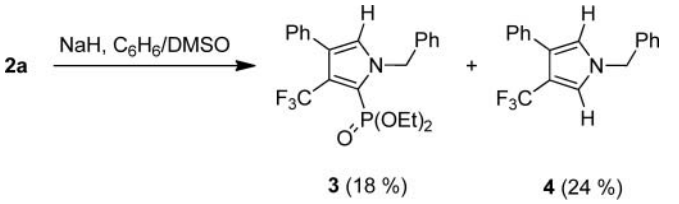
The enaminoketone **2b** was isolated as 6:4 mixture of diastereomers (based on ^{19}F NMR and confirmed by ^{31}P NMR spectroscopy). The enaminoketone **2c** was obtained as only one diastereomer (one signal in the ^{31}P NMR spectrum), and its *E* configuration was confirmed by the nuclear Overhauser effect spectroscopy (NOESY) correlation between the vinylic and the methyl protons of the acetyl group. We tried to cyclize the enaminoketone

Table 1 Synthesis of enaminoketones **2a–c**

2	R^1	R^2	Conditions	Yield (%)
a	CF_3	Ph	NEt_3/Et_2O, r.t., 96 h	59
b	CF_3	COOEt	THF, r.t., 48 h	68
c	CH_3	Ph	NEt_3/Et_2O, r.t., 240 h	63

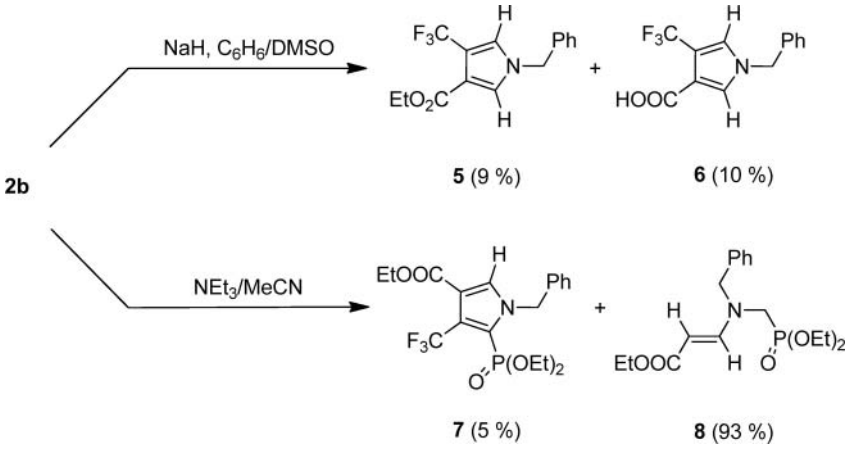
Note: r.t., room temperature.

2a with NEt_3 (3 eq.) in MeCN as a solvent by refluxing for 72 h but only the starting enaminoketone was recovered. However, when we used hard basic conditions—NaH (2 eq.), C_6H_6/dimethyl sulfoxide (DMSO)—which were also used for the cyclization of nonphosphorylated enaminoketones,[12] we obtained 2-phosphonopyrrole **3** and the dephosphorylated[5a] pyrrole **4** (Scheme 2).



Scheme 2

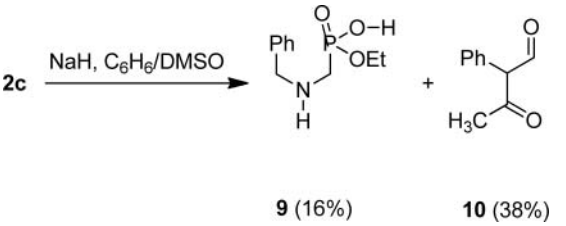
The structure of **3** was confirmed by a NOESY experiment, in which a correlation between the H-5 of the pyrrole ring and the benzylic protons was observed. The structure of **4** was confirmed by the heteronuclear multiple bond correlation (HMBC) experiment in which the signal of the benzyl carbon atom correlates with the signals of the pyrrole protons H-1 and H-5. In addition, the NOESY spectrum displays a correlation between the benzylic protons and the protons H-1 and H-5 of the pyrrole ring, while no correlation between H-1 and H-5 of the pyrrole ring is observed. Thus only the products of 5-exotrig cyclization have been obtained, and in contrast to nonphosphorylated enaminoketones,[12] no 3-exotrig cyclization products were found. From the reaction of enaminoketone **2b** under the same experimental conditions, only the dephosphorylated products of a 5-exotrig cyclization **5** and **6** were isolated (Scheme 3).



Scheme 3

The structure of these products was established by NOESY experiments, which show a correlation between the benzylic protons and the two pyrrole protons and no correlation between the two pyrrole protons. Since the presence of an electron-withdrawing group (COOEt) may favor carbon–phosphorus bond cleavage under basic conditions,[5a] we

examined the reaction of **2b** under mild basic conditions using NEt_3 (3 eq.) in MeCN as solvent on refluxing for 20 h. Thus, the 2-phosphonopyrrole **7** was formed together with enaminoester **8**. The structure of pyrrole **7** was confirmed by the NOESY correlation between H-2 of the pyrrole ring and the benzylic protons. The structure of enaminoester **8** was confirmed by the ^{1}H NMR spectra. The characteristic coupling constant of the two protons at the double bond is about 13 Hz that indicates the presence of the *E*-isomer instead of the *Z*-isomer. This indication was confirmed by a NOESY experiment, in which a correlation between the protons of two methylene groups attached to nitrogen and the vinylic proton H-2 is observed. When we tried to cyclize enaminoketone **2c**, which contains a methyl group instead of a trifluoromethyl group, and mild basic conditions (NEt_3 3 eq., MeCN, refluxing for 7 days) were applied, the unreacted substrate was almost quantitatively recovered. However, when hard basic conditions were applied (NaH, 2 eq., C_6H_6/DMSO), only the hydrolysis products **9**, the known 2-acetylphenylacetaldehyde **10**,[13] and 43% of unreacted substrate were obtained (Scheme 4).



Scheme 4

Thus in contrast to fluorinated or not phosphorylated[12] enaminoketones in this case, no pyrroles were formed.

CONCLUSION

In summary, we have presented a first synthetic approach to 2-phosphono-pyrroles containing a trifluoromethyl group. The preparation requires enaminoketones which have never been used previously as starting materials for the synthesis of 2-phosphonopyrroles. Although the yields are low and the method failed for nonfluorinated enaminoketone **2c**, in case of **2b**, it enabled the synthesis of trifluoromethyl and phosphonyl functionalized enaminoester **8**. As far as we know, the synthesis of this kind of compounds is still of great interest for their synthetic and biological applications.[14]

EXPERIMENTAL

Melting points (mp) are uncorrected. NMR spectra were obtained with a Bruker DPX 250, a Bruker Avance III 600, a Bruker Avance II Plus 700, a Varian Gemini 200, and a Tesla BS 687 spectrometer operating at 600, 700, and 80 MHz for ^{1}H (TMS); 151, 63, and 50 MHz for ^{13}C; 235 and 565 MHz for ^{19}F ($CFCl_3$); and 101 and 80 MHz for ^{31}P (H_3PO_4). Electrospray ionization-mass spectrometry (ESI-MS) spectra were recorded with a Bruker Esquire-LC instrument. High-resolution mass spectra [HRMS; electron-impact (EI), 70 eV] were recorded with a Finnigan MAT 95 instrument. The elemental analysis was performed by the Laboratory of Microanalysis of the Centre of Molecular and

Macromolecular Studies, Polish Academy of Science, Łódź. Starting acroleines **1a–c** were obtained according to a literature method.[10,15]

Synthesis of Enaminoketones 2a–c: General Procedure

To a solution of (benzylaminomethyl)phosphonic acid diethyl ester (2.57 g, 10.0 mmol, for **2a,c**; 5.14 g, 20.0 mmol, for **2b**) in Et_2O (30.0 mL, for **2a,c**) or tetrahydrofuran (THF; 20.0 mL, for **2b**), NEt_3 (1.36 g, 13.4 mmol, for **2a,c**) and the chloroacroleine **1a–c** (9.0 mmol) was added under argon atmosphere. The mixture was stirred at room temperature (time given in Table 1). In the case of **3c**, an additional portion of chloroacroleine **1c** (0.77 g, 3.0 mmol) was added after a period of 120 h and stirring was continued for additional 120 h. The precipitate, if present, was filtered off, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel, hexane/Et_2O, 6:4–2:8) to afford **2a–c** as yellow oils.

[Benzyl-(4,4,4-trifluoro-3-oxo-2-phenylbut-1-enyl)amino]methylphosphonic Acid Diethyl Ester (2a). Yield: 59%. ^{1}H NMR ($CDCl_3$, 80 MHz): $\delta = 1.32$ (t, $^3J_{HH} = 7.1$ Hz, 6H, CH_3), 3.30 (d, $^2J_{PH} = 11.2$ Hz, 2H, CH_2), 3.92–4.33 (m, 6H, CH_2), 7.13–7.37 (m, 5H, arom-H), 7.85 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 16.4$ (d, $^3J_{PC} = 5.6$ Hz, CH_3), 51.4 (d, $^1J_{PC} = 184.6$ Hz, CH_2P), 62.1 (CH_2N), 62.8 (d, $^2J_{PC} = 7.1$ Hz, CH_2O), 118.1 (q, $^1J_{FC} = 291.1$ Hz, C-4), 127.7 (C_{arom}), 128.1 (C_{arom}), 128.4 (C_{arom}), 129.0 (C_{arom}), 132.1 (C_{arom}), 133.3 (C_{arom} or C-2), 134.7 (C_{arom} or C-2), 153.5 (C-1), 178.2 (q, $^2J_{FC} = 32.0$ Hz, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = 19.1$. ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -75.7$. HRMS (EI) Calcd. for $C_{22}H_{25}F_3NO_4P$: 455.1473. Found: 455.1475.

[Benzyl(diethoxyphosphorylmethyl)amino]methylene-4,4,4-trifluoro-3-oxo-butyric Acid Ethyl Ester (2b). Yield: 68%. ^{1}H NMR ($CDCl_3$, 80 MHz): $\delta =$ 1.17–1.41 (m, 9H, CH_3), 3.55–4.33 (m, 8H, $CH_2O + CH_2P$), 4.75 (br s, 2H, CH_2N), 7.19–7.44 (m, 5H, arom-H), 7.77 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 13.3$ (CH_3, *Z* or *E*), 13.4 (CH_3, *Z* or *E*), 15.9 (CH_3, *Z* or *E*), 16.0 (CH_2 *Z* or *E*), 44.7 (d, $^1J_{PC} =$ 154.1 Hz, CH_2, *Z* or *E*), 51.9 (d, $^1J_{PC} = 154.7$ Hz, CH_2, *Z* or *E*), 55.7 (CH_2N, *Z* or *E*), 61.0 (CH_2O), 62.7 (CH_2O), 64.6 (CH_2O), 100.0 (br s, C-2), 116.8 (q, $^1J_{FC} = 289.3$ Hz, C-4), 127.8 (C_{arom}), 128.3 (C_{arom}), 128.7 (C_{arom}), 128.8 (C_{arom}), 129.0 (C_{arom}), 133.0 (C_{arom}), 133.4 (C_{arom}), 156.0 (CHN, *Z* or *E*), 156.6 (CHN, *Z* or *E*), 165.8 (C-1), 165.9 (br s, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = 19.3$ (br s), 17.7 (br s), 63:37. ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -71.9$ (br s), -75.8 (br s), 59:41. Anal. Calcd. for $C_{19}H_{25}F_3NO_6P$: C, 50.56; H, 5.58%. Found: C, 49.94; H, 5.74%.

[Benzyl-((*E*)-3-oxo-2-phenylbut-1-enyl)amino]methylphosphonic Acid (2c). Yield: 63%. ^{1}H NMR ($CDCl_3$, 80 MHz): $\delta = 1.31$ (t, $^3J_{HH} = 7.1$ Hz, 6H, CH_3), 1.96 (s, 3H, CH_3), 3.28 (d, $^2J_{PH} = 10.3$ Hz, 2H, CH_2P), 3.91–4.23 (m, 4H, CH_2O), 4.27 (s, 2H, CH_2N), 7.01–7.43 (m, 10H, C_6H_5), 7.71 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 15.8 (d, $^3J_{PC} = 5.6$ Hz, CH_3), 27.0 (C-4), 46.7 (d, $^1J_{CP} = 156.7$ Hz, CH_2P), 55.2 (CH_2N), 61.7 (d, $^2J_{PC} = 7.0$ Hz, CH_2O), 112.6 (C-2), 126.5 (CH_{arom}), 126.8 (CH_{arom}), 127.1 (CH_{arom}), 127.7 (CH_{arom}), 128.0 (CH_{arom}), 131.0 (CH_{arom}), 135.2 (C_{arom}), 136.7 (C_{arom}), 147.4 (C-1), 196.0 (C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = 20.4$. HRMS (EI) Calcd. for $C_{22}H_{28}NO_4P$: 401.1756. Found: 401.1745.

Reactions of Enaminoketones in the Presence of Sodium Hydride

Under argon atmosphere, sodium hydride (0.16 g, 6.5 mmol) was added to a solution of DMSO (4.0 mL) in benzene (10.5 mL), and the suspension was stirred at room

temperature for 30 min. A solution of the respective enaminoketone **2a**–**c** (3.2 mmol) in benzene (3.5 mL) was added for a period of 5 min, and stirring was continued for 72 h. Subsequently diethyl ether (30 mL) was added. The mixture was extracted with water (3×10.0 mL for **2a**,**c**; 1×10 mL for **2b**). The organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was separated by column chromatography (silica gel, petroleum ether/Et_2O 4:6–2:8) to give pyrroles **3–5** or unreacted **2c** was recovered. The combined water phase was acidified to pH ≈ 2 with HCl (aqueous solution, 3 mol/L) and extracted with Et_2O (3×30 mL). The organic phases were combined, the precipitate of **9** (in the case of **2c**) was filtered, and the filtrate was dried over $MgSO_4$. After evaporation of the solvent, the products **6** and **10**[13] were obtained. The pyrrole **6** required additional purification by column chromatography (silica gel, petroleum ether/Et_2O 2:8).

(1-Benzyl-4-phenyl-3-trifluoromethyl-1*H*-pyrrol-2-yl)phosphonic Acid Di-ethyl Ester (3). Yield: 18%. Colorless crystals, mp 76–78°C. ^{1}H NMR ($CDCl_3$, 80 MHz): $\delta = 1.25$ (t, $^3J_{HH} = 7.1$ Hz, 6H, CH_3), 4.01 (m, 4H, CH_2O), 5.69 (s, 2H, CH_2N), 6.87 (d, $^5J_{PH} = 5.3$ Hz, 1H, CHN), 7.15–7.42 (m, 10H, arom-H). ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 16.0$ (d, $^3J_{PC} = 6.6$ Hz, CH_3), 53.1 (CH_2N), 62.5 (d, $^2J_{PC} = 5.4$ Hz, CH_2O), 119.3 (dq, $^1J_{PC} = 220.9$ Hz, $^3J_{FC} = 3.1$ Hz, C-2), 120.5 (dq, $^2J_{PC} = 14.3$ Hz, $^2J_{FC} = 35.3$ Hz, C-3), 123.0 (q, $^1J_{CF} = 269.6$ Hz, CF_3), 125.9 (dq, $^3J_{PC} = 11.0$ Hz, $^3J_{FC} = 2.5$ Hz, C-4), 127.2 (CHN), 127.4 (CH_{arom}). 127.76 (CH_{arom}), 127.8 (CH_{arom}), 128.0 (CH_{arom}), 128.7 (CH_{arom}), 129.3 (CH_{arom}), 133.6 (C_{arom}), 137.5 (C_{arom}). ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = 5.7$ (q, $^4J_{FP} = 2.4$ Hz). ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -51.4$ (d, $^4J_{PF} = 2.6$ Hz). Anal. Calcd. for $C_{22}H_{23}F_3NO_3P$: C, 60.41; H, 5.30%. Found: C, 60.49; H, 5.20%.

1-Benzyl-3-phenyl-4-trifluoromethyl-1*H*-pyrrole (4). Yield: 24%. Yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 5.10$ (s, 2H, CH_2), 6.79 (d, $^4J_{HH} = 2.0$ Hz, 1H, CHN), 7.09 (m, CHN), 7.24–7.28 (m, 10H, arom-H). ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 53.6$ (CH_2N), 112.3 (q, $^2J_{FC} = 35.4$ Hz, C-4), 121.3 (C-2), 122.4 (q, $^3J_{FC} = 5.8$ Hz, C-5), 123.8 (q, $^3J_{FC} = 2.0$ Hz, C-3), 124.1 (q, $^1J_{FC} = 266.7$ Hz, CF_3), 126.6 (CH_{arom}), 127.3 (CH_{arom}), 128.1 (CH_{arom}), 128.2 (CH_{arom}), 128.3 (CH_{arom}), 128.9 (CH_{arom}), 133.9 (C_{arom}), 136.3 (C_{arom}). ^{19}F NMR ($CDCl_3$, 565 MHz): $\delta = -54.5$. HRMS (EI) Calcd. for $C_{18}H_{14}F_3N$: 301.1078. Found: 301.1074.

1-Benzyl-4-trifluoromethyl-1*H*-pyrrole-3-carboxylic Acid Ethyl Ester (5). Yield: 9%. Yellow oil. ^{1}H NMR ($CDCl_3$, 700 MHz): $\delta = 1.35$ (t, $^3J_{HH} = 7.0$ Hz, 3H, CH_3), 4.30 (q, $^3J_{HH} = 7.0$ Hz, 2H, CH_2), 5.07 (s, 2H, CH_2), 7.02 (d, $^4J_{HH} = 2.1$ Hz, CHN), 7.19 (d, $J_{HH} = 7.0$ Hz, 2H, arom-H), 7.38–7.42 (m, 4H, CHN + arom-H). ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 14.1$ (CH_3), 54.1 (CH_2N), 60.2 (CH_2O), 114.0 (C-3), 114.9 (q, $^2J_{FC} = 37.8$ Hz, C-4), 122.7 (q, $^1J_{CF} = 266.8$ Hz, CF_3), 123.4 (q, $^3J_{CF} = 6.1$ Hz, CHN), 127.5 (CH_{arom}), 128.6 (CH_{arom}), 128.9 (CH_{arom}), 129.1 (CHN), 135.0 (C_{arom}), 162.6 (COO). ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -57.7$. HRMS (EI) Calcd. for $C_{15}H_{14}F_3NO_2$: 297.0977. Found: 297.0968.

1-Benzyl-4-trifluoromethyl-1*H*-pyrrole-3-carboxylic Acid (6). Yield: 10%. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 5.06$ (s, 2H, CH_2N), 7.02 (d, $^4J_{HH} = 2.4$ Hz, 1H, CHN), 7.17–7.19 (m, 2H, arom-H), 7.35–7.41 (m, 3H, arom-H), 7.45 (d, $^4J_{HH} = 2.4$ Hz, 1H, CHN). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 54.2$ (CH_2N), 115.3 (q, $^2J_{FC} = 37.4$ Hz, C_{arom}), 122.4 (q, $^1J_{FC} = 265.2$ Hz, CF_3), 123.8 (q, $^3J_{FC} = 6.1$ Hz, C_{arom}), 127.6 (CH_{arom}), 128.7 (CH_{arom}), 129.1 (CH_{arom}), 130.3 (CH_{arom}), 133.6 (C_{arom}), 135.0 (COOH). ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -57.9$. HRMS (EI) Calcd. for $C_{13}H_{10}F_3NO_2$: 269.0664. Found: 269.0661.

Benzylaminomethylphosphonic Acid Ethyl Ester (9). Yield: 16%. Colorless crystals, mp 198–200°C. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 1.26$ (t, $^3J_{HH} = 7.2$ Hz, 3H,

CH_3), 2.77 (d, $^2J_{PH}$ = 12.6 Hz, 2H, CH_2P), 3.92 (m, 2H, CH_2), 7.23–7.32 (m, 3H, arom-H), 7.54 (d, J_{HH} = 7.2 Hz, arom-H), 10.35 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 16.9 (d, $^3J_{PC}$ = 7.6 Hz, CH_3), 42.5 (d, $^1J_{PC}$ = 138.9 Hz, CH_2P), 52.8 (d, $^3J_{PC}$ = 12.1 Hz, CH_2N), 60.7 (d, $^2J_{PC}$ = 4.5 Hz, CH_2O), 128.7 (CH_{arom}), 128.9 (CH_{arom}), 130.9 (CH_{arom}), 131.1 (C_{arom}). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 8.28. m/z (ESI/MeOH): 252 (100%, M+Na]$^+$). Anal. Calcd. for $C_{10}H_{16}NO_3P$: C, 52.40; H, 7.04%. Found: C, 52.63; H, 7.17%.

Reaction of Enaminoketone 2b in the Presence of Triethylamine

Under argon atmosphere, a solution of enaminoketone **2b** (1.65 g, 3.6 mmol) and NEt_3 (1.12 g, 11.0 mmol) in MeCN (14.0 mL) was refluxed for 20 h. Then the solvent was evaporated and the residue was separated by column chromatography (silica gel, hexanes/Et_2O, 1:1) to afford 2-phosphonopyrrole **7** and β-enaminoester **8** as yellow oils.

1-Benzyl-5-(diethoxyphosphoryl)-4-trifluoromethyl-1*H*-pyrrole-3-carboxylic Acid Ethyl Ester (7). Yield: 5%. ^1H NMR ($CDCl_3$, 80 MHz): δ = 1.13–1.43 (m, 9H, CH_3), 3.75–4.14 (m, 4H, CH_2O), 4.30 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2O), 5.70 (s, 2H, CH_2N), 7.08–7.37 (m, 5H, C_6H_5), 7.50 (d, $^4J_{PH}$ = 5.1 Hz, 1H, CHN). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 14.1 (CH_3), 16.0 (d, $^3J_{PC}$ = 6.6 Hz, CH_3), 53.8 (CH_2N), 60.8 (CH_2O), 62.8 (d, $^2J_{PC}$ = 5.5 Hz, CH_2O), 115.9 (dq, $^3J_{PC}$ = 10.8 Hz, $^3J_{FC}$ = 3.3 Hz, C-5) 121.8 (q, $^1J_{FC}$ = 269.7 Hz, CF_3), 122.6 (dq, $^2J_{PC}$ = 14.7 Hz, $^2J_{FC}$ = 37.8 Hz, C-4), 127.3 (CH_{arom}), 128.1 (CH_{arom}), 128.8 (CH_{arom}), 133.6 (d, $^3J_{PC}$ = 11.2 Hz, CHN), 136.9 (C_{arom}), 162.2 (COO). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 4.5 (q, $^4J_{PF}$ = 2.5 Hz). ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −53.7 (d, $^4J_{PF}$ = 2.6 Hz). HRMS (EI) Calcd. for $C_{19}H_{23}F_3NO_5P$: 433.1266. Found: 433.1263.

(*E*)-3-Benzyl(diethoxyphosphorylmethyl)amino]acrylic Acid Ethyl Ester (8). Yield: 93%. ^1H NMR ($CDCl_3$, 80 MHz): δ = 1.28 (q, $^3J_{HH}$ = 6.8 Hz, 9H, CH_3), 3.42 (d, $^2J_{PH}$ = 9.5 Hz, 2H, CH_2P), 3.96–4.33 (m, 6H, CH_2O), 4.51 (s, 2H, CH_2N), 4.82 (dd, $^3J_{HH}$ = 13.2 Hz, $^4J_{HP}$ = 1.6 Hz, 1H, CHN), 7.16–7.36 (m, 5H, C_6H_5), 7.59 (d, $^4J_{HH}$ = 13.1 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.2 (CH_3), 16.1 (d, $^3J_{PC}$ = 5.6 Hz, $2CH_3$), 45.5 (br d, $^1J_{CP}$ = 146.9 Hz, CH_2P), 56.3 (br s, CH_2N), 58.7 (CH_2O), 62.1 (d, $^2J_{PC}$ = 7.0 Hz, CH_2O), 87.0 (C-2), 127.2 (CH_{arom}), 127.6 (CH_{arom}), 128.5 (CH_{arom}), 135.1 (C_{arom}), 151.5 (C-3), 168.9 (C-1). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 20.4. m/z (ESI, MeOH) 356.0 (18.7%, M+H]$^+$), 378.1 (100%, M+Na]$^+$). HRMS (EI) Calcd. for $C_{17}H_{26}NO_5P$: 355.1548. Found: 355.1542.

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