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A convenient one-pot two-step synthesis of pyrazolylphosphonates from ethynylphosphonate

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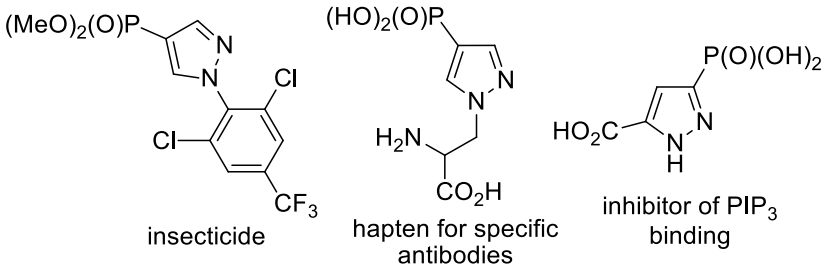

Figure S1 Some examples of bioactive pyrazolylphosphonates.

1. General Information

Reagents were used as they were purchased, unless otherwise indicated. Diethyl ethynylphosphonate was prepared by modified literature procedure [S1]. Flash chromatography was performed on silica gel using petroleum ether and EtOAc or DCM and MeOH as eluents. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on 400 MHz spectrometers. Chemical shifts (ppm) were recorded with the solvent signal as the internal standard ($CHCl_3$, ^{1}H NMR 7.26 ppm, ^{13}C NMR 77.16 ppm). Chemical shifts are expressed in ppm and *J* values are given in Hz. Mass spectra were obtained by ESI on an Orbitrap spectrometer.

2. Synthesis and Characterization

*Diethyl ethynylphosphonate **2*** [S1]. To a stirred solution of ethynyltrimethylsilane (4.6 mL, 32.6 mmol) in freshly distilled THF (20 ml), 3 M EtMgBr (10.7 mL, 32.2 mmol) in ether was added dropwise at 0 °C under Ar. The mixture was stirred for 1.5 h at rt, and then cooled to 0 °C. At this temperature, freshly prepared diethyl chlorophosphate [S2] (5 mL, 34.4 mmol) was added, and the mixture was stirred for additional 15 min without cooling. The mixture was treated with NH_4Cl (sat. aq., 30 mL) and extracted with Et_2O (3 × 50 mL). The organic extract was washed with brine (30 mL) and concentrated under reduced pressure. The residue was dissolved in EtOH (40 mL), and then $KF{\cdot}2H_2O$ (3 g, 31.6 mmol) was added. After stirring for 4 h, the mixture was evaporated, diluted with water (50 mL) and extracted with Et_2O (3 × 30 mL). The organic extract was washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by column chromatography with EtOAc/petroleum ether (1:1) as eluent. Colorless oil, yield: (4.44 g, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24−4.14 (m, 4H), 2.90 (d, $^{3}J_{H,P}$ = 13.2 Hz, 1H), 1.37 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.24.

*General procedure for the synthesis of 3-oxoprop-1-yn-1-ylphosphonates **3a-j** and pyrazol-3-ylphosphonates **4a-j***. A 8 ml glass vial was charged with diethyl ethynylphosphonate **2** (40.5 mg, 0.25 mmol), CuI (4.8 mg, 0.025 mmol), DIPEA (40 μL, 0.25 mmol), dry dichloromethane (1 mL) and acylchloride **1a-j** (0.25 mmol) under argon. The vial was closed with Teflon cap, and the mixture was stirred at room temperature for 16 h. For isolation of **3a-j**, the mixture was evaporated, and residue was purified by column chromatography on silica gel using EtOAc-hexane as eluent. For the preparation of **4a-j**, after completion of formation of **3a-j** (16 h), hydrazine hydrate (18 μL, 0.375 mmol) was added. After stirring for 1 h, the solvent was evaporated and residue was purified by column chromatography on silica gel using

CH_2Cl_2/MeOH as the eluent. Known compounds **3a,d-i** [S3], **3k** [S4], **4a-h** [S5] gave satisfactory spectroscopic data that are in agreement with those reported. New compounds were fully characterized.

*Diethyl [3-(4-methoxyphenyl)-3-oxoprop-1-yn-1-yl]phosphonate **3b*** was prepared according to the general procedure from 4-methoxybenzoyl chloride (37 μL, 0.3 mmol). Yield 71% (53 mg), colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $^3J_{H,H}$ = 8.9 Hz, 2H), 6.95 (d, $^3J_{H,H}$ = 8.9 Hz, 2H), 4.29 - 4.19 (m, 4H), 3.88 (s, 3H), 1.39 (t, $^3J_{H,H}$ = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.35 (d, $^3J_{C,P}$ = 3.2 Hz), 165.48, 132.44, 129.01, 114.34, 92.13 (d, $^2J_{C,P}$ = 43.6 Hz), 79.56 (d, $^1J_{C,P}$ = 280.1 Hz), 64.19 (d, $^2J_{C,P}$ = 6.1 Hz), 55.80, 16.16 (d, $^3J_{C,P}$ = 7.5 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ -8.77; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}O_5P$ 297.0892, found 297.0890.

*Diethyl [3-(2-methoxyphenyl)-3-oxoprop-1-yn-1-yl]phosphonate **3c*** was prepared according to the general procedure from 2-methoxybenzoyl chloride (41 μL, 0.3 mmol). Yield 71% (53 mg), colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.90 (m, 1H), 7.59 - 7.51 (m, 1H), 7.05 - 6.95 (m, 2H), 4.28 - 4.14 (m, 4H), 3.91 (s, 3H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.21 (d, $^3J_{C,P}$ = 3.8 Hz), 160.44, 136.52, 132.44, 125.07, 120.64, 112.37, 94.15 (d, $^2J_{C,P}$ = 44.4 Hz), 78.58 (d, $^1J_{C,P}$ = 284.8 Hz), 63.96 (d, $^2J_{C,P}$ = 5.9 Hz), 55.89, 16.13 (d, $^3J_{C,P}$ = 6.6 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ -8.15; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}O_5P$ 297.0892, found 297.0897.

*Diethyl [3-(adamantan-1-yl)-3-oxoprop-1-yn-1-yl]phosphonate **3j*** was prepared according to the general procedure from 1-adamantanecarbonyl chloride (59.6 mg, 0.3 mmol). Yield 90% (73 mg), colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 - 4.14 (m, 4H), 2.05 (br. s, 3H), 1.84 - 1.80 (m, 6H), 1.76 - 1.61 (m, 6H), 1.37 (td, $^3J_{H,H}$ = 7.1, $^4J_{H,P}$ = 0.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.71 (d, $^3J_{C,P}$ = 3.4 Hz), 91.30 (d, $^2J_{C,P}$ = 42.0 Hz), 79.60 (d, $^1J_{C,P}$ = 278.2 Hz), 64.05 (d, $^2J_{C,P}$ = 5.9 Hz), 47.19, 37.51, 36.28, 27.59, 16.15 (d, $^3J_{C,P}$ = 6.5 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ -8.84; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{26}O_4P$ 325.1569, found 325.1561.

*Diethyl (5-(tert-butyl)-1H-pyrazol-3-yl)phosphonate **4i*** was prepared according to the general procedure from pivaloyl chloride (39 μL, 0.3 mmol). Yield 89% (58 mg), white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 6.51 (d, $^3J_{H,P}$ = 1.7 Hz, 1H), 4.24 - 4.09 (m, 4H), 1.32 (s, 9H), 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.16 (d, $^3J_{C,P}$ = 11.0 Hz), 137.27 (d, $^1J_{C,P}$ = 226.9 Hz), 107.62 (d, $^2J_{C,P}$ = 22.0 Hz), 62.85 (d, $^2J_{C,P}$ = 5.7 Hz),

31.45, 30.36, 16.32 (d, $^{3}J_{C,P}$ = 6.6 Hz); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ 9.64; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{22}N_2O_3P$ 261.1368, found 261.1362.

Diethyl [5-(adamantan-1-yl)-1H-pyrazol-3-yl]phosphonate ***4j*** was prepared according to the general procedure from 1-adamantanecarbonyl chloride (59.6 mg, 0.3 mmol). Yield 85% (72 mg), white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (br. s., 1H), 6.47 (d, $^{3}J_{H,P}$ = 1.5 Hz, 1H), 4.22 - 4.02 (m, 4H), 2.04 (br. s, 3H), 1.95 - 1.92 (m, 6H), 1.79 - 1.68 (m, 6H), 1.30 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.89 (d, $^{3}J_{C,P}$ = 10.1 Hz), 137.92 (d, $^{1}J_{C,P}$ = 229.1 Hz), 106.86 (d, $^{2}J_{C,P}$ = 22.2 Hz), 62.82 (d, $^{2}J_{C,P}$ = 5.6 Hz), 42.36, 36.56, 33.28, 28.40, 16.34 (d, $^{3}J_{C,P}$ = 6.7 Hz); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ 11.08; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{28}N_2O_3P$ 339.1838, found 339.1833.

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[S2]. G.M. Steinberg, *J. Org. Chem*., 1950, **15**, 637.

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3. ^{1}H and ^{13}C NMR spectra of new compounds

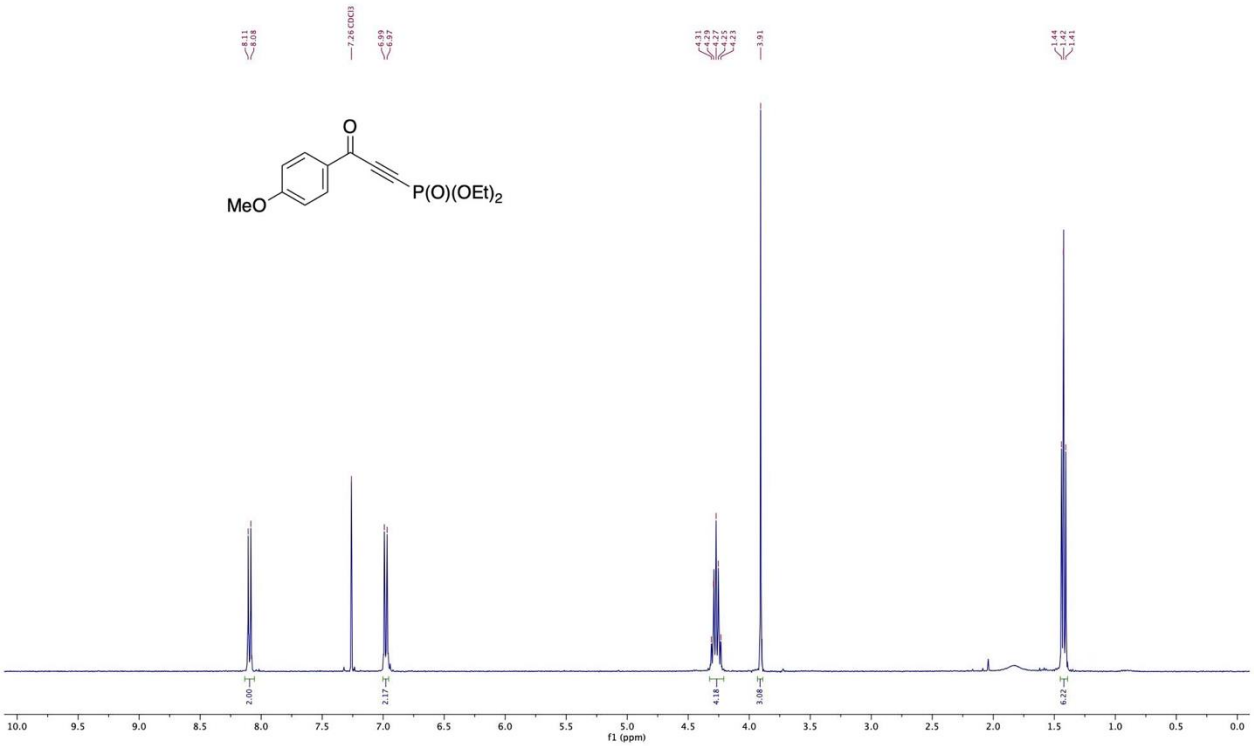

Figure S1. ^{1}H NMR spectrum of **3b**.

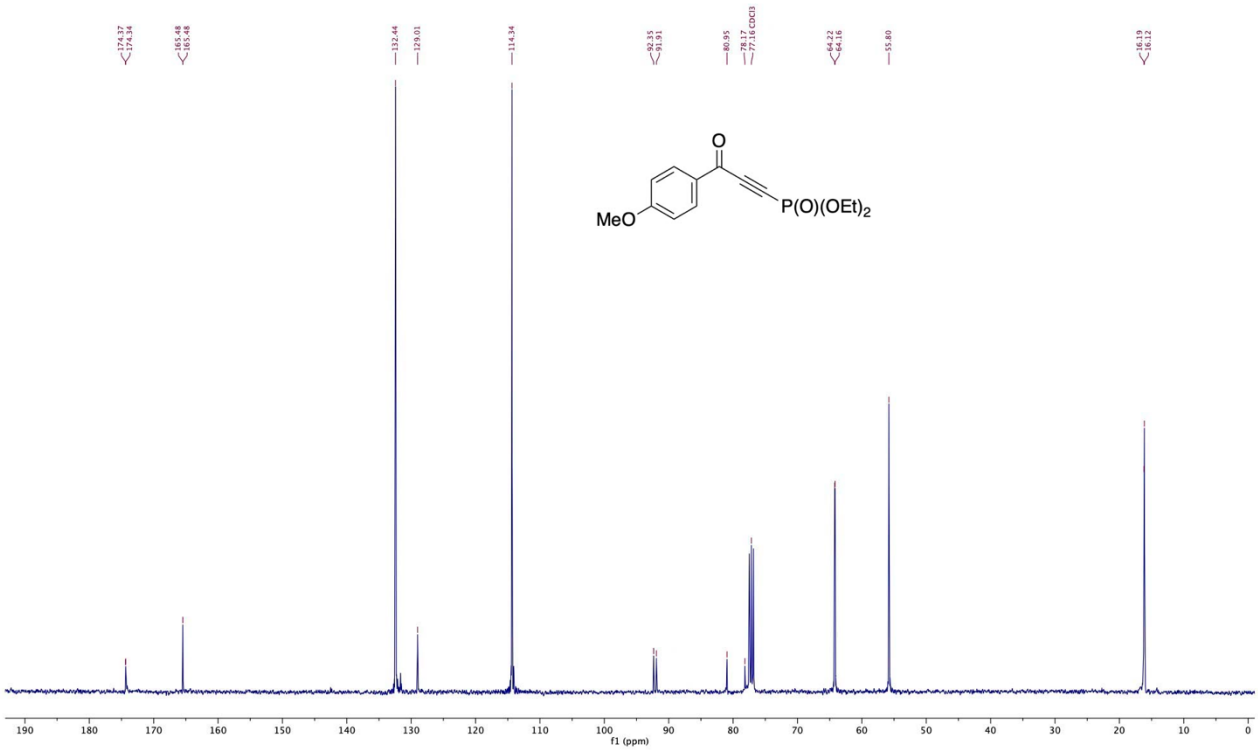

Figure S2. ^{13}C NMR spectrum of **3b**.

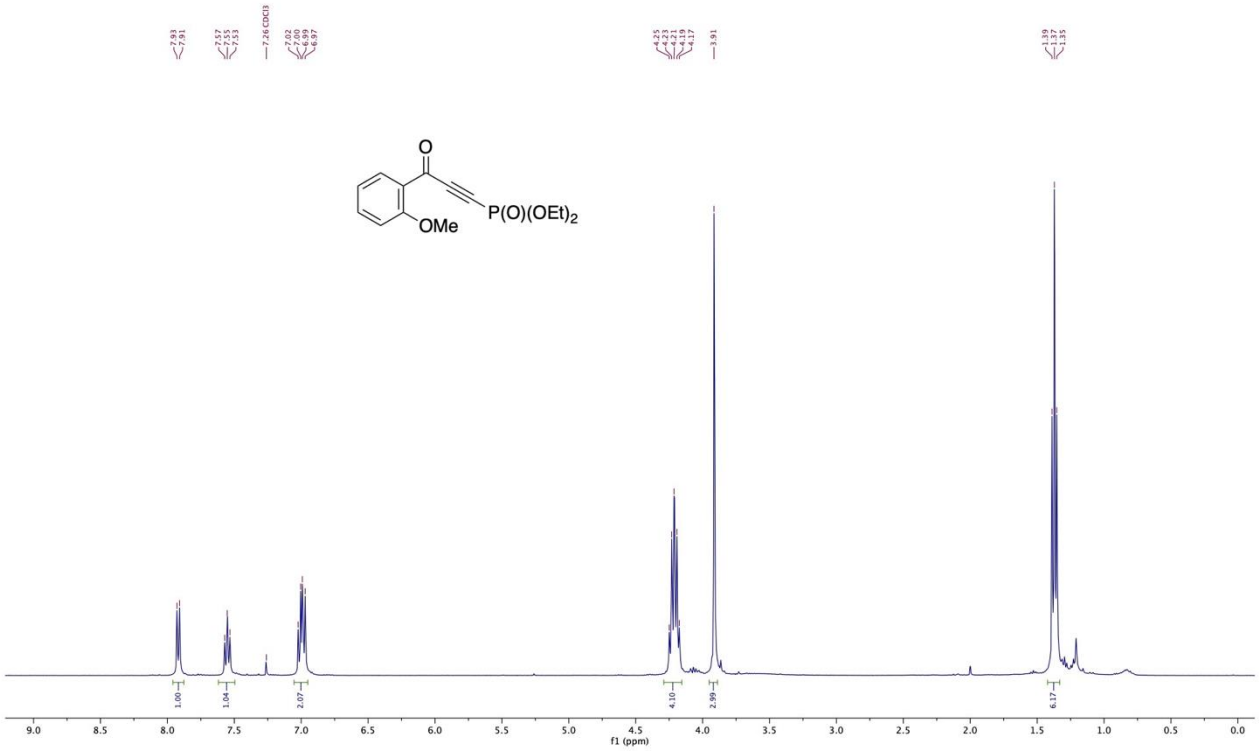

Figure S3. ^{1}H NMR spectrum of **3c**.

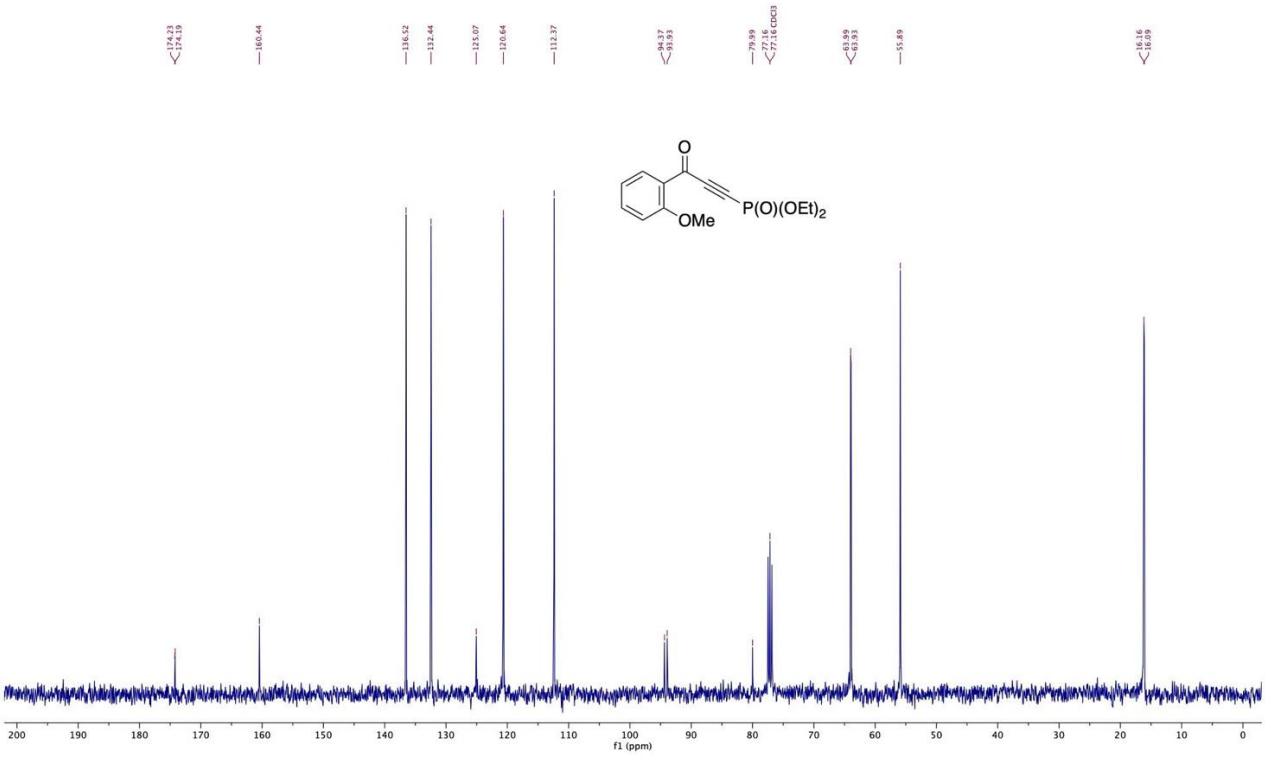

Figure S4. ^{13}C NMR spectrum of **3c**.

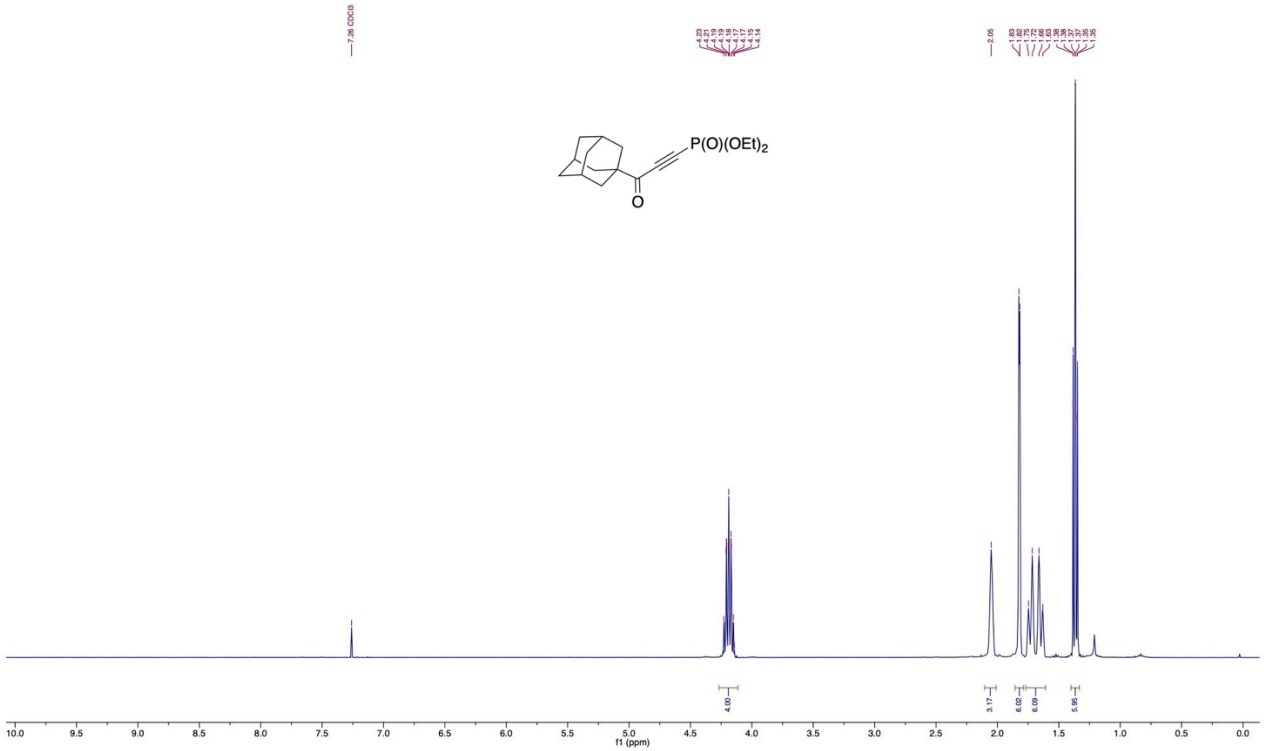

Figure S5. ^{1}H NMR spectrum of **3j**.

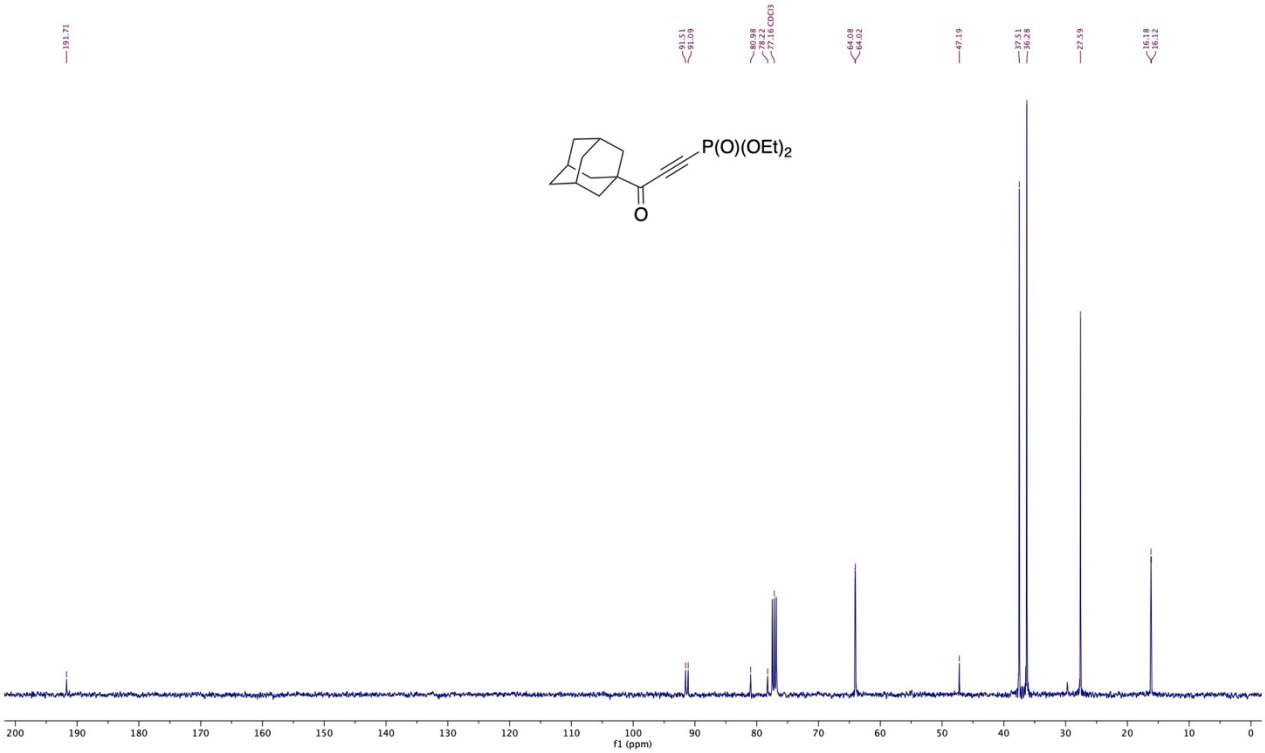

Figure S6. ^{13}C NMR spectrum of **3j**.

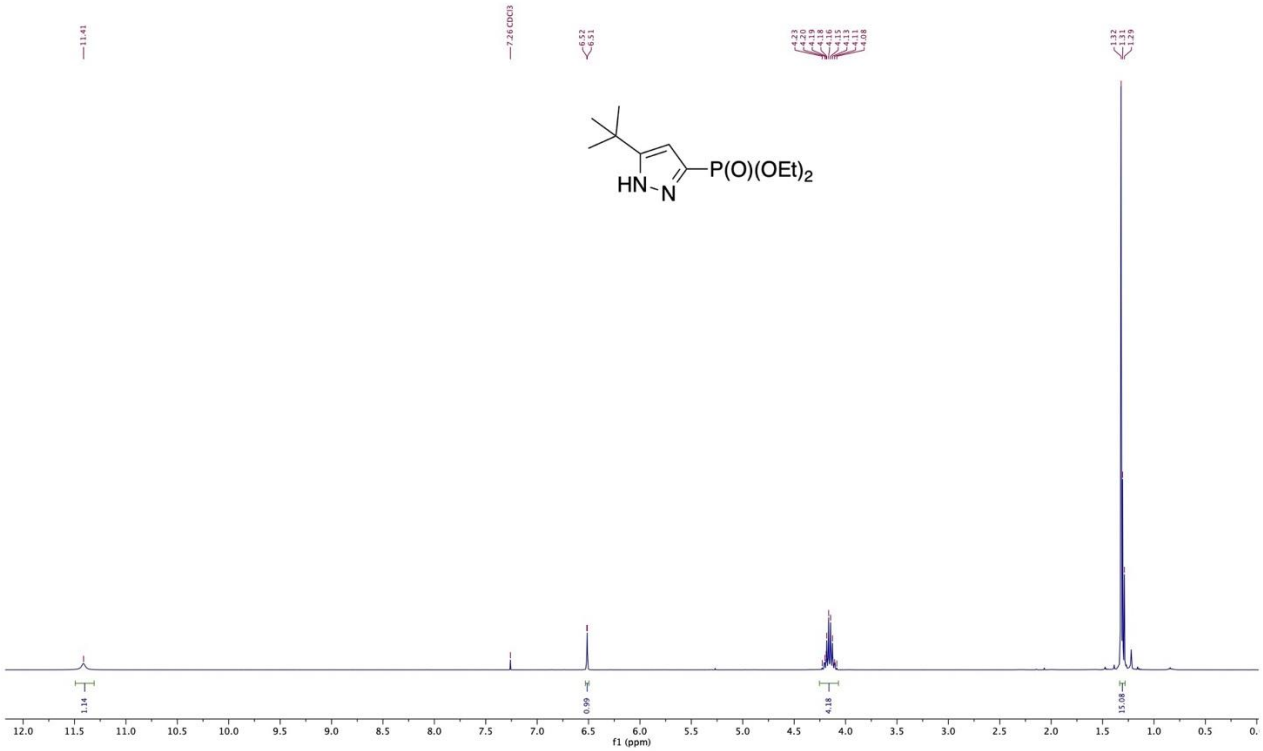

Figure S7. ^{1}H NMR spectrum of **4i**.

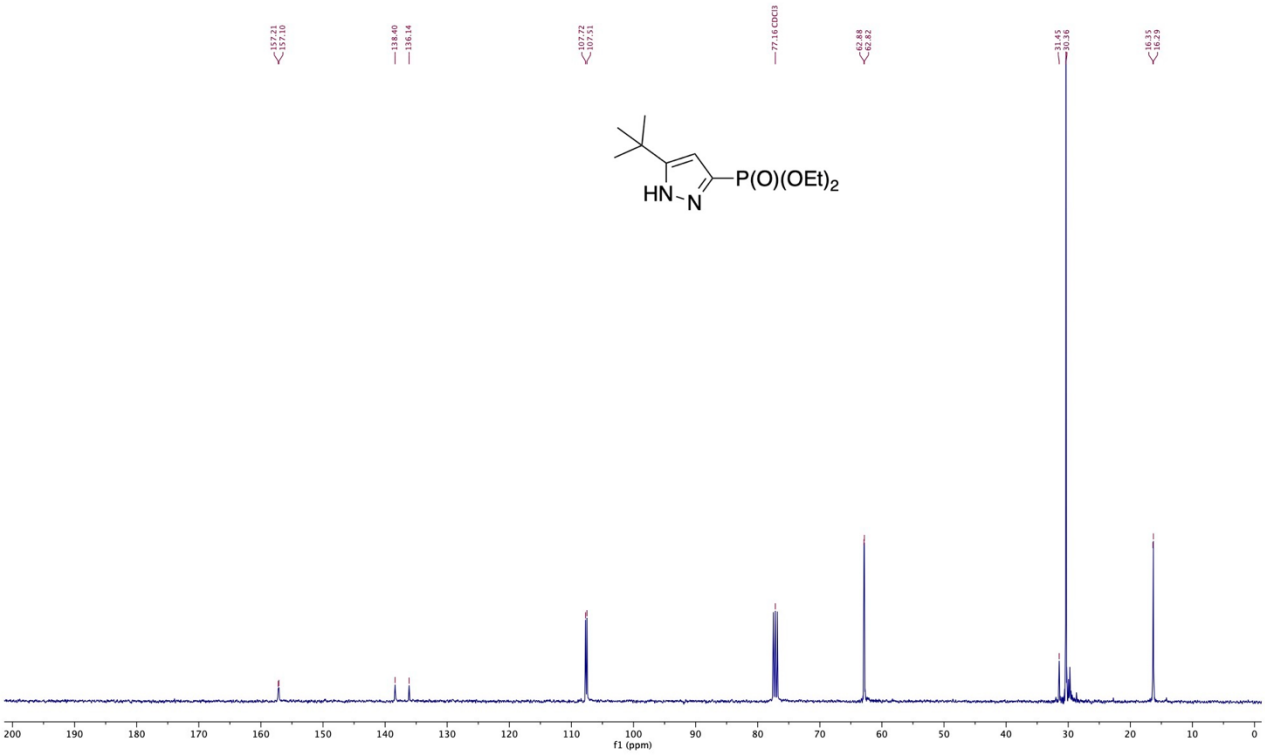

Figure S8. ^{13}C NMR spectrum of **4i**.

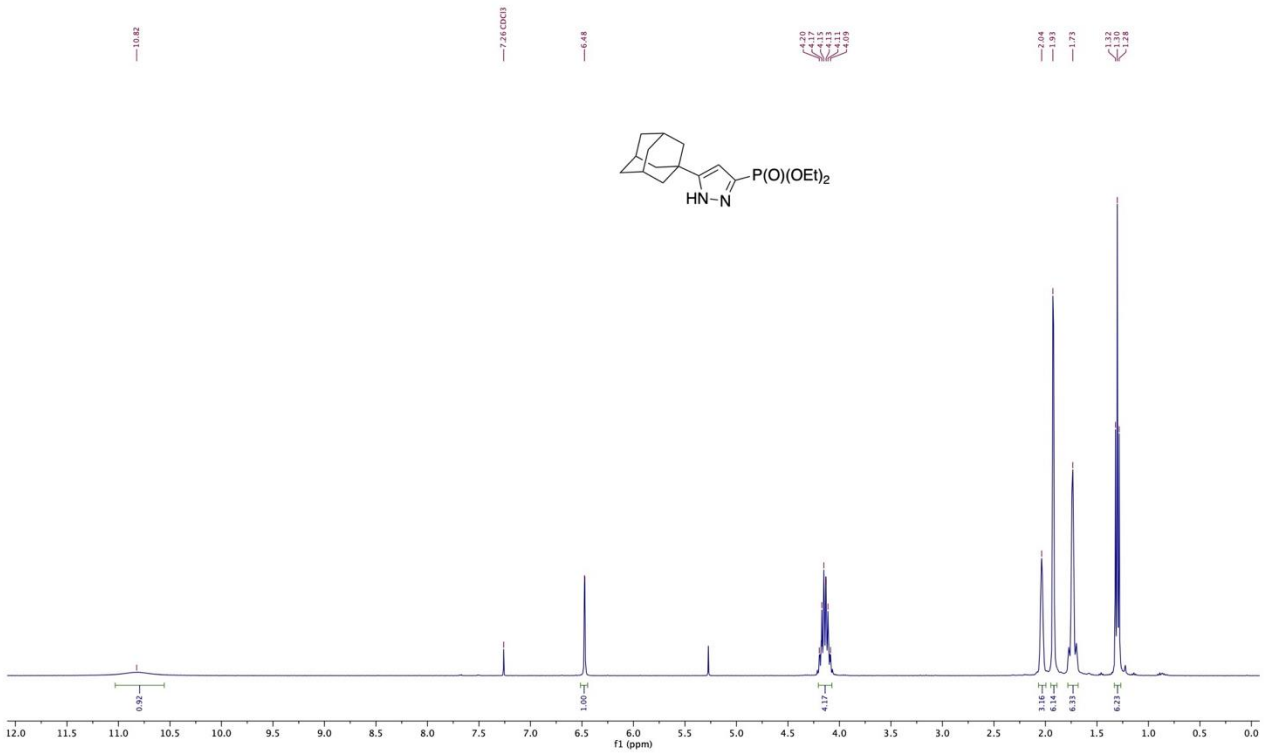

Figure S9. ^{1}H NMR spectrum of **4j**.

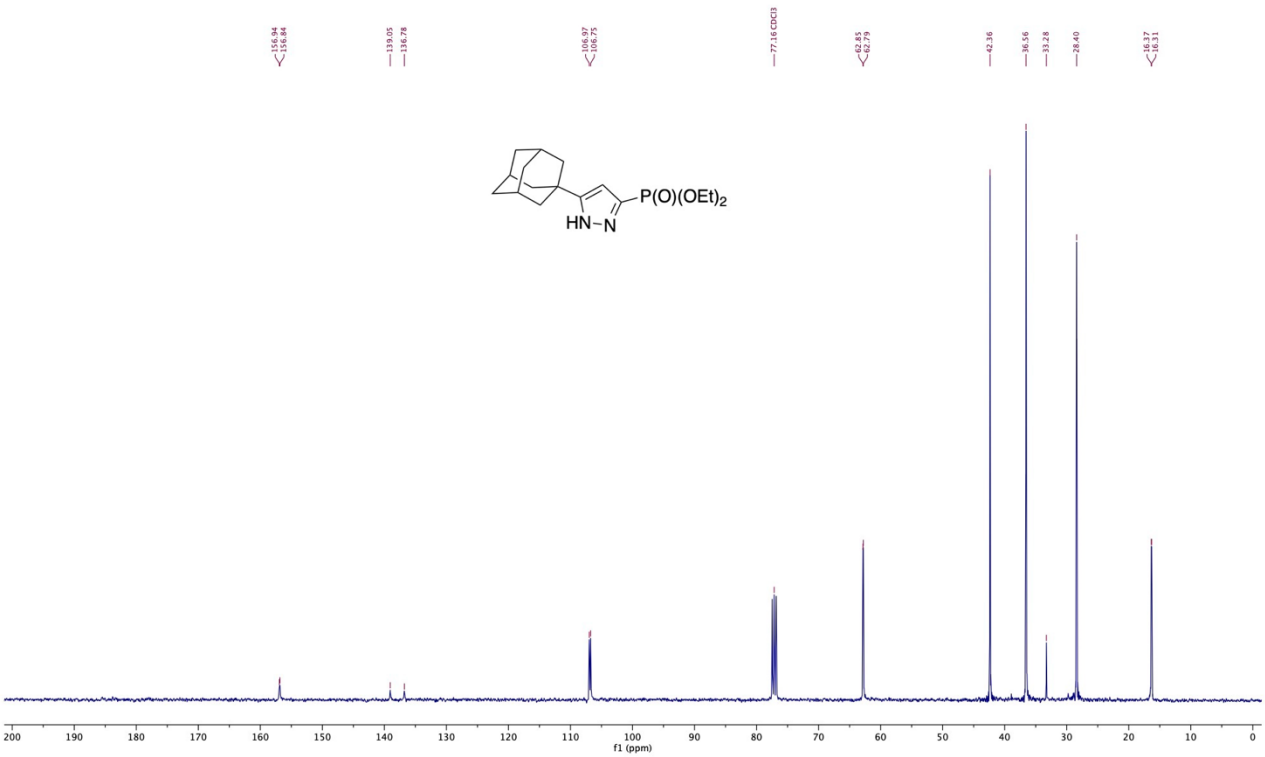

Figure S10. ^{13}C NMR spectrum of **4j**.