Triphenylphosphite as a good reagent for the diastereoselective synthesis of phosphonate esters

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Abstract
The reaction between dialkyl acetylenedicarboxylates and N-H acids such as pyrazole and indazole in the presence of triphenylphosphite at room temperature led to stable phosphonate ester derivatives 4a-f. The configuration of compounds 4a-f (2S*,3R*) was determined on the basis of coupling constants predicted from the Karplus equation.

Keywords: N-H acids, acetylenic esters, triphenylphosphite, Karplus equation, diastereomer, phosphonate esters

Introduction
In recent years there has been an increasing interest in the synthesis of organophosphorus compounds, in particular those bearing a carbon atom bound to a phosphorus atom. This interest has resulted from the recognition of the value of such compounds in a wide range of industrial, biological and chemical synthetic aspects. The successful attack by nucleophilic trivalent phosphorus on a carbon atom is facilitated when the latter is part of, or conjugated with, a carbonyl group, or when it is part of an unsaturated bond otherwise activated. There are many studies on the reaction between trivalent phosphorus nucleophiles and α, β-unsaturated carbonyl compounds in the presence of a proton source such as an alcohol or a phenol. New or improved methods for phosphonate synthesis continue to attract much attention because phosphonates have biologically important properties and serve as natural products, analogues of phosphates, phosphonopeptides, amino acid analogues and pro drugs. Also the phosphonate esters have physiological activity within the cell.
Results and Discussion

In the current work, we wish to report a simple, short, neutral stereoselective synthesis of phosphonate esters at room temperature from reaction between triphenylphosphite 1 and acetylenic esters 2 in the presence of N-H acids. The use of pyrazole and indazole 3 led to 4 in fairly high yield (see Scheme 1). These reactions were carried out in diethyl ether as solvent at room temperature and were finished within a few hours. The $^1$H and $^{13}$C NMR spectrum of the crude product clearly indicated the formation of phosphonate esters 4a-f. Any products other than 4a-f could not be detected by NMR spectroscopy. The structures of compounds 4a-f were deduced from their IR, $^1$H, $^{13}$C and $^{31}$P NMR spectra. The 500 MHz $^1$H NMR spectra of compound 4a displayed two sharp lines ($\delta$= 3.71, 3.79) arising from methoxy protons, along with signals for methine protons at $\delta$= 4.62 ppm ($^3$J$_{PH}$=21.2 Hz, $^3$J$_{HH}$=10.8 Hz) and $\delta$= 5.82 ppm ($^3$J$_{PH}$=8.4 Hz, $^3$J$_{HH}$=10.8 Hz) which appear as two doublets of doublet, respectively, for the O=P-CH-CH and O=P-CH-CH groups. The vicinal proton-proton coupling constant ($^3$J$_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation. Typically, $J_{gauche}$ varies between 1.5 and 5 Hz and $J_{anti}$ between 10 and 14 Hz. Observation of $^3$J$_{HH}$=10.8 Hz for the vicinal protons in compound 4a (see Experimental section) indicates an anti arrangement for
these protons. Since compound 4a possess two stereogenic centers, two diastereoisomers with anti HCCH arrangements are possible. The three-bond carbon-phosphorus coupling, $^{3}J_{CP}$, depends on the configuration, as expected, the transoid coupling being larger than the cisoid ones. The Karplus relation can be derived from the data for organophosphorus compounds with tetra and pentavalent phosphorus. The observation of $^{3}J_{CP}$ of 18.6 Hz for the ester C=O group (see Experimental section), is in a good agreement with the $2S^{*}$,3R*-4a and its mirror image $2R^{*}$,3S*-4a geometries (see Scheme 2). Although the presence of the $^{31}P$ nucleus complicates both the $^1H$ and $^{13}C$ NMR spectra of 4a, it helps in the assignment of the signals by long-range couplings with the $^1H$ and $^{13}C$ nuclei (see Experimental section). The $^1H$ and $^{13}C$ NMR spectra of (4b-f) are similar to those of 4a, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts (see Experimental section). The structural assignments made on the basis of the $^1H$ and $^{13}C$ NMR spectra of compounds (4a-f) were supported by the IR spectra. The carbonyl region of the spectra exhibited two distinct absorption bands for each compound (see Experimental section). Of special interest is the ester absorption at 1745-1719 cm$^{-1}$ for these compounds.

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\begin{align*}
&\text{Scheme 2} \\
&\begin{array}{ccc}
&\text{(C}_6\text{H}_5\text{O})_2\text{P} & Z \\
&\text{H}^{\text{ii}} & \text{H}^{\text{iii}} \\
&\text{MeO}_2\text{C} & \text{CO}_2\text{Me} \\
\text{2S}* ,3\text{R}*-4\text{a} (\text{or } 2\text{R}^*,3\text{S}^*) \\
\end{array}
&\begin{array}{ccc}
&\text{(C}_6\text{H}_5\text{O})_2\text{P} & \text{CO}_2\text{R} \\
&\text{H}^{\text{ii}} & \text{H}^{\text{iii}} \\
&\text{MeO}_2\text{C} & Z \\
\text{2R}* ,3\text{R}*-4\text{a} (\text{or } 2\text{S}^*,3\text{S}^*) \\
\end{array}
\end{align*}
\]

**Experimental Section**

**General Procedures.** Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer respectively. Also, the $^1H$, $^{13}C$, and $^{31}P$ NMR spectra were obtained from a BRUKER DRX-500 AVANCE instrument with CDCl$_3$ as solvent at 500.1, 125.8, and 202.4 MHz respectively. In addition, the mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Dialkyl acetylenedicarboxylates, triphenylphosphite, pyrazole and indazole were purchased from Fluka, (Buchs, Switzerland) and used without further purifications.

**Preparation of (2S,3R*)-dimethyl-2-(pyrazole-1-yl)-3-(diphenoxyphosphonato)butane dioate (4a).** To a magnetically stirred solution of triphenylphosphite (0.31g, 1mmol) and pyrazole (0.07g, 1mmol) in diethyl ether (10ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.14g, 1mmol) in diethyl ether (5ml) at -10 °C over 10 min. After
approximately 24 hours stirring at room temperature, the solvent was removed under reduced pressure and product washed with cold diethyl ether (2×5mL).

White powder. 97%, mp=125-127°C. IR (KBr) (νmax, cm⁻¹): 1745 and 1719 (C=O), 1257 (P=O). Anal. Calcd for C21H21N2O7P (444): C, 56.63; H, 4.80; N, 6.25; Found: C, 56.76; H, 4.73; N, 6.31.

1H NMR (500.1 MHz, δ, CDCl3): 3.71 and 3.79 (6H, 2s, 2CMe3), 4.62 (1H, dd, JPH=21.2 Hz, JHH=10.8 Hz, P-CH-CH), 5.82 (1H, dd, JPH=8.4 Hz, JHH=10.8 Hz, P-CH-CH), 6.28-7.66 (13H, m, Haro).

13C NMR (125.8 MHz, δ, CDCl3): 47.96 (d, JCP=134.8 Hz, P-C), 53.05 and 53.20 (s, 2OCMe3), 61.72 (s, 2JCP=17.3 Hz, P-C=C), 106.29 and 125.39 (2C of 2C6H5), 120.04 and 120.30 (2d, JPC=4.7 Hz Cortho of 2C6H5), 125.29 and 125.39 (2C para of 2C6H5), 129.64 and 129.73 (2Cmeta of 2C6H5), 131.92 and 141.17 (2Cortho of 2C6H5), 149.47 and 149.88 (2d, JCP=9.0 Hz Cipso of 2C6H5), 166.64 (d, JCP=6.2 Hz, C=O), 167.04 (d, JCP=18.6 Hz, C=O).

31P NMR (202.4 MHz, δ, [s, (PhO)2P=O]).

(2S*,3R*)-Diethyl-2-(pyrazole-1-yl)-3-(diphenoxyphosphonato)butanedioate (4b). White powder, 96%, mp=124-126°C. IR (KBr) (νmax, cm⁻¹): 1741 and 1719 (C=O), 1269 (P=O). Anal.

Calcd for C23H25N2O7P (472): C, 58.35; H, 5.35; N, 6.02; Found: C, 58.47; H, 5.30; N, 5.93.

1H NMR (500.1 MHz, δ, CDCl3): 1.14 and 1.25 (6H, 2t, JHH=7.1 Hz, 2OCMe3), 4.16 and 4.25 (4H, 2ABX3system, 2OCMe2), 4.60 (1H, dd, JPH=21.2 Hz, JHH=11.0 Hz, P-CH-CH), 5.77 (1H, dd, JPH=8.8 Hz, JHH=11.0 Hz, P-CH-C), 6.24-7.64 (13H, m, Haro).

13C NMR (125.8 MHz, δ, CDCl3): 13.77 and 13.82 (2OCMe3), 48.06 (d, JCP=134.6 Hz, P-C), 83.33 and 83.41 (2OCMe3), 105.97 (1Cortho of 2C6H5), 120.24 and 120.44 (2d, JPC=4.6 Hz Cortho of 2C6H5), 125.39 and 125.45 (2Cpara of 2C6H5), 129.64 and 129.66 (2Cmeta of 2C6H5), 131.97 and 141.22 (2Cortho of 2C6H5), 149.72 and 150.07 (2d, JCP=9.6 Hz Cipso of 2C6H5), 166.22 (d, JCP=6.0 Hz, C=O), 167.08 (d, JCP=19.0 Hz, C=O).

31P NMR (202.4 MHz, δ, 10.85 [s, (PhO)2P=O]).

(2S*,3R*)-Di-tert-butyl -2-(pyrazole-1-yl)-3-(diphenoxyphosphonato)butanedioate (4c). White powder, 92%, mp=124-126°C. IR (KBr) (νmax, cm⁻¹): 1739 and 1722 (C=O), 1273 (P=O). Anal.

Calcd for C27H33N2O7P (528): C, 61.50; H, 6.19; N, 5.37; Found: C, 61.36; H, 6.25; N, 5.93.

1H NMR (500.1 MHz, δ, CDCl3): 1.36 and 1.47 (18H, 2CMe3), 4.52 (1H, dd, JPH=20.9 Hz, JHH=11.1 Hz, P-CH-CH), 5.64 (1H, dd, JPH=12.1 Hz, JHH=11.1 Hz, P-CH-C), 6.24-7.61 (13H, m, Haro).

13C NMR (125.8 MHz, δ, CDCl3): 27.62 and 27.70 (2CMe3), 48.06 (d, JCP=134.6 Hz, P-CH), 62.01 (d, JCP=3.3 Hz, P-CH), 62.41 and 62.55 (2OCMe2), 106.07 (1Cortho of 2C6H5), 120.24 and 120.44 (2d, JPC=4.6 Hz Cortho of 2C6H5), 125.39 and 125.45 (2Cpara of 2C6H5), 129.64 and 129.66 (2Cmeta of 2C6H5), 131.97 and 141.22 (2Cortho of 2C6H5), 149.72 and 150.07 (2d, JCP=9.6 Hz Cipso of 2C6H5), 166.22 (d, JCP=6.0 Hz, C=O), 167.08 (d, JCP=19.0 Hz, C=O).

31P NMR (202.4 MHz, δ, 10.85 [s, (PhO)2P=O]).

(2S*3R*)-Dimethyl-2-(indazole-1-yl)-3-(diphenoxyphosphonato)butanedioate (4d). White powder, 98%, mp=132-134°C. IR (KBr) (νmax, cm⁻¹): 1745 and 1719 (C=O), 1271 (P=O). Anal.

Calcd for C25H23N2O7P (494): C, 61.03; H, 4.51; N, 5.73; Found: C, 60.73; H, 4.66; N, 5.67.

1H NMR (500.1 MHz, δ, CDCl3): 3.52 and 3.77 (6H, 2s, 2CMe3), 4.87 (1H, dd, JPH=21.0 Hz, JHH=11.2 Hz, P-CH-CH), 6.24 (1H, dd, JPH=8.9 Hz, JHH=11.2 Hz, P-CH-CH), 6.63-8.02 (15H, 2CMe3).
m, H_{aro}). 13C NMR (125.8 MHz, δ, CDCl3): 47.84 (d, 1J_{CP}=135.9 Hz, P-CH), 53.28 and 53.41 (s, 2OCH_{3}), 58.66 (d, 2J_{CP}=3.9 Hz, P-C-CH), 109.71 and 119.62 (2C, C_{7}H_{5}N_{2}), 120.21 and 120.40 (2d, 3J_{PC}= 4.4 Hz C_{ortho} of 2C_{6}H_{5}), 121.60 and 124.23 (2C, C_{7}H_{5}N_{2}), 125.56 and 125.64 (C_{para} of 2C_{6}H_{5}), 127.38 (1C, C_{7}H_{5}N_{2}), 129.38 and 129.69 (C_{meta} of 2C_{6}H_{5}), 135.69 and 140.76(2C, C_{7}H_{5}N_{2}), 149.36 and 149.74 (2d, 2J_{CP}=9.8 Hz, C_{ipso} of 2C_{6}H_{5}), 167.05 (d, 3J_{CP}= 5.9 Hz, C=O), 168.23 (d, 2J_{CP}=19.3 Hz, C=O). 31P NMR (202.4 MHz, δ, 11.20 [s, (PhO)_{2}P=O].

(2S*,3R*)-Diethyl-2-(indazol-1-yl)-3-(diphenoxyphosphonato)butanedioate (4e). White powder, 95%, mp=128-130 °C. IR (KBr) (ν_{max}, cm^{-1}): 1738 and 1720 (C=O), 1272 (P=O). Anal. Calcd for C_{27}H_{27}N_{2}O_{7}P (522): C, 62.21; H, 5.11; N, 5.41, Found: C, 62.07; H, 5.17; N, 5.36. 1H NMR (500.1 MHz, δ, CDCl3): 1.14 and 1.25 (6H, 2t, 3J_{HH}=7.1 Hz, 2C_{H3}), 4.13 and 4.25 (4H, m, 2ABX_{3} system, 2OC_{H2}), 4.59 (1H, dd, 2J_{PH}=21.5 Hz, 3J_{HH}=11.1 Hz, P-CH-CH), 5.67 (1H, dd, 3J_{PH}=8.8 Hz, 3J_{HH}=11.1 Hz, P-CH-CH), 6.20 -7.56 (15H, m, H_{aro}). 13C NMR (125.8 MHz, δ, CDCl3): 14.13 and 14.39 (2C_{H3}), 45.33 (d, 1J_{CP}=132.3 Hz, P-CH), 62.50 (d, 2J_{CP}=7.3 Hz, P-CH), 62.67 and 62.94 (2OC_{H2}), 109.54 and 119.78 (2C, C_{7}H_{5}N_{2}), 120.68 and 120.91 (2d, 3J_{PC}=4.3 Hz C_{ortho} of 2C_{6}H_{5}), 121.15 and 124.56 (2C, C_{7}H_{5}N_{2}), 125.61 and 125.68 (C_{para} of 2C_{6}H_{5}), 127.25 (1C, C_{7}H_{5}N_{2}), 129.56 and 129.71 (C_{meta} of 2C_{6}H_{5}), 135.84 and 141.04 (2C, C_{7}H_{5}N_{2}), 149.69 and 150.05 (2d, 2J_{CP}=9.6 Hz, C_{ipso} of 2C_{6}H_{5}), 166.16 (d, 3J_{CP}=6.1 Hz, C=O), 167.21 (d, 2J_{CP}=19.5 Hz, C=O). 31P NMR (202.4 MHz, δ, 10.85 [s, (PhO)_{2}P=O].

(2S*,3R*)-Di-tert-butyl-2-(indazole-1-yl)-3-(diphenoxyphosphonato)butanedioate (4f). White powder, 91%, mp=112-115 °C. IR (KBr) (ν_{max}, cm^{-1}): 1736 and 1725 (C=O), 1283 (P=O). Anal. Calcd for C_{31}H_{35}N_{2}O_{7}P (578): C, 64.51; H, 5.17; N, 4.86, Found: C, 64.36; H, 6.06; N, 4.84. 1H NMR (500.1 MHz, δ, CDCl3): 1.26 and 1.52 (18H, 2C_{Me3}), 4.73 (1H, dd, 2J_{PH}=22.1 Hz, 3J_{HH}=11.2 Hz, P-CH-CH), 6.02 (1H, dd, 3J_{PH}=8.9 Hz, 3J_{HH}=11.2 Hz, P-CH-CH), 6.67 -8.01 (15H, m, H_{aro}). 13C NMR (125.8 MHz, δ, CDCl3): 27.62 and 27.75 (2C_{Me3}), 48.46 (d, 1J_{CP}=134.5 Hz, P-CH), 59.70 (d, 2J_{CP}=4.0 Hz, P-C-CH), 83.13 and 83.37 (2C_{Me3}), 109.82 and 119.58 (2C, C_{7}H_{5}N_{2}), 120.32 and 120.72 (2d, 3J_{PC}= 4.7 Hz C_{ortho} of 2C_{6}H_{5}), 122.19 and 124.17 (2C, C_{7}H_{5}N_{2}), 125.20 and 125.49 (C_{para} of 2C_{6}H_{5}), 126.88 (1C, C_{7}H_{5}N_{2}), 129.28 and 129.36 (C_{meta} of 2C_{6}H_{5}), 135.38 and 140.72 (2C, C_{7}H_{5}N_{2}), 149.68 and 147.99 (2d, 2J_{CP}=9.5 Hz, C_{ipso} of 2C_{6}H_{5}), 163.89 (d, 3J_{CP}= 6.5 Hz, C=O), 165.63 (d, 2J_{CP}= 20.3 Hz, C=O). 31P NMR (202.4 MHz, δ, 10.85 [s, (PhO)_{2}P=O].

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References


