Stereoselective one-pot synthesis of functionalised phosphonates by three-component reaction between trimethylphosphite, dialkyl acetylenedicarboxylates and aldehyde semicarbazones

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Three-component reaction between dialkyl acetylenedicarboxylates, trimethylphosphite, and aldehyde semicarbazones leads to functionalised phosphonates in good yields.

Keywords: acetylenic esters, semicarbazones; phosphonates; trimethylphosphite

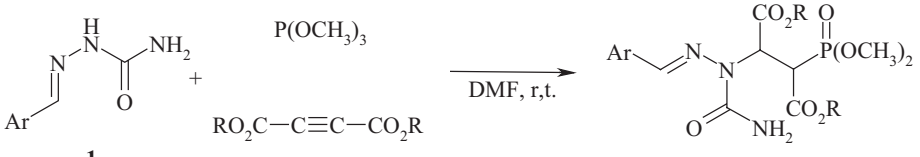
The successful attack by nucleophilic trivalent phosphorus on a carbon atom is facilitated when the later is conjugated with a carbonyl group or when it is part of an unsaturated bond otherwise activated.[1-8] There have been many studies on reactions between trivalent phosphorus nucleophiles and unsaturated carbonyl compounds in the presence of a proton source such as an alcohol.[1] The reaction of phosphites and dimethyl acetylenedicarboxylate (DMAD) in the presence of naphthols reported to produce phosphonate derivatives.[9] We report here an efficient synthetic route to functionalised phosphonates using trimethylphosphite, dialkyl acetylenedicarboxylates and aldehyde semicarbazones. Thus, reaction of semicarbazone **1** with acetylenic ester **2** in the presence of trimethylphosphite leads to the corresponding phosphonate **3** in 89–95% yields (Scheme 1).

The structure of compounds **3a–e** were deduced from their elemental analyses and their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The mass spectra of these phosphonates are fairly similar and display molecular ion peaks.

The 500 MH_Z ^{1}H NMR spectrum of **3a** exhibites signals for vicinal methine protons at δ 4.23 and 5.49 ppm as two sets of doublet of doublets, with $^2J_{HP}$ = 20 H_Z, $^3J_{HP}$ = 5 H_Z and $^3J_{HH}$ = 11 H_Z. The vicinal proton-proton coupling constants can be obtained from the Karplus equation.[10,11] Typically, J_{gauche} varies between 1.5 and 5 H_Z and J_{anti} between 10 and 14 H_Z. Observation of $^3J_{HH}$ = 11 H_Z for vicinal protons in compound **3a** indicates an anti arrangement for these centres. Since compound **3a** possesses two stereogenic centres, two diastereomers with anti HCCH arrangements are possible (Scheme 2). The three-bond carbon–phosphorus coupling, $^3J_{CP}$, depends on configuration, as expected, transoid couplings being larger than cisoid ones.[12] The observation for $^3J_{CP}$ of 19 H_Z for the ester carbonyl carbon, is in agreement with the (*2R, 3S*)-**3a** and its mirror image (*2S, 3R*)-**3a** geometries. The NMR spectra of compounds **3b–e** also show only (*2R, 3R*)-**3a** isomer and its enantiomer.

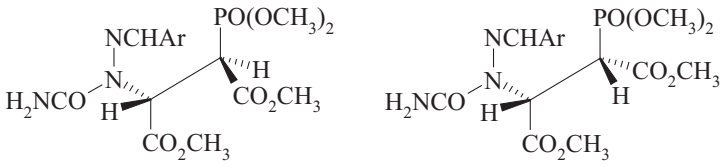
On the basis of the well-established chemistry of trivalent phosphorus nucleophiles[1-7] it is reasonable to assume that compounds **3** result from the initial addition of trimethylphosphite to acetylenic ester **2** and subsequent protonation of the 1 : 1 adduct by semicarbazone **1** (Scheme 3). Then, the positively charged ion **4** is attacked by the anion of semicarbazone to form ylide **5** that is hydrolysed to phosphonate **3**.

In summary functionalised phosphonates may be prepared by a simple, one-pot three-component reaction between acetylenic esters, aldehyde semicarbazones, and trimethylphosphite. The present method carries the advantage



3	Ar	R	%Yield
a	*m*-CH_3O-phenyl	CH_3	95
b	*p*-CH_3-phenyl	CH_3	91
c	*p*-CH_3-phenyl	C_2H_5	94
d	*m*-CH_3O-phenyl	C_2H_5	90
e	*p*-Cl-phenyl	C_2H_5	89

Scheme 1



Scheme 2 (*2S,3R*)-**3a** or (*2R,3S*)-**3a** (*2R,3R*)-**3a** or (*2S,3S*)-**3a**

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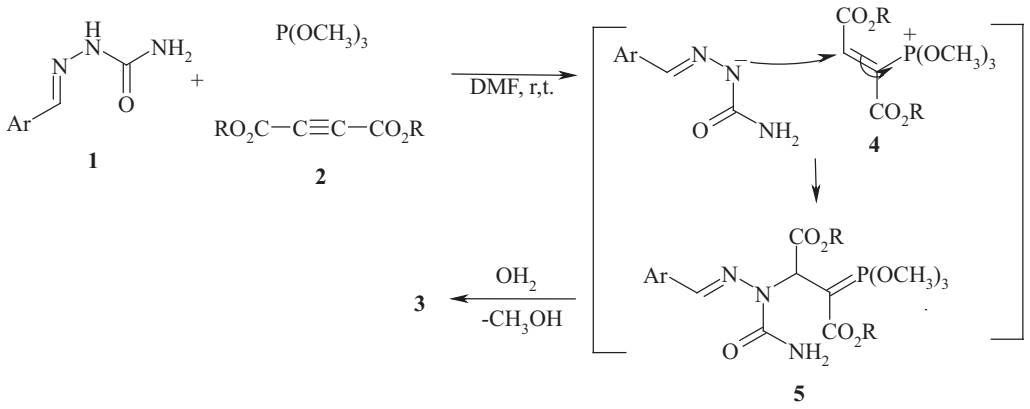

Scheme 3

that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500, 125.8 and 202.5 MHz, respectively. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained on solution in d6-DMSO using TMS as internal standard or 85% H_3PO_4 as external standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Dimethyl2-(dimethoxyphosphoryl)-3-[5-(3-methoxyphenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinate (**3a**): to a magnetically stirred solution of trimethylphosphite (0.25 g, 2 mmol) and 3-methoxybenzaldehyde semicarbazone (0.45 g, 2 mmol) in DMF (10 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in DMF (3 ml) at room temperature over 2 min. The reaction mixture was then stirred for 24 h. Water (50 ml) was added and the mixture was extracted by dichloromethane (3 × 20 ml). The organic phase was washed with water (3 × 20 ml), and dried over anhydrous sodium sulfate. Solvent was evaporated and the residue was crystallised from ethyl acetate–hexane mixture. Colourless crystals; m.p. 122–123°C, IR (KBr)(ν_{max}, cm^{-1}): 3390, 3255 (NH_2), 1740, 1692 (C=O, ester). Analyses: Calcd. for $C_{17}H_{24}N_3O_9P$: C, 45.85; H, 5.43; N, 9.44%. Found: C, 45.8; H, 5.3; N, 9.4%. MS (*m/z*, %): 445 (M, 5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 3.55 (3 H, d $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.58 (3 H, d $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.57, 3.73 and 3.83 (9 H, 3 s, 3 OCH_3), 4.23 (1 H, dd $^{3}J_{HH}$ = 11 H_Z, $^{2}J_{HP}$ = 20 H_Z, CHP), 5.49 (1 H, dd $^{3}J_{HH}$ = 11 H_Z, $^{3}J_{HP}$ = 5 H_Z, CHN), 6.78 (2 H, broad s, NH_2), 6.94–7.45 (4 H, m, 4 CH aromatic), 8.02 (1 H, s, N=CH). ^{13}C NMR (75.5 MH_Z, d_6-DMSO): δ 45.07 (d, $^{1}J_{CP}$ = 130 H_Z, CH), 52.38 (d, $^{2}J_{CP}$ = 3 H_Z, CH), 52.35 and 53.45 (2 OCH_3), 53.94 and 54.32 (2 d, $^{2}J_{CP}$ = 6 HZ, $P(OCH_3)_2$), 56.10 (OCH_3), 112.56, 116.44, 121.43, 130.44, 136.88, and 160.41 (aromatic), 137.79 (C=N), 157.57 (C=O), 168.30 (C=O, ester), 170.19 (d, $^{3}J_{CP}$ = 19 H_Z, C=O ester). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 22.47.

Dimethyl 2-(dimethoxyphosphoryl)-3-[5-(4-methylphenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinate (**3b**): Colourless crystals; m.p. 147–149°C, IR (KBr)(ν_{max}, cm^{-1}): 3470, 3345 (NH_2), 1741, 1727, 16932 (3 C=O, ester). Analyses: Calcd. for $C_{17}H_{24}N_3O_8P$: C, 47.55; H, 5.63; N, 9.79%. Found: C, 47.4; H, 5.6; N, 9.9%. MS (*m/z*, %): 429 (3). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.34 (3 H, s, CH_3), 3.55 (6 H, d $^{3}J_{PH}$ = 11 Hz, $P(OCH_3)_2$), 3.57 and 3.73 (6 H, 2 s, 2 OCH_3), 4.23 (1 H, dd $^{3}J_{HH}$ = 11 H_Z, $^{2}J_{HP}$ = 20 H_Z, CHP), 5.49 (1 H, dd $^{3}J_{HH}$ = 11 H_Z, $^{3}J_{HP}$ = 3 H_Z, CHN), 6.78 (2 H, broad s, NH_2), 7.24 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 7.80 (2 H, d $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 8.00 (1 H, s, N=CH). ^{13}C NMR (75.5 MH_Z, d_6-DMSO): δ 21.84 (CH_3), 45.06 (d, $^{1}J_{CP}$ = 131 H_Z, CH), 52.38 (d, $^{2}J_{CP}$ = 3 H_Z, CH), 53.35 and 53.44 (2 OCH_3), 53.92 and 54.29 (2 d, $^{2}J_{CP}$ = 6 HZ, $P(OCH_3)_2$), 128.22, 130.02, 132.77 and 138.81 (aromatic), 139.84 (C=N), 157.62 (C=O), 168.36 (d, $^{2}J_{CP}$ = 4 H_Z, C=O ester), 170.24 (d, $^{3}J_{CP}$ = 19 H_Z, C=O ester). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 22.44.

Diethyl 2-(dimethoxyphosphoryl)-3-[5-(4-methylphenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinate (**3c**): Colourless crystals; m.p. 135–137°C, IR (KBr)(ν_{max}, cm^{-1}): 3467, 3333 (NH_2), 1743, 1727, 1688 (3 C=O, ester). Analyses: Calcd. for $C_{19}H_{28}N_3O_8P$: C, 49.89; H, 6.17; N, 9.19%. Found: C, 50.0; H, 6.3; N, 9.1%. MS (*m/z*, %): 457 (4). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.09 and 1.26 (6 H, 2 t $^{3}J_{HH}$ = 7 H_Z, 2 CH_3), 2.34 (3 H, s, CH_3), 3.56 (6 H, d $^{3}J_{PH}$ = 11 Hz, $P(OCH_3)_2$), 3.98–4.23 (5 H, m, 2 CH_2 and CHP), 5.41 (1 H, dd $^{3}J_{HH}$ = 10 H_Z, $^{3}J_{HP}$ = 3 H_Z, CHN), 6.78 (2 H, broad s, NH_2), 7.22 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 7.79 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 7.97 (1 H, s, N=CH). ^{13}C NMR (75.5 MH_Z, d_6-DMSO): δ 14.68 and 14.73 (2 CH_3), 21.84 (CH_3), 45.06 (d, $^{1}J_{CP}$ = 130 H_Z, CHP), 52.42 (d, $^{2}J_{CP}$ = 3 H_Z, CHN), 53.91 and 54.27 (2 d, $^{2}J_{CP}$ = 6 H_Z, $P(OCH_3)_2$), 62.01 and 62.18 (2 CH_2), 128.22, 130.01, 132.80 and 138.55 (aromatic), 139.79 (C=N), 157.60 (C=O), 167.76 (d, $^{2}J_{CP}$ = 4 H_Z, C=O ester), 169.50 (d, $^{3}J_{CP}$ = 19 H_Z, C=O ester). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 22.33.

Diethyl2-(dimethoxyphosphoryl)-3-[5-(3-methoxyphenyl)-2-oxo-1, 3,4-triazapent-4-en-3-yl]succinate (**3d**): Colourless crystals; m.p. 130–131°C, IR (KBr)(ν_{max}, cm^{-1}): 3460, 3343 (NH_2), 1743, 1725, 1691 (3 C=O, ester). Analyses: Calcd. for $C_{19}H_{28}N_3O_9P$: C, 48.20; H, 5.96; N, 8.88%. Found: C, 48.2; H, 5.8; N, 9.0%. MS (*m/z*, %): 473 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 and 1.26 (6 H, 2 t $^{3}J_{HH}$ = 7 H_Z, 2 CH_3), 3.55 (3 H, d $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.58 (3 H, d $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.83 (3 H, s, OCH_3), 3.98-4.23 (5 H, m, 2 CH_2 and CHP), 5.43 (1 H, dd $^{3}J_{HH}$ = 10 H_Z, $^{3}J_{HP}$ = 4 H_Z, CHN), 6.78 (2 H, broad s, NH_2), 6.94-7.49 (4 H, m, 4 CH aromatic), 7.99 (1 H, s, N=CH). ^{13}C NMR (75.5 MH_Z, $CDCl_3$): δ 14.68 and 14.73 (2 CH_3), 45.17 (d, $^{1}J_{CP}$ = 129 H_Z, CH), 52.47 (d, $^{2}J_{CP}$ = 4 H_Z, CH), 53.88 and 54.24 (2 d, $^{2}J_{CP}$ = 6 H_Z, $P(OCH_3)_2$), 56.11 (OCH_3), 62.02 and 62.20 (2 CH_2), 112.61, 116.41, 121.13, 130.44, 136.92, and 160.43 (aromatic), 138.55 (C=N), 157.57 (C=O), 167.87 (d, $^{2}J_{CP}$ = 4 H_Z, C=O, ester), 170.19 (d, $^{3}J_{CP}$ = 18 H_Z, C=O ester). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 22.53.

Diethyl 2-(dimethoxyphosphoryl)-3-[5-(4-chlorophenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinate (**3e**): Colourless crystals; m.p. 126–128°C, IR (KBr)(ν_{max}, cm^{-1}): 3459, 3341 (NH_2), 1741, 1719, 1690 (3 C=O, ester). Analyses: Calcd. for $C_{18}H_{25}ClN_3O_8P$: C, 45.24; H, 5.27; N, 8.79%. Found: C, 45.2; H, 5.4; N, 8.7%. MS (*m/z*, %): 477 (2). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.10 and 1.26 (6 H, 2 t $^{3}J_{HH}$ = 7 H_Z, 2 CH_3), 3.57 (6 H, d $^{3}J_{PH}$ = 11 Hz, $P(OCH_3)_2$), 3.97–4.22 (5 H, m, 2 CH_2 and CHP), 5.44 (1 H, dd $^{3}J_{HH}$ = 10 H_Z, $^{3}J_{HP}$ = 3 H_Z, CHN), 6.89 (2 H, broad s, NH_2), 7.47 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 7.97 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 CH aromatic), 8.03 (1 H, s, N=CH). ^{13}C NMR (75.5 MH_Z, d_6-DMSO): δ 14.53 and 14.74 (2 CH_3), 45.66 (d, $^{1}J_{CP}$ = 130 H_Z, CH), 52.45 (d, $^{2}J_{CP}$ = 3 H_Z, CHN), 53.93 and 54.34 (2 d, $^{2}J_{CP}$ = 6 HZ, $P(OCH_3)_2$), 62.18 and 62.43 (2 CH_2), 129.40, 130.00, 132.80 and 134.57 (aromatic), 137.88 (C=N), 157.49 (C=O), 167.86 (C=O ester), 169.39 (d, $^{3}J_{CP}$ = 19 H_Z, C=O ester). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 21.98.

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