# One-pot synthesis of stable phosphite ylides by three component reaction between acetylenic esters, aldehyde semicarbazones and tributyl or triethyl phosphite

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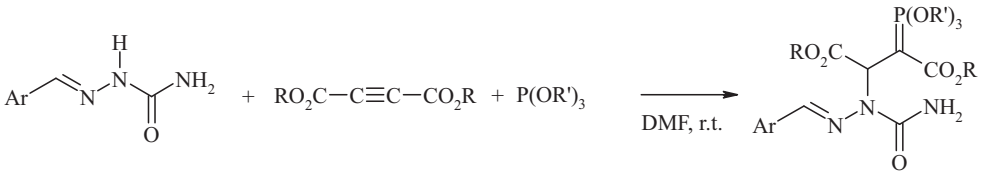
Three-component reaction between acetylenic esters, aldehyde semicarbazones and tributyl- or triethyl phosphite leads to stable crystalline phosphite ylides at one step in nearly quantitative yields.

**Keywords:** acetylenic esters, semicarbazones, phosphite ylides, tributyl phosphite, triethyl phosphite

In recent years, there has been increasing interest in the synthesis of organophosphorus compounds. This is due to the value of such compounds in a variety of biological, industrial, and chemical synthetic uses.[1] Several methods have been described for the novel synthesis of organophosphorus compounds.[2,3] 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 the reactions between trivalent phosphorus nucleophiles and unsaturated carbonyl compounds in the presence of a proton source such as an alcohol.[1] The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols reported to produce phosphite ylide derivatives which are stable at low temperatures, but converted to phosphonate derivatives by warming or by treatment with water.[9] There are other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all of them proceeding through a phosphite ylide intermediate.[10-12] However, this intermediate has not been isolated nor characterised in any of these works and usually hydrolysed or rearranged to the corresponding phosphonates. In another work, we have reported that the three-component reaction between trimethyl phosphite, acetylenic esters and aldehyde semicarbazones, leads to phosphonate derivatives passing from phosphite ylide intermediate.[13] In order to explore the scope of this reaction, we decided to investigate the same reaction with other phosphites such as tributyl phosphite, triethyl phosphite or triphenyl phosphite. Thus, the reaction between tributyl or triethyl phosphite **3** and acetylenic ester **2** in the presence of aldehyde semicarbazone **1** was carried out in DMF at room temperature. The only isolated product was stable crystalline phosphite ylide **4** obtained in excellent yield (Scheme 1).

The three-component reaction between triethyl phosphite, benzaldehyde semicarbazone and diethyl acetylendicarboxylate also afforded the phosphite ylide **4f**. However, no product was isolated from the similar reaction between triphenyl phosphite, acetylenic esters and semicarbazones except the starting semicarbazone.

The structures of compounds **4a–f** result from their IR, $^{1}$H, $^{13}$C, and $^{31}$P NMR spectra. The mass spectra of the ylides **4** are fairly similar and display molecular ion peaks. The $^{1}$H NMR spectrum of **4a** shows the presence of three butoxy groups. It also exhibits two sharp lines at δ = 3.44 and 3.60 ppm for the protons of two methyls of methoxy groups and a doublet ($^{3}J_{HP}$ = 6 $H_Z$) at 6.36 for methine proton which is coupled with phosphorus atom. The HC=N proton appears at δ = 7.93 ppm and the aromatic protons resonate as multiples at δ = 7.28–7.65 ppm. A broad singlet is observed at δ = 6.75 ppm for $NH_2$ protons which was disappeared after the addition of $D_2O$ to the $d_6$-DMSO solution of **4a**. The $^{31}$P NMR spectrum of compound **4a** displays a signal at 53.6 ppm. This shift is similar to those observed for other stable phosphite ylides.[9]




**1** **2** **3** **4**

| **4** | Ar | R | R' | %Yield* |
|---|---|---|---|---|
| **a** | Phenyl | Me | Bu | 95 |
| **b** | *p*-Cl-$C_6H_4$ | Et | Bu | 97 |
| **c** | *m*-$CH_3O$-$C_6H_4$ | Me | Bu | 92 |
| **d** | *m*-$CH_3O$-$C_6H_4$ | Et | Bu | 88 |
| **e** | *m*-$CH_3O$-$C_6H_4$ | t-Bu | Bu | 94 |
| **f** | Phenyl | Et | Et | 95 |

* Isolated yield.

**Scheme 1**

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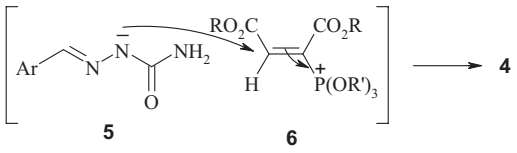
On the basis of the well-established chemistry of trivalent phosphorus nucleophiles[1-7] it is reasonable to assume that the ylide **4** results from the initial addition of trialkyl phosphite to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid (Scheme 2). Then, the positively charged ion **6** is attacked by the anion of the NH-acid **5** to form the phosphite ylide **4**.

In summary, stable crystalline phosphite ylides may be prepared by a simple, one-pot three-component reaction between acetylenic esters, aldehyde semicarbazones, and tributyl phospite or triethyl phosphite. The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification.




**Scheme 2**

## Experimental

Melting points were determined with an electrothermal 9100 apparatus. 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 solution in $d_6$-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.

*General procedure*

To a magnetically stirred solution of phosphite (2 mmol) and semicarbazone (2 mmol) in DMF (10 ml) was added drop-wise a mixture of dialkyl acetylenedicarboxylate (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.

*Dimethyl 2-(tributoxyphosphoranylidene)-3-[5-phenyl-2-oxo-1,3,4-triazapent-4-en-3-yl]succinat* **(4a)**: Colourless crystals, m.p. 77–80°C, IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3480, 3345 ($NH_2$), 1746, 1690 (2 C=O, ester), 1645 (C=O, amid). Analyses: Calcd. for $C_{26}H_{42}N_3O_8P$: C, 56.21; H, 7.62; N, 7.56%. Found: C, 55.9; H, 7.6; N, 7.8. MS (*m/z*,%): 555 (6). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.77 (9 H, t, 3 $CH_3$), 1.19 (6 H, sextet, 3 $CH_2$), 1.49 (6 H, quintet, 3 $CH_2$), 3.44 (3 H, s, $OCH_3$), 3.60 (3 H, s, $OCH_3$), 3.88 (6 H, t, $POCH_2$), 6.36 (1 H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.65 (2 H, broad s, $NH_2$), 7.28–7.65 (5 H, m, 5 CH aromatic), 7.93 (1 H, s, N=CH). $^{13}C$ NMR (125.8 MHz, $d_6$-DMSO): δ 13.70 (3 $CH_3$), 18.41(3 $CH_2$), 31.76 (d, $^{3}J_{cp}$ = 7 Hz, 3 $CH_2$), 41.46 (d, $^{1}J_{cp}$ = 144 Hz, C = P), 49.85 and 52.23 (2 $OCH_3$), 54.87(d,$^{2}J_{cp}$ = 14 Hz, CHN), 67.89 (d, $^{2}J_{cp}$ = 6 Hz, 3 $OCH_2$), 126.77, 128.91, 136.15 and 143.56 (aromatic), 157.29 (C=N), 159.32 (C=O), 169.05 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 171.78 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR (202.5 MHz, $d_6$-DMSO): δ 53.6.

*Diethyl 2-(tributoxyphosphoranylidene)-3-[5-(4-chlorophenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinat* **(4b)**: Colourless crystals, m.p. 117–119°C. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3495, 3360 ($NH_2$), 1746, 1688 (2 C=O, ester), 1642 (C=O, amid). Analyses: Calcd. for $C_{28}H_{45}ClN_3O_8P$: C, 54.41; H, 7.34; N, 6.80%. Found: C, 54.3; H, 7.3; N, 6.9 MS (*m/z*,%): 618 (5). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.78 (9 H, t, 3 $CH_3$), 1.07 and 1.13 (6 H, 2 t, 2 $CH_3$), 1.18 (6 H, sextet, 3 $CH_2$), 1.49 (6 H, quintet, 3 $CH_2$), 3.88 (6 H, t, $POCH_2$), 3.94 and 4.04 (4-H, m, 2 $OCH_2$), 6.34 (1 H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.63 (2 H, broad s, $NH_2$), 7.40–7.68 (4 H, m, 4 CH aromatic), 7.96 (1 H, s, N=CH). $^{13}C$ NMR (125.8 MHz, $d_6$-DMSO): δ 13.71 (3 $CH_3$), 14.43 and 15.35 (2 $CH_3$ of ethy groups), 18.44 (s, 3 $CH_2$), 31.81 (d, $^{3}J_{cp}$ = 7 Hz, 3 $CH_2$), 41.46 (d, $^{1}J_{cp}$ = 143 Hz, C = P), 54.97 (d, $^{2}J_{cp}$ = 14 Hz, CHN), 58.02 and 60.66 (2 $OCH_2$), 67.74 (d, $^{2}J_{cp}$ = 6 Hz, 3 $OCH_2$), 128.38, 128.97, 135.16 and 142.12 (aromatic), 157.24 (C=N), 162.71 (C=O), 168.69 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 171.16 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR (202.5 MHz, $d_6$-DMSO): δ 54.3

*Dimethyl 2-(tributoxyphosphoranylidene)-3-[5-(3-methoxyphenyl-2-oxo-1,3,4-triazapent-4-en-3-yl]succinat* **(4c)**: Colourless crystals, m.p. 107–110°C. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3475, 3340 ($NH_2$), 1743, 1685 (2 C=O, ester), 1640 (C=O, amid). Analyses: Calcd. for $C_{27}H_{44}N_3O_9P$: C, 55.37; H, 7.57; N, 7.18%. Found: C, 55.2; H, 7.5; N, 7.4. MS (*m/z*,%): 585(7). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.78 (9 H, t, 3 $CH_3$), 1.19 (6 H, sextet, 3 $CH_2$), 1.49 (6 H, quintet, 3 $CH_2$), 3.44 (3 H, s, $OCH_3$), 3.59 (3 H, s, $OCH_3$), 3.77 (3 H, s, $OCH_3$), 3.88 (6 H, t, $POCH_2$), 6.35 (1 H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.67 (2 H, broad s, $NH_2$), 7.12–7.34 (4 H, m, 4 CH aromatic), 7.89 (1H, s, N=CH). $^{13}C$ NMR (125.8 MHz, $d_6$-DMSO): δ 13.75 (s, 3 $CH_3$), 18.51 (s, 3 $CH_2$), 31.82 (d, $^{3}J_{cp}$ = 7 Hz, 3 $CH_2$), 41.51 (d, $^{1}J_{cp}$ = 145 Hz, C = P), 49.84 and 52.24 (2 $OCH_3$), 55.25 (d,$^{2}J_{cp}$ = 14 Hz, CHN), 55.59 (s, $OCH_3$), 67.90 (d, $^{2}J_{cp}$ = 6 Hz, 3 $OCH_2$), 110.90, 115.57, 119.94, 129.97, 138.27 and 143.69 (aromatic), 157.29 (C=N), 159.98 (C=O), 169.12 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 171.81 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR (202.5 MHz, $d_6$-DMSO): δ 54.0.

*Diethyl 2-(tributoxyphosphoranylidene)-3-[5-(3-methoxyphenyl)-2-oxo-1,3,4-triazapent-4-en-3-yl]succinat* **(4d):** Colourless crystals, m.p. 72–75°C. IR (KBr)($\nu_{max,}$ $cm^{-1}$): 3540, 3355($NH_2$), 1742, 1698 (2 C=O, ester), 1639 (C=O, amid). Analyses: Calcd. for $C_{29}H_{48}N_3O_9P$: C, 56.76; H, 7.88; N, 6.85%. Found: C, 56.6; H, 7.8; N, 7.0. MS (*m/z*,%): 613(9). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.79 (9 H,t, 3 $CH_3$), 1.07 and 1.14 (6 H, 2 t, 2 $CH_3$ of ethyl groups), 1.19 (6 H, sextet, 3 $CH_2$), 1.50 (6 H, quintet, 3 $CH_2$), 3.75 (3 H, s, $OCH_3$), 3.89 (6 H, t, $POCH_2$), 3.95 and 4.07 (4 H, m, 2 $OCH_2$), 6.33 (1 H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.66 (2 H, broad s, $NH_2$), 7.13–7.64 (4 H, m, 4 CH aromatic), 7.95 (1H, s, N=CH). $^{13}C$ NMR (125.8 MHz, $d_6$-DMSO): δ 13.71 (s, 3 $CH_3$), 14.43 and 15.36 (2 $CH_3$), 18.53 (s, 3 $CH_2$), 31.85 (d, $^{3}J_{cp}$ = 7 Hz, 3 $CH_2$), 41.42 (d, $^{1}J_{cp}$ = 141 Hz, C = P), 54.95 (d, $^{2}J_{cp}$ = 14 Hz, CHN), 55.49 ($OCH_3$), 57.96 and 60.72 (2 $OCH_2$), 67.73 (d, $^{2}J_{cp}$ = 6 Hz, 3 $OCH_2$), 110.83, 115.38, 119.97, 129.91, 139.52 and 143.70 (aromatic), 157.28 (C=N), 159.97 (C=O), 168.65 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 171.28 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR (202.5 MHz, $d_6$-DMSO): δ 53.7.

*Di-t-butyl2-(tributoxyphosphoranylidene)-3-[5-(3-methoxyphenyl-2-oxo-1,3,4-triazapent-4-en-3-yl]succinate* **(4e):** Colourless crystals, m.p. 103–106°C, IR(KBr) ($\nu_{max}$, $cm^{-1}$): 3400, 3290 ($NH_2$), 1737, 1689 (2 C=O, ester), 1641 (C=O, amid). Analyses: Calcd. for $C_{33}H_{56}N_3O_9P$: C, 59.18; H, 8.43; N, 6.27%. Found: C, 58.9; H, 8.4; N, 6.1%. MS (*m/z*,%): 669 (10). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.79 (9 H, t, 3 $CH_3$), 1.19 (6 H, sextet, 3 $CH_2$), 1.37 (s, 9 H), 1.39 (s, 9 H), 1.50 (6 H, quintet, 3 $CH_2$), 3.75 (3 H, s, $OCH_3$), 3.86 (6 H, t, $POCH_2$), 6.18 (1H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.72 (2 H, broad s, $NH_2$), 7.18–7.34 (4 H, m, 4 CH aromatic), 8.05 (1 H, s, N=CH). $^{13}C$ NMR (125.8 MHz, $d_6$-DMSO): δ 13.82 (3 $CH_3$), 18.52 (3 $CH_2$), 28.24 and 29.06 (6 $CH_3$ of 2 t-Bu), 31.97 (d, $^{3}J_{cp}$ = 7 Hz, 3 $CH_2$), 41.41 (d, $^{1}J_{cp}$ = 141 Hz, C = P), 55.43 (d, $^{2}J_{cp}$ = 14 Hz, CHN), 55.62 ($OCH_3$), 67.18 (d, $^{2}J_{cp}$ = 6 Hz, 3 $OCH_2$), 76.98 and 79.63 (2 O–$C(CH_3)_3$), 110.97, 115.31, 119.80, 129.80, 137.80 and 143.44 (aromatic), 157.31 (C=N), 159.91 (C=O), 168.25 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 169.99 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR (202.5 MHz, $d_6$-DMSO): δ 54.5.

*Diethyl 2-(triethoxyphosphoranylidene)-3-[5-phenyl-2-oxo-1,3,4-triazapent-4-en-3-yl]succinat* **(4f):** Colourless crystals, m.p. 78–81°C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3540,3355 ($NH_2$), 1742, 1698 (2 C=O, ester), 1639 (C=O, amid). Analyses: Calcd. for $C_{22}H_{34}N_3O_8P$: C, 52.90; H, 6.86; N, 8.41%. Found: C, 52.9; H, 6.7; N, 8.6%. MS (*m/z*,%): 499 (11). $^{1}H$ NMR (500 MHz, $d_6$-DMSO): δ 0.98 1.12 (15 H, m, 5 $CH_3$), 3.95 – 4.05 (10 H, m, 5 $OCH_2$), 6.28 (1 H, d, $^{3}J_{HP}$ = 16 Hz, CHN), 6.54 (2 H, broad s, $NH_2$), 7.32 – 7.66 (5 H, m, 5 CH aromatic), 7.97 (1H, s, N=CH). $^{13}C$ NMR(125.8 MHz, $d_6$-DMSO): δ 13.75 (d, $^{3}J_{CP}$ = 6 $H_Z$, 3 $CH_3$), 14.21 and 14.33 (2 $CH_3$), 41.46 (d, $^{1}J_{cp}$ = 141 Hz, C=P), 54.73 (d,$^{2}J_{cp}$ = 14 Hz, CHN), 62.89 and 93.22 (2 $OCH_2$), 65.32 (d, $^{2}J_{cp}$ = 7 Hz, 3 $POCH_2$), 126.42, 128.90, 137.11 and 143.56 (aromatic), 157.29 (C=N), 159.32 (NC=O), 169.05 (d, $^{2}J_{cp}$ = 19 Hz, C=O ester), 171.78 (d, $^{3}J_{cp}$ = 19 Hz, C=O ester). $^{31}P$ NMR(202.5 MHz, $d_6$-DMSO): δ 54.2.

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