Three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylates and 3-(3,5-dimethyl pyrazol-1-yl)-3-oxo propionitrile

Mohammad Anary-Abbasinejad[a], Alireza Hassanabadi[b]* and Nafiseh Esmikhani[c]

[a]*Young Researchers Club, Islamic Azad University, Anar Branch, Anar, Iran*
[b]*Department of Chemistry, Islamic Azad University, Zahedan Branch, P.O. Box 98135-978, Zahedan, Iran*
[c]*Department of Chemistry, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran*

Protonation of the reactive 1:1 intermediate produced in the reaction between dialkyl acetylenedicarboxylates and triphenylphosphine by 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile leads to vinylphosphonium salts which undergo Michael addition with the conjugate base of the CH-acid to produce highly functionalised, salt-free phosphorus ylides in excellent yields.

Keywords: dialkyl acetylenedicarboxylates, phosphorus ylides, triphenylphosphine, CH-acid

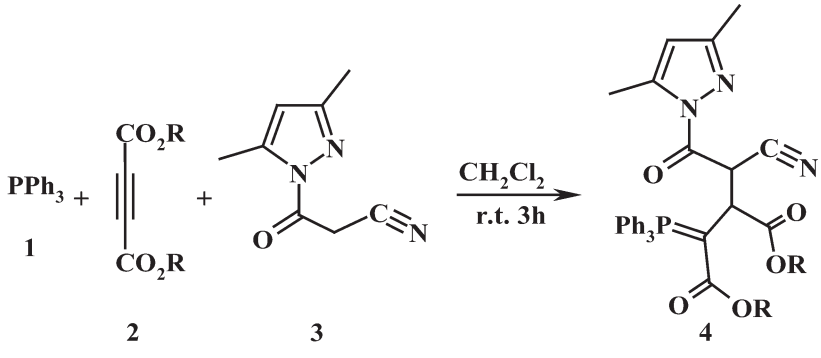
Phosphorus ylides are reactive systems, which take part in many reactions of value in organic synthesis.[1–3] Organophosphorus compounds bearing a carbon atom bound directly to a phosphorus atom, are synthetic targets of interest, at least because of their value for a variety of industrial, biological and chemical synthetic uses.[1–3] Several methods have been developed for the preparation of phosphorus ylides. These ylides are usually prepared by treatment of an appropriate phosphonium salt with a base; the corresponding phosphonium salts are usually obtained from the phosphine and an alkyl halide.[1,2] Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated olefins.[1,2] Reaction of acetylenic esters with triphenylphosphine in the presence of an organic compound possessing an acidic-hydrogen has been recently reported to produce phosphorus ylides.[4–6] In continuation of our works on the reaction between triphenylphosphine and acetylene diesters in the presence of organic N–H, O–H or C–H acids,[7–13] we report here an efficient synthetic route to stable phosphorus ylides using three-component reactions between dialkyl acetylenedicarboxylates (DAAD's), triphenylphosphine and 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile **3**.

Results and discussion

The reaction of the 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile **3** with DAAD **2** in the presence of triphenylphosphine **1** leads to the corresponding ylide **4** in good yields (Scheme 1).

The NMR spectra of ylides **4a–c** are consistent with the presence of two rotamers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the C–C bond due to partial double bond character is slow on the NMR time scale at room temperature (Scheme 2).

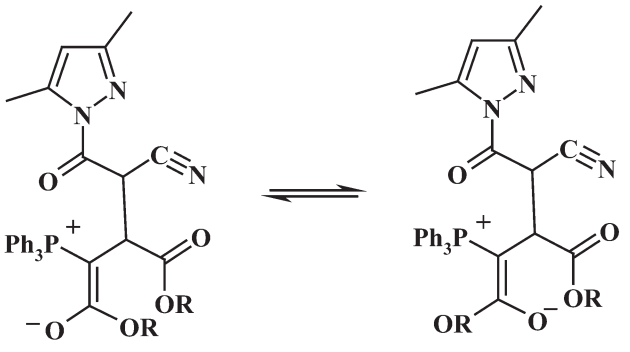
The ^{1}H NMR spectrum of compound **4a** displays two sharp lines (δ 3.15, 3.61 ppm) for the protons of two methoxy groups, and two sharp lines (δ 2.22, 2.40 ppm) for the protons of two methyl groups of pyrazol and a doublet at 6.30 ($^{3}J_{HH}$ = 10 H_Z, CH–CN) for methine proton and two doublet at 3.30 ($^{3}J_{PH}$ = 9 H_Z, $^{3}J_{HH}$ = 5 H_Z, P=C–CH) for methine proton which is coupled with phosphorus atom and multiplets between 7.41 and 7.85 ppm for aromatic protons. ^{13}C NMR spectrum of compound **4a** showed 36 distinct signals, which is consistent with the proposed structure. The ^{31}P NMR spectrum of compound **4a** consists of one signal at 25.49 ppm. This shift is



4	R	Yield
a	Me	90
b	Et	95
c	t-Bu	92

Scheme 1 Three-component reaction between triphenylphosphine, DAAD's and 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile.

* Correspondent. E-mail: ar_hasanabadi@yahoo.com



Scheme 2 Two rotamers of compounds **4**.

similar to those observed for other stable phosphorus ylides.[14,15] The structural assignments made on the basis of the NMR spectra of compounds **4a** are supported by their IR spectra. The carbonyl region of the spectrum exhibits absorption bands at 1723 and 1624 cm^{-1} for the carbonyl groups. Compounds **4a** possess two chiral centres and two diastereoisomers might be expected. However, the NMR data show the existence of only one isomer. From analysis of the NMR spectra of compound **4** we could not distinguish the relative configurations of the products. Similar reactions between acetylenic diesters, triphenylphosphine and CH-acidic compounds have been reported to produce phosphorus ylides in a diastereoselective manner. The configurations of these ylides have been established by X-ray crystallographic analysis. Comparing the coupling constants in the NMR spectra of **4a** with those reported in this reference we think the isolated product is 4-(3S,4S) or (3R,4R). Compounds **4b** and **4c** were similarly isolated as a single diastereoisomer.

It is reasonable to assume that ylide **4** results from the initial addition of triphenylphosphine to DAAD and subsequent protonation of the 1:1 adduct by the CH-acidic 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile.The positively charged ion **5** is then attacked by the anion **6** to form the phosphorane **4** (Scheme 3).

In summary, we report here that three-component reaction between dialkyl acetylenedicarboxylates and triphenylphosphine by 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile produces functionalised phosphoranes in good yields. The advantages of the reported method are simple available starting materials, short reaction time, simple work-up, neutral reaction conditions and high yields.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the Analytical Laboratory of Islamic University Yazd Branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer in solution in $CDCl_3$ using TMS as an internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Compound **3** was prepared as previously described in the literature.[16]

Preparation of compounds **4a-c**; *general procedure*

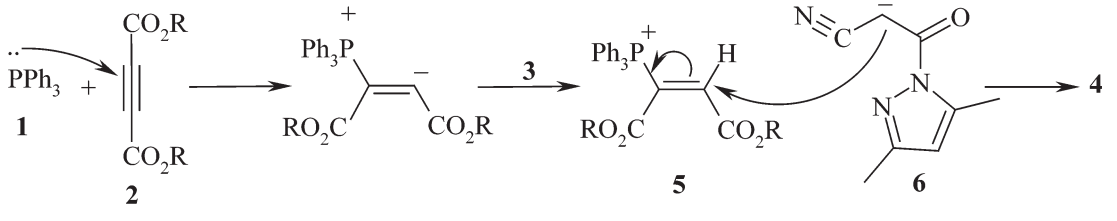
To a magnetically stirred solution of triphenylphosphine (2 mmol) and 3-(3,5-dimethyl pyrazol-1-yl)-3-oxopropionitrile (2 mmol) in dichloromethane (10 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate (2 mmol) in dichloromethane (3 mL) at room temperature for 2 min. The reaction mixture was then stirred for 3h. The solvent was evaporated under reduced pressure. The solid was filtered and washed with diethyl ether to give the pure product.

Dimethyl 2-[1-Aminomethyl-2-(3,5-dimethyl-pyrazol-1-yl)-2-oxoethyl]-3-(triphenyl-λ^5-phosphanylidene)-succinate (**4a**): Yield: 90%; colourless crystals; m.p. 142–143 °C. IR (KBr) (ν_{max}, cm^{-1}): 1723, 1624 (C=O). Calcd for ($C_{32}H_{30}N_3O_5P$): C, 67.7 2; H, 5.33; N, 7.40. Found: C, 67.6; H, 5.5; N, 7.5%. MS (*m/z*, %): 567. (M, 6).

Major isomer (60%):^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 2.40 (s, 3H, CH_3), 3.15 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.30 (dd, $^3J_{PH}$ = 9 H_Z, $^3J_{HH}$ = 5 H_Z, P=C–CH), 5.93 (s, 1H, C–CH=C), 6.30 (d, 1H, $^3J_{HH}$ = 10 H_Z, CH–CN)*, 7.41–7.85 (m, 27H, arom)* (*For two conformational isomers).^{13}C NMR ($CDCl_3$): δ = 14.33, 14.48 (2CH_3), 39.30 (d, $^1J_{PC}$ = 123.25 H_Z, C=P), 44.85 (d, $^2J_{PC}$ = 13.25 H_Z, CH), 49.51, 52.57 (2 OCH_3), 65.10 (CH–CN)*, 112.55 (C=C–N), 118.11 (CN), 123.58 (C=C), 127.10 (d, $^1J_{PC}$ = 92 H_Z, C^{ipso}), 129.44 (d, $^3J_{PC}$ = 12.2 H_Z, C^{meta}), 132.57 (d, $^4J_{PC}$ = 7 H_Z, C^{ortho}), 134.56 (d, $^2J_{PC}$ = 2 H_Z, C^{para}), 144.43, 153.35 (C, arom), 166.03 (C=O)*. 170.03 (d, $^2J_{PC}$ = 12.6 H_Z, C=O)*, 173.98 (d, $^3J_{PC}$ = 11.76 H_Z, C=O)*. ^{31}P NMR ($CDCl_3$): δ 25.49 Minor isomer (40%): ^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), δ, 3.45 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.32 (dd, $^3J_{PH}$ = 9 H_Z, $^3J_{HH}$ = 5 H_Z, 1H, P=C–CH), 5.96 (s, 1H, C–CH=C) . ^{13}C NMR ($CDCl_3$): δ = 14.41, 14.48 (2CH_3), 39.30 (d, $^1J_{PC}$ = 123.25 H_Z, C=P), 44.49 (d, $^2J_{PC}$ = 13.25 H_Z, CH), δ 51.86, 52.57, (2 OCH_3), 112.63 (C=C–N), 117.99 (CN), 126.40 (d, $^1J_{PC}$ = 92 H_Z, C^{ipso}), 128.94 (d, $^3J_{PC}$ = 12.3 H_Z, C^{meta}), 131.62 (d, $^4J_{PC}$ = 2 H_Z, C^{ortho}), 133.01 (d, $^2J_{PC}$ = 10 H_Z, C^{para}), 144.66, 153.42 (C, arom), 165.71 (C=O)*. ^{31}P NMR ($CDCl_3$): δ 26.85.

Diethyl 2-[1-Aminomethyl-2-(3,5-dimethyl-pyrazol-1-yl)-2-oxoethyl]-3-(triphenyl-λ^5-phosphanylidene)-succinate (**4b**): Yield: 95%; colourless crystals; m.p. 145–146 °C. IR (KBr) (ν_{max}, cm^{-1}): 1723, 1624 (C=O). Calcd for ($C_{34}H_{34}N_3O_5P$): C, 68.56; H, 5.75; N, 7.05. Found: C, 68.7; H, 5.9; N, 6.9%. MS (*m/z*, %): 595. (M, 4).

Major isomer (60%):^{1}H NMR ($CDCl_3$): δ = 0.46 (t, $^3J_{HH}$ = 10 H_Z, CH_3), 1.10 (t, $^3J_{HH}$ = 10 H_Z, CH_3), δ = 2.21 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.30 (dd, $^3J_{PH}$ = 9 H_Z, $^3J_{HH}$ = 5 H_Z, P=C–CH), 3.72 (m, 2H, OCH2), 3.98 (m, 2H, OCH2), 5.93 (s, 1 H, C–CH=C), 6.31 (d, 1H, $^3J_{HH}$ = 10 H_Z, CH–CN), 7.47–7.83 (m, 27 H, arom)* (*For two conformational isomers).^{13}C NMR ($CDCl_3$): δ = 14.32 (2CH_3), 14.53 (2CH_3), 39.30 (d, $^1J_{PC}$ = 125.25 H_Z, C=P), 45.18 (d, $^2J_{PC}$ = 13.25 H_Z, CH), 58.10, 61.50 (2 OCH_2), 66.20 (CH–CN)*, 112.51 (C=C–N), 118.28 (CN), 123.58 (C=C), 126.45 (d, $^1J_{PC}$ = 91 H_Z, C^{ipso}), 128.96 (d, $^3J_{PC}$ = 12.2 H_Z, C^{meta}), 132.53 (d, $^4J_{PC}$ = 2.5 H_Z, C^{para})*, 134.53 (d, $^2J_{PC}$ = 5 H_Z, C^{ortho}), 144.38, 153.22 (C, arom), 166.24 (C=O), 170.11 (d, $^3J_{PC}$ = 11.76 H_Z, C=O)*, 173.56 (d, $^3J_{PC}$ = 5 H_Z, C=O)*. ^{31}P NMR ($CDCl_3$): δ 25.49 Minor isomer (40%): ^{1}H NMR ($CDCl_3$): δ = 1.15 (t, $^3J_{HH}$ = 10 H_Z, CH_3), 1.21 (t, $^3J_{HH}$ = 10 H_Z, CH_3), δ = 2.23 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), δ, 3.45 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.33 (dd, $^3J_{PH}$ = 9 H_Z, $^3J_{HH}$ = 5 H_Z, 1H, P=C–CH), 4.11 (m, 4H, 2OCH_2),



Scheme 3 Suggested mechanism for formation of ylides **4**.

5.96 (s, 1H, C–CH=C), 6.22 (d, 1H, $^{3}J_{HH}$ = 10 H_Z, CH–CN). ^{13}C NMR ($CDCl_3$): δ = 14.35 ($2CH_3$), δ = 15.15 ($2CH_3$), 38.50 (d, $^{1}J_{PC}$ = 125.25 H_Z, C=P), 44.68 (d, $^{2}J_{PC}$ = 13.25 H_Z, CH), δ 58.83, 61.57, (2 OCH_2), 112.57 (C=C–N), 118.08 (CN), 126.60 (d, $^{1}J_{PC}$ = 91 H_Z, C^{ipso}), 129.08 (d, $^{3}J_{PC}$ = 12.2 H_Z, C^{meta}), 134.64 (d, $^{2}J_{PC}$ = 5 H_Z, C^{ortho}), 144.55, 153.42 (C, arom), 166.06 (C=O). ^{31}P NMR ($CDCl_3$): δ 26.85.

Di-t-butyl 2-[1-Aminomethyl-2-(3,5-dimethyl-pyrazol-1-yl)-2-oxo-ethyl]-3-(triphenyl-λ^5-phosphanylidene)-succinate (**4c**): Yield: 92%; colourless crystals; m.p. 149–151 °C. IR (KBr) (ν_{max}, cm^{-1}): 1723, 1624 (C=O). Calcd for ($C_{38}H_{42}N_3O_5P$): C,70.03; H,6.50; N,6.45. Found: C,70.2; H,6.6; N,6.5%. MS (*m/z*, %):651. (M, 6). Major isomer (60%):^{1}H NMR ($CDCl_3$): δ = 0.95 (s, $3CH_3$), 1.32 (s, $3CH_3$), δ = 2.22 (s, 6 H, $2CH_3$), 3.17 (dd, $^{3}J_{PH}$ = 9 H_Z, $^{3}J_{HH}$ = 5 H_Z, P=C–CH), 5.91 (s, 1 H, C–CH=C), 6.20 (d, 1H, $^{3}J_{HH}$ = 10 H_Z, CH–CN), 7.40–7.82 (m, 27 H, arom)* (*For two conformational isomers).^{13}C NMR ($CDCl_3$): δ = 14.57 ($2CH_3$), δ = 28.43, 28.78 ($6CH_3$), 39.30 (d, $^{1}J_{PC}$ = 130.25 H_Z, C=P), 46.03 (d, $^{2}J_{PC}$ = 13.25 H_Z, CH), 66.27 (CH–CN)*, 81.32 (2C), 112.32 (C=C–N), 118.72 (CN), 123.58 (C=C), 127.10 (d, $^{1}J_{PC}$ = 91.5 H_Z, C^{ipso}), 126.85 (d, $^{3}J_{PC}$ = 10 H_Z, C^{meta}), 132.53 (s, C^{para})*, 134.53 (d, $^{2}J_{PC}$ = 6.25 H_Z, C^{ortho}), 144.30, 153.03 (C, arom), 166.31 (C=O), 168.60 (d, $^{3}J_{PC}$ = 11.76 H_Z, C=O)*, 172.74 (d, $^{3}J_{PC}$ = 5 H_Z, C=O). ^{31}P NMR ($CDCl_3$): δ 25.49 Minor isomer (40%): ^{1}H NMR ($CDCl_3$): δ = 1.37 (s, $3CH_3$), 1.48 (s, $3CH_3$), δ = 2.40 (s, 6 H, $2CH_3$), δ = 3.10 (dd, $^{3}J_{PH}$ = 9 H_Z, $^{3}J_{HH}$ = 5 H_Z, 1H, P=C–CH), 5.95 (s, 1H, C–CH=C), 6.28 (d, 1H, $^{3}J_{HH}$ = 10 H_Z, CH–CN). ^{13}C NMR ($CDCl_3$): δ = 14.26 (CH_3), δ = 14.36 (CH_3), δ = 28.38, 29.26 ($6CH_3$), 40.45 (d, $^{1}J_{PC}$ = 130.25 H_Z, C=P), 44.96 (d, $^{2}J_{PC}$ = 13.25 H_Z, CH), δ = 81.26, (2C), 112.44 (C=C–N), 118.26 (CN), 126.08 (d, $^{1}J_{PC}$ = 91.5 H_Z, C^{ipso}), 128.95 (d, $^{3}J_{PC}$ = 10 H_Z, C^{meta}), 134.58 (d, $^{2}J_{PC}$ = 6.25 H_Z, C^{ortho}), 144.45, 153.03 (C, arom), 166.22 (C=O) 172.34 (d, $^{3}J_{PC}$ = 5 H_Z, C=O). ^{31}P NMR($CDCl_3$): δ = 26.85.

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