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One-pot synthesis of phosphonato esters from reaction between triethyl phosphite and dimethyl acetylenedicarboxylate in the presence of CH-acid and phenolic compounds

Khatereh Khandan-Barani[a]*, Malek Taher Maghsoodlou[b] and Samira Kianpour[b]

[a]*Department of Chemistry, Islamic Azad University, Zahedan Branch, P.O. Box 98135-978, Zahedan, Iran.*
[b]*Department of Chemistry, Faculty of Science, The University of Sistan & Baluchestan, P. O. Box 98135-674 Zahedan, Iran.*

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Abstract: Phosphonato esters were obtained from the 1:1:1 reaction between triethyl phosphite and dimethyl acetylenedicarboxylate in the presence of dimedone and phenolic compounds, such as p-cresol and 2,6-dimethyl phenol without using any catalyst at room temperature in good yields.

Keywords: Three-component reaction, Dimethyl acetylenedicarboxylate; Triethyl phosphite; Phosphonate esters; One-pot.

Introduction

Formation of P-C bonds is of considerable importance in organophosphorus chemistry [1, 2]. 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 [3, 4]. Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [5, 6]. They are known to exhibit various biological activities such as antibacterial, anticancer, antifungal, antitumor, and antihypertensive [7-12].

Trivalent phosphorus compound is known to be a nucleophile, whereas it behaves as an electron donor toward good electron acceptor either in the ground or excited state [13, 14]. 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 [15, 16]. In the current work, the reaction of triethyl phosphite **1** with dimethyl acetylenedicarboxylate **2** in the presence of dimedone and phenolic compounds **3a-c**, such as p-cresol and 2,6-dimethyl phenol leads to the corresponding phosphonato esters **4** in good yields (Scheme **1**).

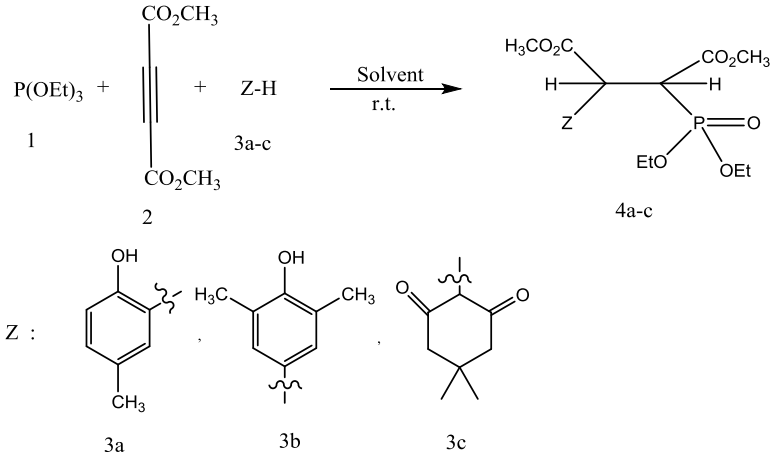
*Corresponding author. Tel: (+98) 5433443600, Fax: (+98) 5433441099, E-mail: kh_khandan_barani@yahoo.com

Results and discussion

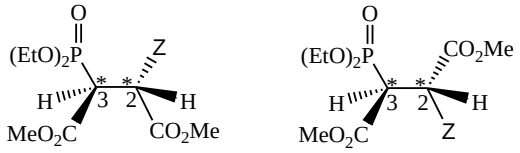
In the current work, we reported a simple and neutral stereoselective synthesis of phosphonato esters at room temperature via reaction between triethyl phosphite **1** and dimethyl acetylenedicarboxylate **2** in the presence of p-cresol, 2,6-dimethyl phenol and dimedone **3a-c**. The use of compounds **3a-c** led to phosphonato esters **4a-c** in good yield (Scheme **1**). These reactions were carried out in diethyl ether, dichloromethane and tetrahydrofuran as solvent for **3a**, **3b** and **3c** respectively, according to the solubility of starting materials and were finished within 12-24 hours.

The structure of compounds **4a-c** was deduced from their IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and elemental

analysis. The mass spectra of compound **4a** displayed molecular ion peaks at appropriate m/z values. The ^{1}H NMR spectrum of compound 4a exhibited two triplet at (δ = 0.93 and 1.27 ppm, ^{3}J = 7.2 Hz), and a multiplet at (δ = 3.99-4.12) readily recognized as arising from the two diastereotopic ethoxy groups. The three singlets at (δ = 2.27 ppm) and (δ = 3.66, 3.82 ppm) belong to the methyl and methoxy protons, along with signals for methine protons at δ = 3.37 and 3.42 ppm (1H, dd, $^3J_{PH}$ = 17.2 Hz, $^3J_{HH}$ = 10.5 Hz) and δ = 4.76 and 4.79 ppm (1H, dd, $^2J_{PH}$ = 12.1 Hz, $^3J_{HH}$ = 10.5 Hz) which appear as two doublet of doublet, respectively, for the O=P-CH-*CH* and O=P-*CH*-CH groups. A multiplet at (δ = 6.93-7.07 ppm), and a singlet at (δ = 7.63 ppm) readily recognized as arising from the aromatic protons and hydroxyl group. The vicinal proton-proton coupling constant ($^3J_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation.[17-20] Typically, J_{gauche} varies between 1.5 and 5 Hz and J_{anti} between 10 and 14 Hz. Observation of $^3J_{HH}$ = 10.5 Hz for the vicinal methine protons in 4a indicates the dominance of the anti arrengement. Scince compound **4a** possesses two stereogenic centres, two diastereomers with anti HCCH arrangement are possible (Scheme **2**).



Scheme 1: Reaction between triethyl phosphite **1** and dimethyl acetylenedicarboxylate **2** in the presence of phenolic compounds and dimedone **3a-c**.



(2S*,3R*)-**4a** or (2R*,3S*)-**4a** (2S*,3S*)-**4a** or (2R*,3R*)-**4a**

Scheme 2: Two diastereomers with anti HCCH arrangement for 4a.

The three-bond carbon-phosphorus coupling, $^3J_{CP}$, 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. [21] The observation of $^3J_{CP}$ 21.1 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 ^{1}H and ^{13}C NMR spectra of **4a**, it helps in the assignment of the signals by long-range couplings with the ^{1}H and ^{13}C nuclei (see Experimental section).

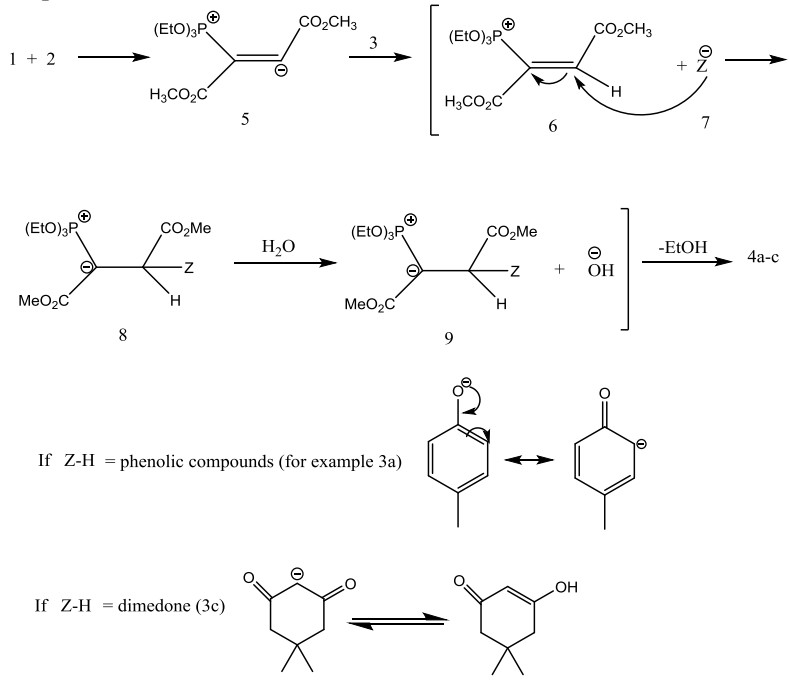
The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a-c** were supported by the IR spectra. The carbonyl region of the spectra exhibited two distinct absorption bands for each compound (see Experimental section).

Although the mechanistic details of the reaction are not clearly known, a plausible rationale may be advanced to explain the product formation. [22] Presumably, the zwitterionic intermediate **5** formed from $(EtO)_3P$ and dimethyl acetylenedicarboxylate was protonated by organic compounds containing O-H or C-H acid to furnish the intermediate **6**, which was then attacked by the anion **7** to produce **8**; this intermediate was protonated to furnish **9**, which was converted to the final product by hydrolysis and loss of ROH (Scheme **3**).

Conclusion

In conclusion, we have described a simple, one-pot and efficient synthesis of stable diethoxy phosphoryl succinate from triethyl phosphites and dimethyl

acetylenedicarboxylates in the presence of p-cresol, 2,6-dimethyl phenol and dimedone containing O-H and C-H acid. The present procedure has the advantage that not only the reaction is performed under neutral conditions but also the reactants can be mixed without any activation or modification.



Scheme 3: Plausible mechanism for the formation of compound **4a-c**.

Experimental

Dimethyl acetylenedicarboxylate, triethyl phosphite, p-cresol, 2,6-dimethyl phenol, dimedone and solvents were purchased from Aldrich and Merk used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT-IR spectrometer, respectively. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX–400 AVANCE instrument with $CDCl_3$ as solvent at 400.2, 100.6 and 162.0 MHz, respectively. Elemental analysis for C and H were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectrum was recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV.

General procedures:

The process for the preparation of *Dimethyl 2-(diethoxyphosphoryl)-3-(2-hydroxy-5-methylphenyl) succinate* (**4a**): **(**It should be noted that the solvent has changed for the synthesis of other compounds.[See results and discussion]).

To a magnetically stirred solution of p-cresol (1 mmol) and triethyl phosphite (1 mmol) in diethyl ether (5 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (1 mmol) in 3 mL of diethyl ether at -5 °C to 10 min. After approximately 12 hours stirring at room temperature, the solvent was removed under reduced pressure, the residual washed with mixture of cold diethyl ether and n-hexane with 1: 1 ratio (2×3 mL). The product **4a** was obtained as white solid, 0.33 g, yield 85%, m.p**.** 128-130°C. IR (KBr) (ν_{max}, cm^{-1}): 3200 (O-H), 1735 (C=O), 1240 (P=O)**.** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 and 1.27 (6H, 2t, $^{3}J_{HH}$ = 7.2 Hz, $2OCH_2$-CH_3), 2.27 (3H, 1s, CH_3-Ar), 3.37 and 3.42 (1H, dd, $^{3}J_{PH}$ = 17.2 Hz, $^{3}J_{HH}$ = 10.5 Hz, *CH*-CH-P), 3.66 and 3.82 (6H, 2s, $2OCH_3$), 3.99-4.12 (4H, m, $2OCH_2$-CH_3), 4.76 and 4.79 (1H, dd, $^{2}J_{PH}$ = 12.1 Hz, $^{3}J_{HH}$ = 10.5 Hz, CH-P), 6.93-7.07 (4H, m, Ar), 7.63 (1H, 1s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.73 and 16.11 (2d, $^{3}J_{PC}$ = 6.2 Hz, $2OCH_2CH_3$), 20.5 (CH_3-Ar), 48.25 (1d, $^{1}J_{PC}$ = 131.6 Hz, P-CH), 43.98 (1s, P-CH-*C*H), 52.75 and 52.77 (2s, $2OCH_3$), 62.58 and 63.54 (2d, $^{2}J_{PC}$= 7.3 Hz, $2OCH_2CH_3$), 115.07, 123.16, 129.01, 130.14, 130.81, 152.22 (Ar), 168.68 (d, $^{2}J_{PC}$ = 5.2 Hz, C=O), 173.28 (d, $^{3}J_{PC}$ = 21.1 Hz, C=O). ^{31}P NMR (162.01 MHz, $CDCl_3$): δ = 22.37 (s, P=O). Anal. Calcd. for $C_{17}H_{25}O_8P$ (388.35): C, 52.58;

H, 6.49. Found: C, 52.65; H, 6.51%. MS *m/z* (%): 388 (M^+, 19), 371 (40), 357 (100), 329 (27), 297 (15).

Dimethyl 2-(diethoxyphosphoryl)-3-(4-hydroxy-3,5-dimethylphenyl)succinate (**4b**):

White solid, 0.32 g, yield 80%, m.p**.** 130-132°C. IR (KBr) (ν_{max}, cm^{-1}): 3311 (O-H), 1732 (C=O), 1255 (P=O)**.** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.12 and 1.17 (6H, 2t, $^3J_{HH}$ = 7.2 Hz, $2OCH_2$-CH_3), 2.02 (6H, 1s, $(CH_3)_2$-Ar), 3.63 and 3.81 (6H, 2s, $2OCH_3$), 3.74 and 3.77 (1H, dd, $^3J_{PH}$ = 19.0 Hz, $^3J_{HH}$ = 12.1 Hz, *CH*-CH-P), 3.88-3.98 (4H, m, $2OCH_2$-CH_3), 4.26 and 4.31 (1H, dd, $^2J_{PH}$ = 8.8 Hz, $^3J_{HH}$ = 12.1 Hz, CH-P), 5.13 (1H, br, OH), 6.96 (2H, 1s, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.99 (1s, CH_3-Ar), 16.04 and 16.08 (2d, $^3J_{PC}$ = 21 Hz, $2OCH_2CH_3$), 48.74 (1d, $^1J_{PC}$ = 131.6 Hz, P-CH), 49.34 (1s, P-CH-*C*H), 52.62 and 52.77 (2s, $2OCH_3$), 62.54 and 67.35 (2d, $^2J_{PC}$= 7.2 Hz, $2OCH_2CH_3$), 123.28, 126.25, 128.85, 150.38 (Ar), 169.34 (d, $^2J_{PC}$ = 5.0 Hz, C=O), 173.34 (d, $^3J_{PC}$ = 21.0 Hz, C=O). ^{31}P NMR (162.01 MHz, $CDCl_3$): δ = 19.51 (s, P=O). Anal. Calcd. for $C_{18}H_{27}O_8P$ (402.38): C, 53.73; H, 6.76. Found: C, 53.80; H, 6.77%.

Dimethyl 2-(diethoxyphosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)succinate (**4c**)*:*

White solid, 0.37 g, yield 89%, m.p**.** 134-136°C. IR (KBr) (ν_{max}, cm^{-1}): 3215 (O-H), 1736 (C=O), 1246 (P=O)**.** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.08 (6H, s, $2CH_3$), 1.18 and 1.29 (6H, 2t, $^3J_{HH}$ = 7.1 Hz, $2OCH_2$-CH_3), 2.19 and 2.44 (4H, 2br, $2CH_2$), 3.58 and 3.79 (6H, 2s, $2OCH_3$), 3.79-4.17 (5H, m, $2OCH_2$-CH_3 , *CH*-CH-P), 4.46 and 4.31 (1H, br, CH-P), 10.24 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.27 (d, $^3J_{PC}$ = 6.0 Hz, $2OCH_2CH_3$), 26.16 and 29.94 (2s, $2CH_3$), 30.80 (s, $C(CH_3)_2$), 37.49 (s, P-CH-*C*H), 43.87 (s, CH_2=COH), 44.51 (1d, $^1J_{PC}$ = 131.0 Hz, P-CH), 50.41 (s, CH_2C=O), 52.41 and 52.64 (2s, $2OCH_3$), 62.89 and 64.36 (2d, $^2J_{PC}$= 8.0 Hz, $2OCH_2CH_3$), 168.98 (d, $^2J_{PC}$ = 6.0 Hz, C=O), 172.61 (d, $^3J_{PC}$ = 21.0 Hz, C=O), 173.63 (s, CH_2=*C*OH), 197.75 (s, CH_2C=O). ^{31}P NMR (162.01 MHz, $CDCl_3$): δ = 22.70 (s, P=O). Anal. Calcd. for $C_{18}H_{29}O_9P$ (420.39): C, 51.43; H, 6.95. Found: C, 51.52; H, 6.99%.

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References

[1] Engel, R.; Cohen, I. J. *Synthesis of Carbon-Phosphorus Bond*; CRC Press: Boca RatonFL, 2004.
[2] Yao, Q. *Tetrahedron Lett*, **2007**, *48*, 2749.
[3] Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, **1979**.
[4] Hudson, H. R. *In The Chemistry of Organophosphorus Compounds*, Hartley F. R. ed., *Vol. 1*. Primary, Secondary, and *Tertiary Phosphates and Heterocyclic Organophosphorus (III) Compounds*; Wiley, New York, **1990**.
[5] Engel, R. *Chem. Rev*, **1977**, *77*, 349.
[6] Kaboudin, B.; Moradi, K.; Sardarian, A. R. *Arkivoc*, **2007**, *(xiii)*, 210.
[7] Dutta, S.; Malla, R. K.; Bandyopadhyay, S.; Spilling, C. D.; Dupureur, C. M. *Bioorg. Med. Chem*, **2010**, *18*, 2265.
[8] Pokalwar, R. U.; Hangarge, R. V.; Maske, P. V.; Shingare, M. S. *Arkivoc*, **2006**, *(xi)*, 196.
[9] Prasad, G. S.; Babu, B. H.; Reddy, K. R.; Haranath, P. R.; Reddy, C. S. *Arkivoc*, **2006**, *(xiii)*, 165.
[10] Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett*, **2008**, *49*, 5652.
[11] Zefirov, N. S.; Matveeva, E. D. *Arkivoc*, **2008**, *(i)*, 1.
[12] Sauer, R.; Tayeb, A. E.; Kaulich, M.; Muller, C. E. *Bioorg. Med. Chem*, **2009**, *17*, 5071.
[13] Nakamura, M.; Miki, M.; Majima, T. *J. Chem. Soc. Perkin Trans*, **2000**, *2*, 1447.
[14] Yasui, S.; Tojo, S.; Majima, T. *J. Org. Chem*, **2005**, *70*, 1276.
[15] George, M. V.; Khetan, S. K.; Gupta, R. K. *Adv. Heterocycl. Chem*, **1976**, *19*, 354.
[16] Burgada, R.; Leroux, Y.; Khoshnieh, Y. U. El. *Tetrahedron Lett*, **1981**, *22*, 3533.
[17] Maghsoodlou, M. T.; Rostami Charati, F.; Habibi-Khorassani, S. M.; Khosroshahrodi, M.; Makha, M. *Iran. J. Chem. Chem. Eng*, **2008**, *27*, 105.
[18] Maghsoodlou, M. T.; Rostami Charati, F.; Habibi-Khorassani, S. M.; Ghasemzadeh, M.; Makha, M. *J. Chem. Res*, **2008**, 55.
[19] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Nassiri, M.; Adhamdous, S. R.; Salehzadeh. J. *J. Chem. Res*, **2008**, 79.
[20] Maghsoodlou, M. T.; Heydari, R.; Hazeri, N.; Habibi-Khorassani, S. M.; Nassiri, M.; Ghasemzadeh, M.; Salehzadeh, J.; Gharechaei, Z. *Heteroatom. Chem*, **2009**, *20*, 240.
[21] Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: New York, 3rd Edn, **1990**.
[22] Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen J. S.; Balagopal, L. *Acc. Chem. Res*, **2003**, *36*, 899.