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Multi-component Process for the Synthesis of Some Phosphonate Derivatives using Water as a Green Solvent

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Abstract

A novel, convenient and efficient multi-component reaction for synthesis of phosphonate derivatives from activated acetylenic compounds with 2-hydroxyacetophenone in the presence of phosphites in water lead to the formation of phosphonates in good yields.

Keywords**:** *Water, Activated acetylenic compounds, 2-hydroxyacetophenone.*

Introduction

One of the powerful tools used to join economic aspects with the environmental concerns is performing organic reactions in water. This strategy consists of two or more synthetic steps, which are carried out in water as a cheap, nontoxic, environmentally friendly solvent, in a one-step reaction, without isolation of any intermediate thus reducing time, saving money, energy and raw materials [1]. Phosphorus compounds are not mostly abundant in nature but they have diverse biological activity and have attracted noteworthy synthetic and pharmacological interest [2, 3]. Phosphonates have important applications in flame retardancy [4, 5] organic synthesis [6], and biological applications [7]. Phosphonates have been used as substitutes of the corresponding esters and acids of high biological activity [8, 9] and as suitable probes for designing antibodies on the basis of transition state models. A large number of methods have appeared describing novel syntheses of organophosphorus compounds [10-13]. Hence, we describe herein the reaction of dialkyl acetylenedicarboxylate with phosphite as the nucleophile in the presence of 2-hydroxyacetophenone. The reaction of 2-hydroxyacetophenone and dialkyl acetylenedicarboxylate **2** in the presence of trialkyl or triaryl phosphite **3** produce phosphonate derivatives **4** in good yield (Scheme 1).

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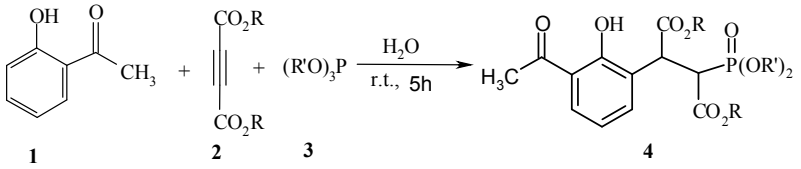


1 2 3 4

2, 3, 4	R	R'	Yield (%) of 4
a	Me	Me	90
b	Et	Me	85
c	*iso*-pro	Me	80
d	Me	Ph	87
e	Et	Ph	80

Scheme 1. Reaction of phosphites, activated acetylenes and 2-hydroxyacetophenone.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively, and were obtained for solutions in $CDCl_3$ using TMS as the internal standard or 85% H_3PO_4 as the external standard.

General procedure for preparation of compounds **4**

To a magnetically stirred solution of dialkyl acethylenedicarboxylate **2** (2 mmol) and 2-hydroxyacetephenone **1** (2 mmol) in water as a solvent was added trimethyl or triphenyl phosphite **3** (2 mmol). Then, the reaction mixture was stirred for 5 h. After completion of reaction (monitored by TLC), the solid residue was filtered and washed by diethyl ether to give compound **4**.

*Dimethyl 2-(3-acetyl-2-hydroxyphenyl)-3-(dimethoxyphosphoryl) succinate (***4a***)*

White powder, m.p. 112-114 °C, 0.69 g, yield 90%. IR (KBr) (ν_{max}/cm^{-1}): 3230, 1735, 1730, 1725, 1692, 1487 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_9P$ (388.31): C, 49.49; H, 5.45. Found: C, 49.53; H, 5.54%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (3 H, s, Me), 2.85 (3 H, d $^{3}J_{HP}$ 11.5 Hz, MeO), 3.75 (3 H, s, MeO), 3.82 (3 H, d $^{3}J_{HP}$ 11.5 Hz, OMe), 3.86 (3 H, s, MeO), 3.96 (1 H, dd $^{2}J_{HP}$ 19.6 Hz $^{3}J_{HH}$ 11.8 Hz, CH), 5.17 (1 H, dd $^{3}J_{HH}$ 11.8 Hz $^{3}J_{HP}$ 8.6 Hz, CH), 7.24 (1 H, d, $^{3}J_{HH}$ 7.5 Hz, CH), 7.54 (1 H, t, $^{3}J_{HH}$ 7.6 Hz, CH), 7.62 (1 H, d, $^{3}J_{HH}$ 7.6 Hz, CH), 8.25 (1 H, s, OH). 13C NMR (125.7 MHz, CDCl^{3}): δ 26.4 (Me), 44.5 (CH), 48.6 (d $^{1}J_{PC}$ 133.8 Hz, CH),

52.2 (OMe), 53.0 (d $^{2}J_{PC}$ 8.5 Hz, MeO), 54.0 (MeO), 54.7 (d, $^{2}J_{PC}$ 8.5 Hz, MeO), 111.2 (d, $^{3}J_{PC}$ 6.2 Hz, C), 121.5 (CH), 122.5 (CH), 123.7 (CH), 137.8 (C), 160.0 (C), 166.4 (d $^{2}J_{PC}$ 5.6 Hz, C=O), 173.2 (d $^{3}J_{PC}$ 22.5 Hz, C=O), 193.4 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.2. MS, *m/z* (%): 388 (M+, 15), 357 (56), 31 (100).

*Diethyl 2-(3-acetyl-2-hydroxyphenyl)-3 (dimethoxyphosphoryl) succinate (***4b***)*

White powder, m.p.123-125 °C, 0.71 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 3238, 1742, 1735, 1725, 1695, 1487, 1254 cm^{-1}. Anal. Calcd for $C_{18}H_{25}O_9P$ (416.36): C, 51.93; H, 6.05. Found: C, 51.86; H, 5.92%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3 H, t, $^{3}J_{HH}$ 7.4 Hz, Me), 1.36 (3 H, t, $^{3}J_{HH}$ 7.4 Hz, Me), 2.54 (3 H, s, Me), 3.12 (3 H, d $^{3}J_{HP}$ 11.7 Hz, MeO), 3.79 (3 H, d $^{3}J_{HP}$ 11.7 Hz, MeO), 4.08 (1 H, dd $^{2}J_{HP}$ 21.4 Hz $^{3}J_{HH}$ 12.5 Hz, CH), 4.26 (2 H, q, $^{3}J_{HH}$ 7.4 Hz, CH_2O), 4.32 (2 H, q, $^{3}J_{HH}$ 7.4 Hz, CH_2O), 5.23 (1 H, dd $^{3}J_{HH}$ 12.5 Hz $^{3}J_{HP}$ 9.5 Hz, CH), 7.17 (1 H, d, $^{3}J_{HH}$ 7.5 Hz, CH), 7.48 (1 H, t, $^{3}J_{HH}$ 7.6 Hz, CH), 7.52 (1 H, d, $^{3}J_{HH}$ 7.6 Hz, CH), 8.16 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (Me), 14.2 (Me), 28.2 (Me), 44.5 (CH), 49.2 (d $^{1}J_{PC}$ 136.2 Hz, CH), 52.4 (d $^{2}J_{PC}$ 8.7 Hz, MeO), 54.8 (d, $^{2}J_{PC}$ 8.7 Hz, MeO), 62.4 (CH_2O), 62.7 (CH_2O), 112.8 (d, $^{3}J_{PC}$ 6.8 Hz, C), 113.6 (CH), 118.5 (CH), 122.5 (CH), 138.6 (C), 160.2 (C), 167.2 (d $^{2}J_{PC}$ 6.3 Hz, C=O), 173.8 (d $^{3}J_{PC}$ 22.5 Hz, C=O), 193.5 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.3.

*Diisopropyl2-(3-acetyl-2-hydroxyphenyl)-3-(dimethoxyphosphoryl) succinate (***4c***)*

Yellow crystals, m.p. 134-136 °C, 0.71 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 3238 1736, 1730, 1725, 1692, 1475, 1287 cm^{-1}. Anal. Calcd for $C_{20}H_{29}O_9P$ (444.41): C, 54.05; H, 6.58. Found: C, 54.12; H, 6.63%. 1H NMR (500 MHz, $CDCl_3$): δ 1.26 (6 H, d, $^{3}J_{HH}$ = 6.8 Hz, 2 CH_3), 1.34 (6 H, d, $^{3}J_{HH}$ = 7.2 Hz, 2 CH_3), 2.65 (3 H, s, Me), 3.12 (3 H, d $^{3}J_{HP}$ 11.8 Hz, MeO), 3.85 (3 H, d $^{3}J_{HP}$ 11.8 Hz, MeO), 4.15 (1 H, dd $^{2}J_{HP}$ 21.5 Hz $^{3}J_{HH}$ 12.4 Hz, CH), 5.25 (1 H, dd $^{3}J_{HH}$ 12.4 Hz $^{3}J_{HP}$ 9.6 Hz, CH), 5.32-5.43 (1 H, m, CH), 5.46-5.52 (1 H, m, CH), 5.68 (1 H, s, CH), 7.23 (1 H, d, $^{3}J_{HH}$ 7.4 Hz, CH), 7.44 (1 H, t, $^{3}J_{HH}$ 7.5 Hz, CH), 7.54 (1 H, d, $^{3}J_{HH}$ 7.5 Hz, CH), 8.07 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.6 (2 CH_3), 22.3 (2 CH_3), 28.3 (Me), 44.2 (CH), 49.5 (d $^{1}J_{PC}$ 135.8 Hz, CH), 52.8 (d $^{2}J_{PC}$ 8.2 Hz, MeO), 54.6 (d, $^{2}J_{PC}$ 8.2 Hz, MeO), 68.8 (CHMe2), 70.2 (CHMe2), 112.5 (d, $^{3}J_{PC}$ 6.4 Hz, C), 113.0 (CH), 118.5 (C), 122.5 (CH), 123.7 (CH), 138.6 (C), 158.4 (C), 168.2 (d $^{2}J_{PC}$ 17.0 Hz, C=O), 170.2 (d $^{3}J_{PC}$ 21.5 Hz, C=O), 192.8 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.7.

*Dimethyl 2-(3-acetyl-2-hydroxyphenyl)-3-(diphenoxyphosphoryl) succinate (***4d***)*

Yellow powder, m.p. 162-164 °C, 0.89 g, yield 87%. IR (KBr) (ν_{max}/cm^{-1}): 3245, 1738, 1734, 1725, 1692, 1468, 1356, 1163 cm^{-1}. Anal.

Calcd for $C_{26}H_{25}O_9P$ (512.45): C, 60.94; H, 4.92. Found: C, 61.05; H, 5.04%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.86 (3 H, s, MeO), 4.17 (1 H, dd $^2J_{HP}$ 21.6 Hz $^3J_{HH}$ 11.8 Hz, CH), 5.32 (1 H, dd $^3J_{HH}$ 12.2 Hz $^3J_{HP}$ 9.5 Hz, CH), 7.16-7.82 (13 H, m, 13 CH), 8.15 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.9 (Me), 51.7 (MeO), 52.6 (MeO), 44.8 (CH), 50.6 (d $^1J_{PC}$ 137.5 Hz, CH), 112.5 (CH), 114.7 (d, $^3J_{CP}$ 7.2 Hz, C), 121.7 (d, $^3J_{CP}$ 7.2 Hz, 2 CH), 122.3 (CH), 123.7 (CH), 123.5 (d, $^3J_{CP}$ 11.2 Hz, C), 123.7 (d, $^3J_{CP}$ 6.7 Hz, 2 CH), 125.6 (CH), 127.2 (CH), 128.6 (2 CH), 129.2 (2 CH), 138.2 (C), 150.2 (d $^2J_{CP}$ 10.6 Hz, C), 153.7 (C), 164.8 (d $^3J_{PC}$ 21.6 Hz, C=O), 169.5 (d $^2J_{PC}$ 18.6 Hz, C=O), 194.7 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.2.

*Diethyl 2-(3-acetyl-2-hydroxyphenyl)-3-(diphenoxyphosphoryl)succinate (***4e***)*

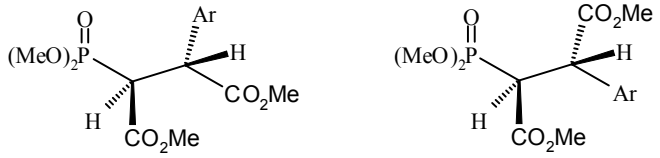
Yellow powder, m.p. 173-175 °C, 0.86 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 3245, 1742, 1735, 1726, 1692, 1587, 1363, 1197 cm^{-1}. Anal. Calcd for $C_{28}H_{29}O_9P$ (540.50): C, 62.22; H, 5.41. Found: C, 62.34; H, 5.56%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (3 H, t, $^3J_{HH}$ 7.5 Hz, Me), 1.45 (3 H, t, $^3J_{HH}$ 7.5 Hz, Me), 4.18 (1 H, dd $^2J_{HP}$ 21.7 Hz $^3J_{HH}$ 12.2 Hz, CH), 4.26 (2 H, q, $^3J_{HH}$ 7.7 Hz CH_2O), 4.36 (2 H, q, $^3J_{HH}$ 7.7 Hz, CH_2O), 5.32 (1 H, dd $^3J_{HH}$ 12.7 Hz $^3J_{HP}$ 9.8 Hz, CH), 7.16-8.04 (13 H, m, 13 CH), 8.17 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (Me), 14.2 (Me), 28.5 (Me), 44.7 (CH), 51.3 (d $^1J_{PC}$ 136.8 Hz, CH), 61.5 (CH_2O), 62.7 (CH_2O), 112.4 (CH), 114.7 (d, $^3J_{CP}$ 7.2 Hz, C), 121.6 (d, $^3J_{CP}$ 7.2 Hz, 2 CH), 122.3 (C), 122.8 (CH), 123.6 (d, $^3J_{PC}$ 11.2 Hz, C), 123.8 (d, $^3J_{PC}$ 6.8 Hz, 2 CH), 125.6 (CH), 127.2 (CH), 128.8 (2 CH), 129.3 (2 CH), 138.3 (C), 149.7 (d $^2J_{PC}$ 10.6 Hz, C), 153.7 (C), 164.3 (d $^3J_{PC}$ 21.6 Hz, C=O), 169.7 (d $^2J_{PC}$ 18.6 Hz, C=O), 194.6 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 20.2.

Results and discussion

As indicated in Scheme 1, the reaction of 2-hydroxyacetophenone 1 and dialkyl acetylenedicarboxylate 2 in the presence of trialkyl or triaryl phosphite 3 produce phosphonate derivatives 4 in good yield.

The ^{1}H NMR spectrum of **4a** displayed one singlet at 2.62 for methyl protons, two singlet at 3.75 and 3.86 for methoxy protons and two set of doublet doublets for vicinal methine protons at δ = 3.96 and 5.17, which appeared as with $^2J_{HP}$ and $^3J_{HP}$ values of 19.6 and 8.6 Hz, respectively. The methoxy groups of the phosphoranyl moiety are diastereotopic and show two separate doublets at 2.85 (3 H, d $^3J_{HP}$ 11.5 Hz, MeO) and 3.82 (3 H, d $^3J_{HP}$ 11.5 Hz, OMe). The hydroxy proton was observed as a broad singlet at δ = 8.25 which disappeared with addition of D2O. Observation of $^3J_{HH}$ = 11.8 Hz for the vicinal methine protons in **4a** specifies the supremacy of anti arrangement. Since compound **4a** possesses two stereogenic centers, two diastereomers with anti HCCH

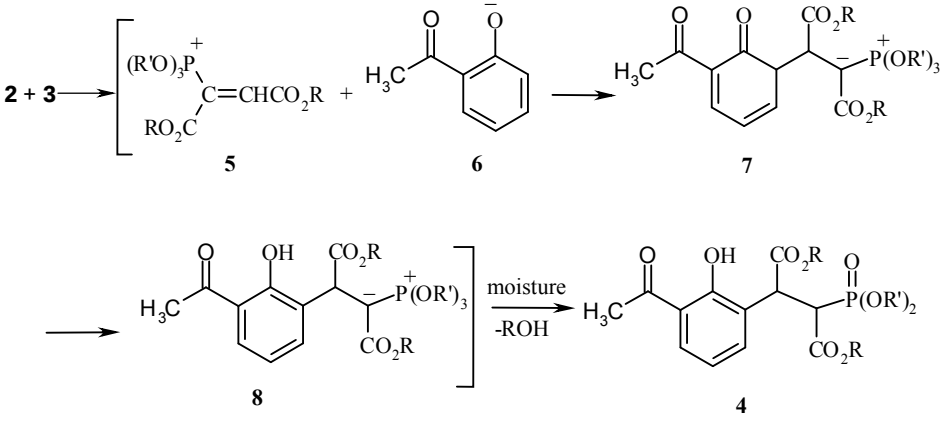
arrangements are possible (Figure 1). The observation of $^{3}J_{CP}$ of 22.5 Hz for the CO_2Me group and $^{3}J_{CP}$ of zero for C of benzen moiety is in agreement with the (*2R,3S*) or (*2S,3R*) diastereoisomer.



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

Figure 1. Two diastereomers of **4a** with anti arrangement.

A proposed mechanism for the formation of compound **4** is shown in Scheme 2. On the basis of phosphorus nucleophiles chemistry [14, 15] it is reasonable to presume that compound **5** results from initial addition of the phosphite to the activated acetylenic compounds and following protonation of the reactive 1:1 adduct, followed by attack of carbon atom of the anion of 2-hydroxyacetophenone **6** to cation **5** to generate ylide **7** and isomerises, under the reaction conditions employed, to ylide **8**. Hydrolysis of 8 leads to phosphonate derivative **4**.



Scheme 2. Proposed mechanism for the formation of **4**.

Conclusion

In conclusion, we investigate the reaction of dialkyl acetylenedicarboxylate with phosphites in the presence of 2-hydroxyacetophenone in water as the solvent that leads to an efficient synthesis of phosphonate derivatives without using any catalyst.

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