Synthesis of Phosphorus Derivatives via Multicomponent Reactions

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Abstract
Stable derivatives of oxaphosphaphenanthrenes were prepared using multicomponent reactions of 3-bromo-2-naphthol, dialkyl acetylenedicarboxylate and trimethyl or triphenyl phosphite under microwave conditions with good yields.

Keywords: Oxaphosphaphenanthrenes, Acetylenic compounds, Trimethyl phosphate, Triphenyl phosphate.

Introduction
Phosphorus compounds containing P–C bonds are not mostly abundant in nature but they have diverse biological activity and have attracted significant synthetic and pharmacological interest [1, 2]. Besides precious applications, their use in the construction of the unsafe compounds sarin, soman, and VX-type chemical warfare agents (CWAs) is of note [3]. Phosphonates have important applications in flame retardancy [4, 5], organic synthesis [6], and biological applications [2c, 7]. Also, 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 noveltysynthesesoforganophosphorus compounds [10-13]. Hence, we describe the reaction of dialkyl acetylenedicarboxylate with a trivalent phosphorus nucleophile such as trimethyl phosphate, or triphenyl phosphate in the presence of 3-bromo-2-naphthol under microwave conditions. This reaction was performed with the microwave irradiation as green source energy for synthesis of heterocyclic compounds.

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Experimental

Material and Equipments

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. 1H, 13C, and 31P spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1, 125.8, and 202.4 MHz, respectively. 1H, 13C, and 31P spectra were obtained for solutions in CDCl₃ using TMS as internal standard or 85% H₃PO₄ as external standard. All the chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. The microwave instrument was applied in a type of MICROSYNTH from Mylestone Company.

General procedure for preparation of compounds 4

To a magnetically stirred solution of dialkyl acetylenedicarboxylate 2 (2 mmol) and 3-bromo-2-naphthol 1 (2 mmol) as an OH-acid in 20 ml CH₃CN was added triphenyl phosphite or trimethyl phosphite 3 (2 mmol) under microwave conditions (In power of 800 w and T=70 °C). The reaction mixture was then stirred for 6h. After completion of reaction (monitored by TLC), the mixture of reaction was purified by preparative TLC on silica gel column chromatography (Merck 230-400 mesh) using n-hexane-EtOAc as eluent to give compound 4.

Spectral Data for the Compounds 4a-4d

**Dimethyl 2,2-diphenoxo-3-bromo-4H-1-oxa-phospha phenanthrene-3,4-dicarboxylate (4a)**

White powder, m.p. 162-64 °C, 1.00 g, yield 87%. IR (KBr) (νmax/cm⁻¹): 1665, 1723 cm⁻¹. Anal. Caled for C₂₈H₂₂BrO₇P (581.35): C, 57.85; H, 3.81. Found: C, 57.78; H, 3.76%.

1H NMR (500 MHz, CDCl₃): 3.25 (3 H, s, MeO), 3.82 (3 H, s, MeO), 5.54 (1 H, d, JHP = 27.6 Hz, CH), 6.85-9.12 (15 H, m, 15 CH).

13C NMR (125.7 MHz, CDCl₃): 42.0 (d, JCP = 232 Hz, C), 42.4 (d, JCP = 8.5 Hz, CH), 50.4 (MeO), 52.2 (OMe), 120.7 (d, JCP = 5.2 Hz, 2 CH), 121.0 (d, JPC = 9.6 Hz, C), 121.7 (d, JPC = 4.6 Hz, 2 CH), 124.3 (CH), 125.7 (CH), 126.2 (CH), 126.5 (CH), 127.6 (CH), 128.5 (CH), 130.0 (m, 4 CH), 130.4 (CH), 131.3 (C), 131.8 (C), 132.2 (C), 148.5 (d, JPC = 9.2 Hz, C), 150.2 (m, 2 C), 167.6 (d, JPC = 16.8 Hz, C=O), 174.5 (C=O). 31P NMR (202 MHz, CDCl₃): 42.4. EIMS: m/z 581 (10, M⁺), 504 (86), 428 (100), 77 (88), 31 (100).

**Diethyl 2,2-diphenoxo-3-bromo-4H-1-oxa-phospha phenanthrene Z-3,4-dicarboxylate (4b)**

Pale yellow powder, m.p. 170-172 °C, 0.95 g, yield 78%. IR (KBr) (νmax/cm⁻¹): 1670, 1728

¹H NMR (500 MHz, CDCl₃): 1.32 (3 H, t, J₉H = 7.4, Me), 1.37 (3 H, t, J₉H = 7.3, Me), 4.22 (2 H, q, J₉H = 7.4, CH₂O), 4.28 (2 H, q, J₉H = 7.4, CH₂O), 5.58 (1 H, d, J₉P = 28.0 Hz, CH), 6.82-9.10 (15 H, m, 15 CH).

¹³C NMR (125.7 MHz, CDCl₃): 13.8 (Me), 14.2 (Me), 42.2 (d, J₁CP = 230 Hz, C), 42.5 (d, J₂CP = 8.7 Hz, CH), 61.7 (CH₂O), 62.3 (CH₂O), 121.2 (d, J₃CP = 5.8 Hz, 2 CH), 121.4 (d, J₄CP = 10.4 Hz, C), 122.3 (d, J₅PC = 5.5 Hz, 2 CH), 124.8 (CH), 126.0 (CH), 126.5 (CH), 127.2 (CH), 127.8 (CH), 129.2 (CH), 130.4 (m, 4 CH), 130.7 (CH), 131.6 (C), 132.2 (C), 132.7 (C), 149.0 (d J₃CP = 28.4 Hz, CH), 7.45 (1 H, t, J₉H = 9.4 Hz, CH), 7.62 (1 H, t, J₉H = 9.4 Hz), 7.82 (1 H, d, J₉H = 9.6 Hz, CH), 7.87 (1 H, d, J₉H = 9.6 Hz, CH), 8.12 (1 H, s, CH).

³¹P NMR (202 MHz, CDCl₃): 42.5.

Dimethyl 2,2-dimethoxy-3-bromo-4H-1-oxa-phospha phenanthrene-3,4-dicarboxylate (4d)
White crystals, m.p. 132-134 °C, 0.64 g, yield 90%. IR (KBr) (νmax/cm⁻¹): 1650, 1727 cm⁻¹. Anal. Calcd for C₁₈H₁₈BrO₇P (457.21): C, 47.29; H, 3.97. Found: C, 47.34; H, 4.03%. ¹H NMR (500 MHz, CDCl₃): 3.62 (3 H, s, MeO), 3.75 (3 H, s, MeO), 3.78 (3 H, d, J₉P = 13.5 Hz, MeO), 3.97 (3 H, d, J₉P = 13.5 Hz, MeO), 5.67 (1 H, d, J₉H = 31.7 Hz, CH), 7.45 (1 H, t, J₉H = 9.4 Hz, CH), 7.62 (1 H, t, J₉H = 9.4 Hz), 7.82 (1 H, d, J₉H = 9.6 Hz, CH), 7.87 (1 H, d, J₉H = 9.6 Hz, CH), 8.12 (1 H, s, CH). ¹³C NMR (125.7 MHz, CDCl₃): 39.4 (d, J₁CP = 225.2 Hz, C), 41.6 (d, J₂CP = 9.4 Hz, CH), 50.4 (MeO), 52.3 (MeO), 55.6 (d, J₃PC = 6.4 Hz, P-OMe), 55.7 (d, J₄PC = 6.4 Hz, P-OMe), 118.4 (d, J₅PC = 6.8 Hz, C), 121.4 (d, J₆PC = 9.5 Hz, C), 124.6 (CH), 125.5 (CH), 127.4 (CH), 128.6 (CH), 130.0 (CH), 131.4 (C), 131.7 (C), 149.2 (d, J₇PC = 8.4 Hz, C-O), 169.6 (J₈PC = 18.4 Hz, C=O). ³¹P NMR (202 MHz, CDCl₃): 42.8.

Diisopropyl 2,2-diphenoxy-3-bromo-4H-1-oxa-phospha phenanthrene-3,4-dicarboxylate (4c)
Pale Yellow powder, m.p. 182-184 °C, 0.90 g, yield 75%. IR (KBr) (νmax/cm⁻¹): 1674, 1735 cm⁻¹. Anal. Calcd for C₃₂H₃₀BrO₇P (637.46): C, 60.29; H, 4.74. Found: C, 60.18; H, 4.65%.

¹H NMR (500 MHz, CDCl₃): 1.35 (6 H, d, J₉H = 6.5 Hz, 2 CH₃), 1.42 (6 H, d, J₉H = 6.8 Hz, 2 CH₃), 5.28-5.36 (1 H, m, CH), 5.38-5.44 (1 H, m, CH), 5.62 (1 H, d, J₉H = 28.4 Hz, CH), 6.85-9.15 (15 H, m, 15 CH). ¹³C NMR (125.7 MHz, CDCl₃): 21.6 (2 CH₃), 22.3 (2 CH₃), 42.6 (d, J₉CP = 234.5 Hz, C), 42.8 (d, J₅CP = 9.3 Hz, CH), 68.8 (CHMe₂), 70.2 (CHMe₂), 121.6 (d, J₆CP = 6.0 Hz, 2 CH), 122.0 (d, J₇PC = 10.5 Hz, C), 122.5 (d, J₈PC = 5.8 Hz, 2 CH), 125.2 (CH), 126.7 (CH), 127.3 (CH), 127.6 (CH), 128.4 (CH), 129.5 (CH), 130.8 (m, 4 CH), 131.2 (CH), 132.3 (C), 132.8 (C), 133.4 (C), 149.4 (d J₉PC = 9.8 Hz, C), 151. (m, 2 C), 168.6 (d J₉PC = 15.8 Hz, C=O), 175.5 (C=O). ³¹P NMR (202 MHz, CDCl₃): 42.3.
Results and discussion

The reaction of dialkyl acetylenedicarboxylate, 3-bromo-2-naphthol and trimethyl or triphenyl phosphite leads to 3-bromo-4H-1-oxa-phosphaphenanthrene-3,4-dicarboxylate derivatives 4 in excellent yields [13b] (Scheme 1).

\[ \begin{align*}
\text{Br} & \quad \text{OH} \\
\text{CO}_2R & \quad \text{CO}_2R \\
\text{R'O}_3P & \quad \text{R'O}_3P
\end{align*} \]

\[ \begin{align*}
\text{CH}_3\text{CN}, \text{M.W.} & \quad 70 \degree \text{C}, 6\text{h}\\
\text{1} & \quad \text{2, 3, 4} \quad \text{R} \quad \text{R'} \quad \text{Yield (\%)} \text{ of 4}
\text{a} & \quad \text{Me} \quad \text{Ph} \quad 87 \\
\text{b} & \quad \text{Et} \quad \text{Ph} \quad 78 \\
\text{c} & \quad \text{iso-pro} \quad \text{Ph} \quad 75 \\
\text{d} & \quad \text{Me} \quad \text{Me} \quad 90 \\
\end{align*} \]

Scheme 1. The reaction between activated acetylene, 3-bromo-2-naphthol and trimethyl or triphenyl phosphite.

The structures of 4a-4d were decided on the basis of their $^1$H, $^{13}$C, and $^{31}$P NMR spectra, IR spectra, elemental analyses, and mass spectrometric data. The $^1$H NMR spectrum of 4a in CDCl$_3$ shows two singlets for methoxy protons at 3.25 and 3.82 ppm and one doublets at $\delta = 5.54$ ($^1J_{pp} = 27.6$ Hz), for the methine proton, along with multiplets at $\delta = 6.85$-9.12 for the aromatic protons. The presence of an ylide ester group in 4a stabilizes by the observation of strong low-frequency carbonyl absorption at 1665 cm$^{-1}$ in the IR spectrum [14]. The other ester carbonyl absorption in 4a appears at 1723 cm$^{-1}$. The $^{13}$C NMR spectrum consisted characteristic carbonyl resonances at $\delta = 167.6$ (d, $^2J_{pc} = 16.8$ Hz), and 174.5 ppm clearly, whereas the ylide carbon atom displays resonances at $\delta = 42.0$ (d, $^1J_{pc} = 232$ Hz) ppm. The observed $^1J_{cp}$ values are typical of an $\alpha$-ylide ester [15]. The $^{31}$P NMR signal was found at $\delta = 42.4$ ppm.

Although the mechanism of this reaction has not been established, a plausible rationalization can be advanced to explain product formation (Scheme 2). On the basis of phosphorus nucleophiles chemistry, it is reasonable to presume that ylide 4 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 3-bromo-2-naphthol 6 to cation 5.
to generate ylide 7 which isomerises under the reaction conditions employed to produce the oxaphosphorane 8. Elimination of ROH from 8 leads to product 4.

Scheme 2. Proposed mechanism for the formation of 4.

The present method carries the advantage that, not only is the reaction performed under microwave conditions, but the educts can be mixed without any activation or modification. The simplicity of the present procedure for the synthesis of oxaphosphaphenanthrenes makes it an interesting alternative to complex multistep approaches.

**Conclusion**

In conclusion, we found that the reaction of activated acetylenic compounds with trimethyl phosphite or triphenyl phosphite in the presence of 3-bromo-2-naphthol leads to a facile synthesis of some functionalized oxaphosphaphenanthrenes under microwave conditions without using any catalyst. Its advantages include ease of synthesis and work-up, high yields and green conditions.

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**References**