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Efficient synthesis of functionalized 2,5-dihydro-1,2-oxaphospholes

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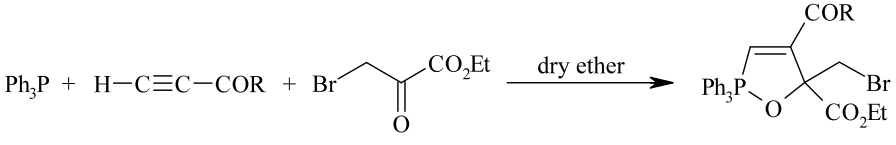
Abstract—Stable derivatives of 2,5-dihydro-1,2-oxaphospholes were obtained in excellent yields from the reaction between electron-deficient acetylenic compounds, and ethyl 3-bromopyruvate or methyl 4-chloroacetoacetate in the presence of triphenylphosphine in dry ether.

In recent years there has been increasing interest in the synthesis of organophosphorus compounds, that is, those bearing a carbon atom bound directly to a phosphorus atom. This interest has resulted from the recognition of the value of such compounds in a variety of biological, industrial and chemical synthetic uses. A large number of methods have appeared describing novel syntheses of organophosphorus compounds.[1–3]

The successful attack by nucleophilic trivalent phosphines on a carbon atom is facilitated when the latter is conjugated with a carbonyl group, or when it is part of an unsaturated bond otherwise activated.[1–9] There have been many studies on reactions between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds in the presence of a proton source such as an alcohol or a CH-acid.[1,9,10]

Here we report a simple one-pot, three-component synthesis of 2,5-dihydro-1,2-oxaphosphole derivatives **2**. Thus, the reaction of triphenylphosphine and 3-butyn-2-one[11,12] or methyl propiolate in the presence of ethyl 3-bromopyruvate leads[13] to 1,2-oxaphosphole **2** (Scheme 1).

The reaction of 3-butyn-2-one with triphenylphosphine in the presence of ethyl 3-bromopyruvate proceeded spontaneously at room temperature in dry ether, and was completed within 1 h. The ^{1}H, ^{13}C, and ^{31}P NMR spectra of the crude product clearly indicated the formation of the fairly stable ethyl 4-acetyl-5-(bromomethyl)-2,2,2-triphenyl-2,5-dihydro-1,2-oxaphosphole-5-carboxylate **2a**. Any product other than **2a** could not be detected by NMR spectroscopy. Methyl propiolate similarly gave rise to **2b**. The structures of **2a** and **2b** were



1 **2**

1, 2	R	%Yield of 2
a	Me	95
b	OMe	90

Scheme 1.

Keywords: 3-butyne-2-one; ethyl-3-bromo-pyruvate; methyl 4-chloroacetoacetate; methyl propiolate; 1,2-oxaphosphole; triphenylphosphine.
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deduced from their elemental analyses and their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The IR spectrum of **2a** exhibited carbonyl group absorptions at 1744 and 1632 cm^{-1} and the absorption bands of the triphenylphosphine moiety around 1429, 1107 and 1009 cm^{-1} (see experimental). The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. Any initial fragmentation involved the loss of OEt, CO_2Et, Br, and Ph_3P moieties.

The ^{1}H NMR spectrum of **2a** displayed signals for methyl protons (of the ethyl group) at $\delta=1.36$ as part of an ABX_3 system ($J_{AX}=7.1$ Hz), the acetyl methyl protons at $\delta=2.01$ ppm, methylene protons ($\delta=4.1$ and 4.53) with an AB system ($J=11.0$ Hz) and methyleneoxy protons ($\delta=4.33$ and 4.38) as part of the ABX_3 system ($J_{AB}=10.4$ Hz, $J_{AX}=7.1$ Hz). The vinylic proton ($\delta=7.24$, $^2J_{HP}=19.1$ Hz) and the triphenylphosphine moiety gave rise to characteristic signals in the aromatic region of the spectrum.

The ^{1}H-decoupled ^{13}C NMR spectra of **2a** showed three characteristic doublets at about $\delta=78.74$ ($^2J_{CP}=14.5$ Hz), 119.95 ($^1J_{CP}=92.9$ Hz) and 198.35 ($^3J_{CP}=6.1$ Hz) for the P–O–C, P–CH= and CH_3CO–C=CH–P moieties, respectively.

The ^{13}C NMR spectra were in agreement with the 1,2-oxaphosphole structure. Partial assignments of these resonances are given in the experimental. The ^{1}H-decoupled ^{31}P NMR spectra of **2a** exhibited a sharp signal at $\delta=18.92$. This shift is similar to those observed for stable hydroxyphosphoranes.[14]

We have not established a mechanism for the formation of **2a** in an experimental manner, but a reasonable possibility is indicated in Scheme 2.

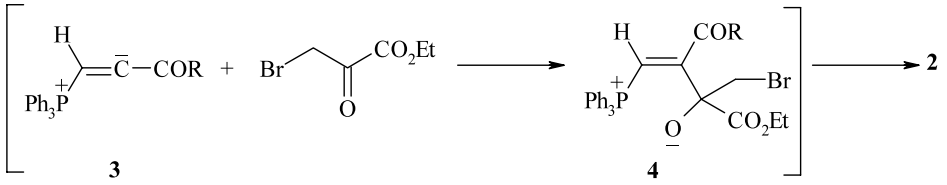
On the basis of the well established chemistry of trivalent phosphorus nucleophiles[1–5] it is reasonable to assume that 1,2-oxaphosphole **2** results from initial addition of triphenylphosphine to the acetylenic compound and subsequent attack of the resulting anion **3** to the carbonyl carbon (ketone) of ethyl 3-bromopyruvate to yield betaine **4** which apparently cyclizes, under the reaction conditions employed, to produce the 1,2-oxaphosphole compounds **2** (Scheme 2).

The reaction of 3-butyn-2-one with methyl 4-chloroacetoacetate in the presence of triphenylphosphine gave the 1:1:1 adduct **5** (Scheme 3).

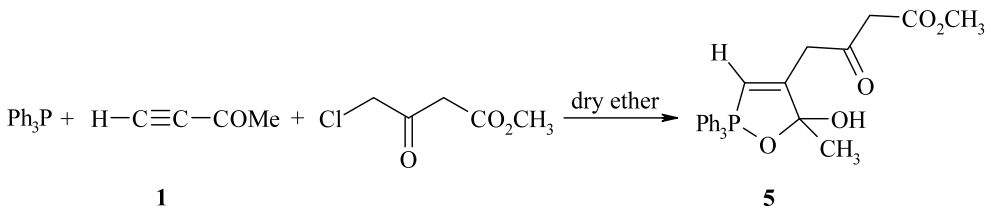
The ^{1}H NMR spectrum of **5** exhibited three sharp lines readily recognized as arising from CH_3 ($\delta=1.8$), CH_3O ($\delta=3.67$) and the OH ($\delta=6.97$) protons. The methylene groups are diastereotopic and show two characteristic AB systems at about $\delta=3.35$ ($J_{AB}=15.8$ Hz) and 4.31 ($J_{AB}=11.6$ Hz) for the CH_2–C=O and O=C–CH_2–C=O moieties, respectively. The vinylic proton ($\delta=7.40$, $^2J_{HP}=18.5$ Hz) and the triphenylphosphine moiety gave rise to characteristic signals in the corresponding region of the spectrum.

The ^{1}H-decoupled ^{13}C NMR spectrum of **5** showed three characteristic doublets at $\delta=76.36$ ($^2J_{CP}=15.5$ Hz), 119.11 ($^1J_{CP}=91.4$ Hz), and 202.35 ($^4J_{CP}=7.1$ Hz) for the P–O–C, P–CH= and OC–CH_2–C=CH–P moieties, respectively. The ^{13}C NMR spectra are in agreement with the structure of 1,2-oxaphosphole **5**. Partial assignments of these resonances are given in the experimental. The ^{1}H-decoupled ^{31}P NMR spectrum of **5** exhibited a sharp signal at $\delta=16.82$ ppm. A mechanism for this transformation is proposed in Scheme 4.

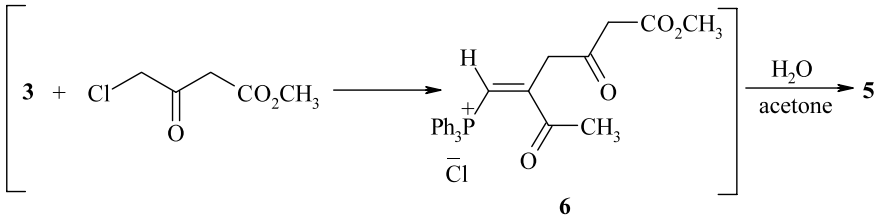
In conclusion, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present one-step procedure makes it an interesting alternative to complex multistep approaches.



Scheme 2.



Scheme 3.



Scheme 4.

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13. The preparation of ethyl 4-acetyl-5-(bromomethyl)-2,2,2-triphenyl-2,5-dihydro-1,2-λ^5-[1,2]-oxaphosphole-5-carboxylate **2a** is described as an example. To a magnetically stirred solution of 0.14 g of 3-butyn-2-one (2 mmol) and 0.39 g of ethyl 3-bromopyruvate (2 mmol) in 5 mL dry diethyl ether was added dropwise a solution of 0.52 g of triphenylphosphine (2 mmol) in 3 mL dry diethyl ether at room temperature over 20 min. The reaction mixture was stirred for 1 h. The resulting solid was then filtered off, and crystallized from *n*-hexane-ethyl acetate. The product was filtered and dried in vacuo to yield **2a**. The product **2a** was obtained as a white powder, mp 160–162°C, 0.5 g, yield 95%. IR (KBr) (ν_{max}, cm^{-1}): 1744 (CO_2Et), 1682 (COMe), 1429, 1107 and 1000 (P–Ph), 1009 (P–O). Anal. calcd for $C_{27}H_{26}BrO_4P$ (525.39): C, 61.72; H, 4.98%. Found: C, 61.6; H, 4.9%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.36 (3H, t, $^3J_{HH}=7.1$ Hz, CH_3), 2.01 (3H, s, H_3CCO), 4.10 (1H, d, $^2J_{HH}=11.1$ Hz, CH), 4.36 (2H, ABX_3, $J_{AX}=J_{BX}=7.1$ Hz, $J_{AB}=10.8$ Hz, $\nu_A=4.33$, $\nu_B=4.38$, OCH_2), 4.53 (1H, d, $^2J_{HH}=11.1$ Hz, CH), 7.24 (1H, d, $^2J_{HP}=19.1$ Hz, P–CH), 7.65 (6H, sextet, $^3J_{HH}=7.6$ Hz, $^3J_{HH}=7.1$ Hz, $^4J_{HP}=3.6$ Hz, $6CH_m$ of Ph_3P), 7.75 (3H, t, $^3J_{HH}=7.1$ Hz, $^5J_{HP}=0.8$ Hz, $3CH_p$ of Ph_3P), 7.83 (6H, q, $^3J_{HP}=13.3$ Hz, $^3J_{HH}=7.6$ Hz, $6CH_o$ of Ph_3P). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.07 (CH_3), 29.40 (H_3CCO), 34.73 (CH_2–Br), 63.08 (OCH_2), 78.74 (d, $^2J_{CP}=14.5$ Hz, *C*–O–P), 118.68 (d, $^1J_{CP}=86.6$ Hz, C_{ipso} of Ph_3P), 119.95 (d, $^1J_{CP}=92.9$ Hz, C=*C*H–P), 130.03 (d, $^3J_{CP}=13.3$ Hz, C_m of Ph_3P), 133.90 (d, $^2J_{CP}=10.7$ Hz, C_o of Ph_3P), 134.48 (d, $^4J_{CP}=2.8$ Hz, C_p of Ph_3P), 161.44 (C=*C*–CO), 169.5 (O=C–O), 198.35 (d, $^3J_{CP}=6.2$ Hz, H_3C–*C*=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 18.92 [$Ph_3PR(OR)$]. MS, *m*/*z* (%): 525 (M^+, 1) 479 (1), 461 (1), 445 (1), 355 (1), 280 (1), 279 (100), 278 (100), 262 (100), 199 (31), 183 (100), 152 (23), 108 (43), 77 (21), 43 (86). **2b**: White powder, mp 155–160°C, 0.48 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1731 (CO_2Et), 1709 (C=C–CO_2Me), 1429, 1102, and 1001 (P–Ph), 1030 (P–O). Anal. calcd for $C_{27}H_{26}BrO_5P$ (541.39): C, 59.9; H, 4.84%. Found: C, 60.0; H, 4.7%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.27 (3H, dt, $^3J_{HH}=6.7$ Hz, CH_3), 3.91 (3H, s, OCH_3), 4.11 (1H, d, $^2J_{HH}=11.3$ Hz, CH), 4.20 (2H, dt, $^3J_{HH}=6.2$, OCH_2), 4.53 (1H, d, $^2J_{HH}=11.3$ Hz, CH), 7.61 (6H, m, $6CH_m$ of Ph_3P), 7.69 (3H, t, $^3J_{HH}=6.7$ Hz, $^5J_{HP}=0.8$ Hz, $3CH_p$ of Ph_3P), 7.79 (6H, q, $^3J_{HP}=13.3$ Hz, $^3J_{HH}=7.6$ Hz, $6CH_o$ of Ph_3P), 7.98 (1H, s, P–CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.00 (CH_3), 36.60 (CH_2–Br), 53.72 (OCH_3), 62.80 (OCH_2), 80.33 (d, $^2J_{CP}=3.0$ Hz, *C*–O–P), 121.66 (d, $^1J_{CP}=94.4$ Hz, C_{ipso} of Ph_3P), 122.82 (d, $^1J_{CP}=95.0$ Hz, C=*C*H–P), 129.90 (d, $^3J_{CP}=13.5$ Hz, C_m of Ph_3P), 133.86 (d, $^2J_{CP}=10.4$ Hz, C_o of Ph_3P), 133.98 (d, $^4J_{CP}=2.8$ Hz, C_p of Ph_3P), 158.85 (C=*C*–CO), 162.60 (d, $^3J_{CP}=20.4$ Hz, CO_2Me) 167.76 (CO_2Et). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 17.26 [$Ph_3P(R)OR$]. MS, *m*/*z* (%): 541 (M^+, 2), 495 (2), 461 (1), 279 (100), 278 (100), 262 (100), 199 (20), 183 (100), 152 (20), 108 (40), 77 (30). **5**: White powder, mp 196–198°C (decomp.), 0.44 g, yield 95%. (KBr) (ν_{max}, cm^{-1}): 1728 (CO_2Me), 1679 (C=O), 1428, 1103, and 1000 (P–Ph), 1007 (P–O). Anal. calcd. for $C_{27}H_{27}O_5P$ (462.48): C, 70.12; H, 5.88%. Found: C, 70.0; H, 5.8%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.87 (3H, s, H_3CCO), 3.35 (2H, AB system, $J_{AB}=15.8$ Hz, CH_2–CO), 4.31 (2H, AB system, $J_{AB}=11.6$ Hz, OC–CH_2–CO), 7.40 (1H, d, $^2J_{HP}=18.5$ Hz, P–CH), 7.67 (6H, sextet, $^3J_{HH}=7.2$ Hz, $^3J_{HH}=7.1$ Hz, $^4J_{HP}=3.4$ Hz, $6CH_m$ of Ph_3P), 7.78 (3H, dt, $^3J_{HH}=7.5$ Hz, $^5J_{HP}=0.8$ Hz, $3CH_p$ of Ph_3P), 7.82 (6H, dd, $^3J_{HP}=13.2$ Hz, $^3J_{HH}=7.9$ Hz, $6CH_o$ of Ph_3P). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 13.08 (H_3C–CO), 42.52 (CH_2–CO), 50.26 (OC–CH_2–CO_2Me), 52.00 (OCH_3), 76.36 (d, $^2J_{CP}=14.5$ Hz, *C*–O–P), 111.67 (d, $^1J_{CP}=87.0$ Hz, C_{ipso} of Ph_3P), 119.11 (d, $^1J_{CP}=91.4$ Hz, C=*C*H–P), 130.16 (d, $^3J_{CP}=13.3$ Hz, C_m of Ph_3P), 134.38 (d, $^2J_{CP}=10.9$ Hz, C_o of Ph_3P), 134.90 (d, $^4J_{CP}=2.8$ Hz, C_p of Ph_3P), 170.70 (P–CH=*C*), 171.80 (CO_2Me), 202.35 (d, $^4J_{CP}=7.2$ Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 16.82 [$Ph_3P(R)OR$]. MS, *m*/*z* (%): 462 (M^+, 2), 445 (1), 431 (2), 403 (2), 387 (2), 367 (5), 353 (2), 330 (1), 303 (10), 262 (100), 183 (71), 152 (13), 108 (46), 77 (25), 51 (33).
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