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Catalyst free synthesis of oxaphospholes derivatives using multicomponent reactions of ninhydrin

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Abstract: The reaction of propiolate with triphenylphosphine (Ph_3P) in the presence of ninhydrin led to oxaphosphole derivatives in good yields. The reaction of dialkyl acetylenedicarboxylates with Ph_3P in the presence of ninhydrin led to other derivatives of oxaphosphole in good to excellent yields without using any catalyst.

Keywords: Propiolate, Triphenylphosphine, Oxaphosphole, Dialkyl acetylenedicarboxylates.

Introduction

Organophosphorus compounds are widely used in organic synthesis [1]. 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 [1-4]. 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 [1-10]. Organophosphorus compounds are synthetic targets of interest, not least because of their value for a variety of industrial, biological, and chemical synthetic uses [11-16]. The physical properties and chemical reactivity of phosphate esters interlinks many areas in chemistry and biology. Introduction of a phosphate monoester into a molecule such as a drug candidate enhances the water solubility, hence altering its bioavailability [17-19].

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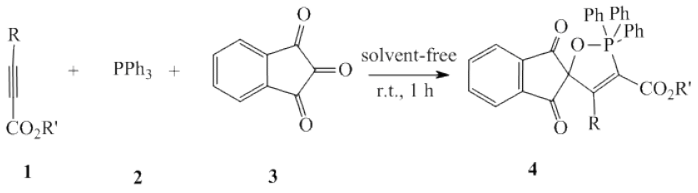
As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds.The reaction of Ph_3P with activated acetylenic compounds in the presence of ninhydrin led to oxaphosphole-4-carboxylate **4** in excellent yields (Scheme **1**).



4	R	R'	%Yield of 4
a	CO_2Me	Me	95
b	CO_2Et	Et	92
c	H	Me	90
d	H	Et	90

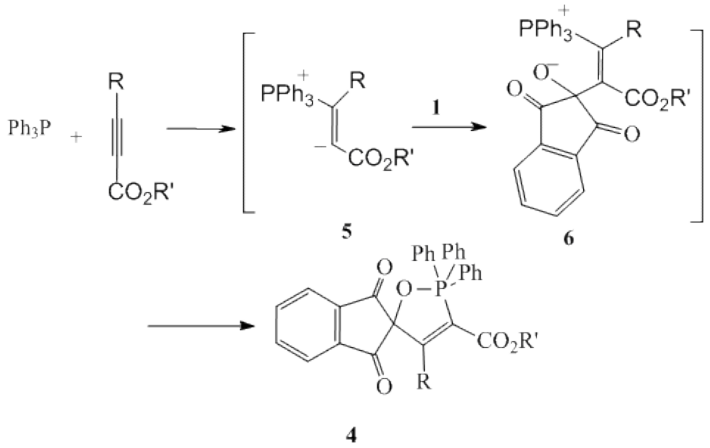
Scheme 1: Synthesis of oxaphosphole derivatives

Result and Discussion

Structures of compounds **4a**–**4f** were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m/z* values. The ^{1}H- and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H-

NMR spectrum of **4a** exhibited a singlet at (δ = 3.25 ppm) arising from the *N*Me proton. The carbonyl groups resonances in the ^{13}C-NMR spectra of **4a** appear at δ = 168.4 ($^{3}J_{CP}$ = 21.2) and 169.7 ppm. The ^{31}P-NMR signal of **2a** was found at (δ = -50.35 ppm). The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 521, which is consistent with the 1:1:1 adduct of Ph_3P, ethyl propiolate and *N*-methylisatin.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between triphenylphosphine **2** and activated acetylenic compounds **1**, which reacts with the carbonyl group of ninhydrin to produce **6**. Cyclization of this zwitterionic intermediate leads to the spiro compound **4** (Scheme 2).



Scheme 2: Proposed mechanism for the synthesis of **4**

Conclusion

In summary, the reaction of activatedacetylenic compounds with ninhydrin in the presence of Ph_3P led to oxaphosphole-4-carboxylate derivatives with potential synthetic interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1, 125.7, and 202.4 MHz, resp.; in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. All of chemicals were obtained from *Fluka* and were used without further purification. Alkylisatins were prepared according to the literature procedure [20].

General procedure for preparation of compounds 4a-f:

To a stirred solution of activated acetylenic compounds **1** (2 mmol) and ninhydrin **3** (2 mmol) under solvent-free conditions was added Ph_3P **2** (2 mmol) at room temperature. The reaction mixture was then stirred for 4 h. After completion of reactions (monitored by TLC (5:1) n-hexane/ethyl acetate, 15 mL water poured into the mixture of reaction. The solid residue was filtered and washed with Et_2O to afforded pure title compounds.

Methyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-4-carboxylate (4a):

Yellow crystals, mp 210-212°C, 0.98 g, yield 94%. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1682, 1459, 1110, 1031 and 1009. MS, *m/z* (%): 521(M^{+}, 5), 476 (66), 278 (85), 243(64), 201 (62), 111 (34), 169 (100), 45 (100). Anal. Calcd for $C_{32}H_{28}NO_4P$ (521.5): C, 73.69; H, 5.41; N, 2.69; found: C, 73.70; H, 5.40; N, 2.70%. ^{1}H-NMR: δ 1.25 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 3.25 (3 H, s, NMe), 4.17 (2 H, q, $^{3}J_{HH}$ = 7.2 Hz, OCH_2), 6.89 (1 H, d, $^{2}J_{HP}$ = 22.7 Hz, CH), 7.09 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.32 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.42 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.48 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.52-7.78 (15 H, m, 15 CH). ^{13}C-NMR: δ 14.3 (Me), 28.1 (NMe), 61.7 (OCH_2), 91.2 (d, $^{2}J_{CP}$ = 49.1 Hz, C_{ipso}), 116.7 (CH), 120.3 (CH), 123.6 (CH), 128.1 (CH), 128.6 (d, $^{3}J_{CP}$ = 10.2 Hz, C), 129.2 (d, $^{3}J_{CP}$ =

21.1 Hz, 6 CH), 129.4 (3 CH), 131.9 (d, $^{2}J_{CP}$ = 31.9 Hz, CH), 135.1 (d, $^{1}J_{CP}$ = 230.1 Hz, 3 C), 149.3 (d, $^{1}J_{CP}$ = 192.3 Hz, CH), 150.4 (C), 157.3 (d, $^{2}J_{CP}$ = 19.3 Hz, C), 168.4 (d, $^{3}J_{CP}$ = 21.2 Hz, C=O), 169.7 (d, $^{3}J_{CP}$ = 17.4 Hz, C=O). ^{31}P-NMR: δ 50.35.

Methyl 1,2-dihydro-2-oxo-1-ethyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-4-carboxylate (4b):

Yellow powder, mp 196-198°C, 0.96 g, yield 90%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1680, 1450, 1100, 1029 and 1010. MS, *m/z* (%): 535(M^{+}, 15), 490 (74), 461(54), 278 (68), 257 (62), 175 (34), 74 (46), 45 (94). Anal. Calcd for $C_{33}H_{30}NO_4P$ (535.6): C, 74.01; H, 5.65; N, 2.62; found: C, 74.00; H, 5.60; N, 2.60%. ^{1}H-NMR: δ 1.24 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 1.37 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 4.13 (2 H, q, $^{3}J_{HH}$ = 7.2 Hz, OCH_2), 4.35 (2 H, m, CH_2), 6.75 (1 H, d, $^{2}J_{PH}$ = 25.4 Hz, CH), 7.34 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.42 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.50 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.73 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.45-7.84 (15H, m, 15 CH).^{13}C-NMR: δ 13.3 (Me), 14.0 (Me), 38.4 (CH_2), 62.1 (OCH_2), 93.2 (d, $^{2}J_{CP}$ = 35.4 Hz, C_{ipso}), 118.3 (CH), 120.4 (CH), 124.2 (CH), 127.4 (CH), 127.9 (d, $^{3}J_{CP}$ = 8.0 Hz, C), 128.4 (d, $^{3}J_{CP}$ = 21.1 Hz, 6 CH), 129.1 (3 CH), 132.0 (d, $^{2}J_{CP}$ = 31.9 Hz, 6 CH), 135.4 (d,$^{1}J_{CP}$ = 226.5 Hz, 3 C), 144.1 (d, $^{1}J_{CP}$ = 194.1 Hz, CH), 149.2 (C), 154.2 (d, $^{2}J_{CP}$ = 15.4 Hz, C), 166.5 (d, $^{3}J_{CP}$ = 21.2 Hz, C=O), 168.7 (d, $^{3}J_{CP}$ = 19.8 Hz, C=O). ^{31}P-NMR: δ 52.42.

Methyl 1,2-dihydro-2-oxo-1-benzyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-4-carboxylate (4c):

Pale yellow crystals, mp 223-225°C, 1.01 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 1730, 1685, 1462, 1210, 1054 and 1022. MS, *m/z* (%): 597(M^{+}, 10), 506 (70), 319 (64), 278 (64), 217 (62), 91 (96), 45 (100). Anal. Calcd for $C_{38}H_{32}NO_4P$ (597.65): C, 76.37; H, 5.40; N, 2.34; found: C, 76.40; H, 5.40; N, 2.35%. ^{1}H-NMR: δ 1.23 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 4.24 (2 H, q, $^{3}J_{HH}$ = 7.2 Hz, OCH_2), 4.82 (2 H, m, CH_2), 6.94 (1 H, d, $^{2}J_{PH}$ = 20.8 Hz, CH), 7.15 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH); 7.26-7.29 (3 H, m, 3 CH), 7.34 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, 2 CH), 7.37 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.44 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.45-7.80 (16 H, m, 16 CH). ^{13}C-NMR: δ 14.1 (Me), 49.2 (CH_2), 61.4 (OCH_2), 91.7 (d, $^{2}J_{CP}$ = 30.2 Hz, C_{ipso}), 117.4 (CH), 120.0 (CH), 122.4 (2 CH), 123.9 (CH), 125.8 (CH), 127.9 (2 CH), 128.2 (CH), 128.6 (d, $^{3}J_{CP}$ = 9.4 Hz, C), 129.1 (*d*, $^{3}J_{CP}$ = 18.5 Hz, 6 CH), 129.9 (3 CH), 132.4 (d, $^{2}J_{CP}$ = 28.4 Hz, 6 CH), 135.6 (C), 137.4 (d,$^{1}J_{CP}$ = 230.2 Hz, 3 C), 145.4 (d, $^{1}J_{CP}$ = 201.3 Hz, CH), 150.4 (C), 157.1 (d, $^{2}J_{CP}$ = 16.2 Hz, C), 169.5 (d, $^{3}J_{CP}$ = 23.5 Hz, C=O), 170.1 (d, $^{3}J_{CP}$ = 20.1 Hz, C=O). ^{31}P-NMR: δ 59.58.

Dimethyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-3,4-dicarboxylate (4d):

Pale yellow crystals, mp 195-197°C, 0.85 g, yield 75%. IR (KBr) (ν_{max}/cm^{-1}): 1752, 1732, 1672, 1478, 1135, 1097 and 1019. MS, *m/z* (%): 565 (M^{+}, 15), 533 (85), 502 (72), 403 (54), 278 (96), 161 (38), 146 (88), 31 (100).Anal. Calcd for $C_{33}H_{28}NO_6P$ (565.56): C, 70.08; H, 4.99; N, 2.48; found: C, 70.10; H, 5.00; N, 2.45%. ^{1}H-NMR: δ 3.27 (3 H, s, NMe), 3.69 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.91 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.08 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.11 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.43 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.47-7.84 (15 H, m, 15 CH). ^{13}C-NMR: δ 26.9 (NMe), 51.7 (OMe), 52.3 (OMe), 90.1 (d, $^{2}J_{CP}$ = 51.2 Hz, C_{ipso}), 116.7 (CH), 120.3 (CH), 123.6 (CH), 128.1 (CH), 128.6 (d, $^{3}J_{CP}$ = 22.4 Hz, C), 129.2 (d, $^{3}J_{CP}$ = 21.1 Hz, 6 CH), 129.4 (3 CH), 131.9 (d, $^{2}J_{CP}$ = 31.9 Hz, 6 CH), 135.1 (d, $^{1}J_{CP}$ = 230.1 Hz, 3 C), 149.3 (C), 150.4 (d, $^{1}J_{CP}$ = 192.3 Hz, C), 163.0 (d, $^{2}J_{CP}$ = 24.2 Hz, C=O), 165.1 (C), 168.4 (d, $^{3}J_{CP}$ = 21.2 Hz, C=O), 169.7 (C=O). ^{31}P-NMR: δ79.45.

Diethyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-3,4-dicarboxylate (4e):

Yellow powder, mp 190-192°C, 0.89 g, yield 75%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1720, 1643, 1478, 1166, 1086 and 1004. MS, *m/z* (%): 593 (M^{+}, 10), 548 (82), 503 (76), 315 (54), 278 (96), 161 (46), 146 (88), 45 (100). Anal. Calcd for $C_{35}H_{32}NO_6P$ (593.6): C, 70.82; H, 5.43; N, 2.36; found: C, 70.80; H, 5.40; N, 2.35%. ^{1}H-NMR: δ 1.23 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 1.48 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, Me), 3.25 (3 H, s, NMe), 3.84 (2 H, q, $^{3}J_{HH}$ = 7.2 Hz, OCH_2), 4.08 (2 H, q, $^{3}J_{HH}$ = 7.2 Hz, OCH_2), 6.95 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.08 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.33 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.35-7.72 (16 H, m, 16 CH). ^{13}C-NMR: δ 13.0 (Me), 13.2 (Me), 26.4 (NMe), 61.4 (OCH_2), 62.4 (OCH_2), 92.0 (d, $^{2}J_{CP}$ = 49.5 Hz, C_{ipso}), 116.2 (CH), 119.5 (CH), 122.9 (CH), 127.9 (CH), 128.4 (d, $^{3}J_{CP}$ = 23.9 Hz, C), 130.1 (d, $^{3}J_{CP}$ = 20.1 Hz, 6 CH), 130.5 (3 CH), 132.0 (d, $^{2}J_{CP}$ = 32.9 Hz, 6 CH), 134.9 (d, $^{1}J_{CP}$ = 230.1 Hz, 3 C), 149.2 (C), 150.4 (d, $^{1}J_{CP}$ = 195.3 Hz, C), 162.9 (d, $^{2}J_{CP}$ = 23.6 Hz, C=O), 166.1 (C), 168.2 (d, $^{3}J_{CP}$ = 23.2 Hz, C=O), 169.2 (C=O). ^{31}P-NMR: δ 75.45.

Dimethyl 1,2-dihydro-2-oxo-1-benzyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-1,2-□^{5}-oxaphosphole]-3,4-dicarboxylate (4f):

Pale yellow crystals, mp 178-180°C, 0.89 g, yield 70%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1642, 1472, 1165, 1090 and 1012. MS, *m/z* (%): 641 (M^+, 10), 610 (84), 579 (74), 368 (54), 278 (96), 237 (46), 146 (88), 91 (96), 31 (100). Anal. Calcd for $C_{39}H_{32}NO_6P$ (641.66): C, 73.00; H, 5.03; N, 2.18; found: C, 73.00; H, 5.05; N, 2.20%. ^{1}H-NMR: δ 3.75 (3 H, s, OMe), 4.11 (3 H, s, OMe), 4.80 (1 H, d, $^2J_{HH}$ = 15.6 Hz, CH), 5.01 (1 H, d, $^2J_{HH}$ = 15.6 Hz, CH), 7.15 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.30 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.36 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.38 (2 H, t, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.45 (2 H, t, $^3J_{HH}$ = 7.7 Hz, 2 CH), 7.54 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.62-7.84 (15 H, m, 15 CH). ^{13}C-NMR: δ 46.2 (NCH_2), 51.4 (OMe), 52.2 (OMe), 89.3 (d, $^2J_{CP}$ = 47.8 Hz, C_{ipso}), 116.5 (CH), 119.1 (CH), 123.4 (2 CH), 123.6 (CH), 125.9 (CH); 127.7 (2 CH), 128.3 (CH), 128.5 (d, $^3J_{CP}$ = 24.2 Hz, C), 128.9 (d, $^3J_{CP}$ = 20.1 Hz, 6 CH), 130.2 (3 CH), 132.4 (d, $^2J_{CP}$ = 34.2 Hz, 6 CH), 135.9 (C), 136.2 (d, $^1J_{CP}$ = 234.5 Hz, 3 C), 148.4 (C), 151.2 (d, $^1J_{CP}$ = 190.1 Hz, C), 162.4 (d, $^2J_{CP}$ = 26.5 Hz, C=O), 164.8 (C), 167.5 (d, $^3J_{CP}$ = 20.3 Hz, C=O), 169.5 (C=O). ^{31}P-NMR: δ 44.2.

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