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Synthesis of Highly Functionalized Stable Heterocyclic Phosphorus Ylides. Cycloaddition Reaction between Conjugated Phosphorus Ylides and Alkyl Propiolates

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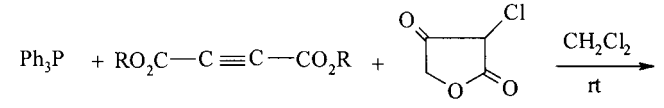
Abstract—Protonation of the reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by 3-chlorotetrahydrofuran-2,4-dione leads to vinylphosphonium salts, which undergo Michael addition with the conjugate base of the CH-acid to produce highly functionalized phosphorus ylides containing a furandione ring system in excellent yields. Using alkyl propiolates, the corresponding phosphorus ylides are formed and undergo [4+2] cycloaddition reaction with the alkyl propiolates to produce hitherto unknown furo[2,3-*b*]pyran ring systems in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Phosphorus ylides are reactive compounds which take part in many reactions of value in the synthesis of organic products.[1–4] Phosphorus ylides are synthetic targets of interest, not least because of their value for a variety of industrial, biological, and chemical synthetic uses.[4–10] Several methods have been developed for preparation of phosphorus ylides. These ylides are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually obtained from the phosphine and an alkyl halide. Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated olefins and in other ways.[4] The phosphonium salts are most often converted to the ylide by treatment with a strong base, though weaker bases can be used if the salt is acidic enough. We wish to report an efficient synthetic route to heterocyclic phosphorus ylides **3** (Scheme 1) and **7** (Scheme 2) using



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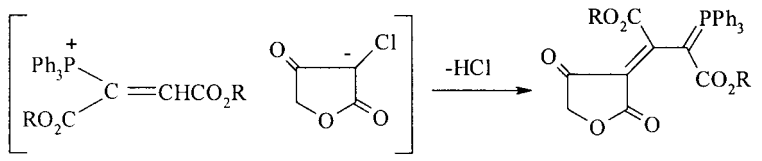

2 **3**

1, 2, 3	R	%Yields of 3
a	Me	85
b	Et	82
c	^{i}Pr	80

Scheme 1.

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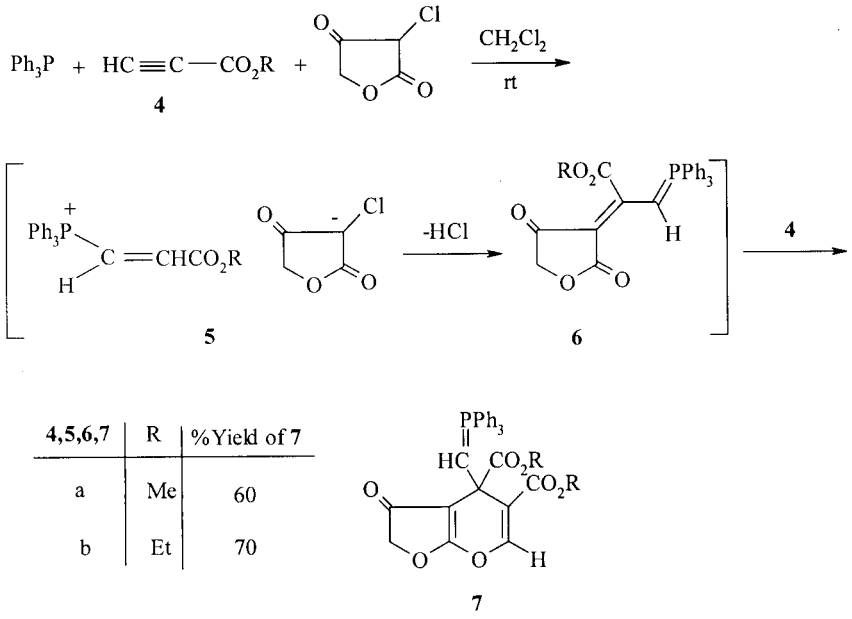

Scheme 2.

triphenylphosphine, electron-deficient acetylenic esters such as dialkyl acetylenedicarbocxylates **1** or alkyl propiolates **4**, and 3-chlorotetrahydrofuran-2,4-dione.

Results and Discussion

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[4–8] it is reasonable to assume that phosphorus ylide **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by 3-chlorotetrahydrofuran-2,4-dione. Then, the positively charged ion is attacked by the carbon atom of the conjugate base of the CH-acid to form stable phosphorane **3**.[11]

The structures of compounds **3a–c** were deduced from their elemental analyses and their high-field ^{1}H, ^{13}C, and ^{31}P NMR and IR spectral data. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra which displayed molecular ion peaks at m/z=502, 530, and 558. Initial fragmentations involve loss from or complete loss of the side chains and scission of the heterocyclic ring system.

The ^{1}H NMR spectrum of **3a** exhibited three sharp lines arising from methoxy (δ=3.24 and 3.95) and methylene (δ=3.75) protons along with the aromatic protons which appear as a multiplet at δ=7.54–7.94. The ^{13}C NMR spectrum of **3a** displayed distinct resonances in agreement with the phosphorane structure. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **3a**, it helps in assignment of the signals by couplings with ^{31}P nuclei (see Experimental). The ^{1}H and ^{13}C NMR spectra of **3b** and **3c** are similar to those of **3a**, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts. The ^{31}P NMR spectra of compounds **3a–c** exhibited, in each case, a single sharp resonance at about δ=21 downfield from 85% H_3PO_4.

The structural assignments made on the basis of the ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds **3a–c** were supported by measurement of their IR spectra. Of special interest is the carbonyl absorption at 1734–1646 cm^{-1} for these compounds. Conjugation with the carbon–carbon double bond appears to be a plausible factor in the reduction of these absorption frequencies.[12]

When alkyl propiolates **4** were employed as Michael acceptors, the reaction proceeds further to produce furo[2,3-*b*]pyran ring system, **7**, in fairly high yields. Compound **7** apparently results from a [4+2] cycloaddition reaction of alkyl propiolate with phosphoranes **6** to give the fused-ring system of phosphonium ylide **7** (Scheme 2). Attempts to isolate the 1:1 adduct **6** were unsuccessful. The yields given for **7** are based on 3-chlorotetrahydrofuran-2,4-dione. Best results were obtained using 1.5 equiv. of the propiolate **4**; more complex reaction mixtures were obtained in presence of 2 equiv. of **4**.

The ^{1}H NMR spectrum of **7a** exhibited three sharp lines arising from methoxy (δ=3.18 and 3.80) and methylene (δ=3.85) protons, together with a doublet with $^{2}J_{PH}$=19 Hz for the P=CH group. The aromatic protons of **7a** appear as a multiplet at δ=7.55–7.90. The sharp signal at δ=8.10 is attributed to the olefinic CH proton. The ^{13}C NMR spectrum of **7a** displayed distinct resonances in agreement with the phosphorane structure and also displayed signals for carbonyl group at δ=166.4, which appears as a doublet with $^{3}J_{PC}$=value of 7.1 Hz, and at δ=167.9 and 176.6 for other carbonyl groups.

The ^{1}H and ^{13}C NMR spectra of **7b** are similar to those of **7a**, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts. The ^{31}P NMR spectra of compounds **7a–b** exhibited, in each case, a single sharp resonance at about δ=20 ppm downfield from 85% H_3PO_4.

In summary, the reaction between electron-deficient acetylenic esters, such as dialkyl acetylenedicarboxylates, or alkyl propiolates, and triphenylphosphine, in the presence of 3-chlorotetrahydrofuran-2,4-dione provides an acceptable method for the preparation of stable heterocyclic phosphorous ylides with variable functionalities.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500, 125.7 and 202.5 MHz, respectively. The mass spectra were recorded on a Finnigan–Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylates **1a**–**c**, alkyl propiolates **4a**,**b**, and 3-chloro-(3*H*,5*H*)-furan-2,4-dione were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of dimethyl 2-[tetrahydrofuran-2,4-dione]-3-(triphenylphosphoranylidene)-butanedioate (3a). General procedure

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol), triethylamine (0.1 ml, 1 mmol) and 3-chloro-(3*H*, 5*H*)-furan-2, 4-dione (0.13 g, 1 mmol) in CH_2Cl_2 (5 ml) was added, dropwise, a mixture of dimethyl acetylenedicarboxylate (0.12 ml, 1 mmol) in CH_2Cl_2 at −10°C over 5 min. After 24 h stirring at room temperature, the product was filtered off and recrystallized from ethanol. Yellow crystals, 0.42 g, mp 224–225°C, yield 85%; IR (KBr) (ν_{max}/cm^{-1}): 1731, 1680 and 1647 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.24 (3H, s, OCH_3); 3.75 (2H, s, CH_2); 3.95 (3H, s, OCH_3); 7.54–7.94 (15H, m, 3 Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 51.55 and 53.30 (2 OCH_3); 70.97 (CH_2); 81.70 (d, $^1J_{PC}$=113 Hz, P═C); 99.81 (d, $^3J_{PC}$=2.3 Hz, P═C–C═*C*); 128.53–134.32 (Ar); 156.95 (d, $^2J_{PC}$=7 Hz, P═C–*C*); 165.86 (d, $^2J_{PC}$=14 Hz, ester C═O); 168.51 (d, $^3J_{PC}$=17 Hz, ester C═O); 171.43 (ester C═O); 192.37 (ketone C═O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 21.31. MS, *m*/*z* (%): 502 (M^+, 10); 443 (11); 262 (100); 183 (61); 59 (19); Anal. Calcd For $C_{28}H_{23}O_7P$ (502.5) C, 66.93; H, 4.61%. Found: C, 66.9; H, 4.6%.

Diethyl 2-[tetrahydrofuran-2,4-dione]-3-(triphenylphosphoranylidene)-butanedioate (3b). Yellow crystals, 0.43 g, mp 216–217°C, yield 82%, IR (KBr) (ν_{max}/cm^{-1}): 1754, 1734, 1674 and 1646 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.69 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3); 1.36 (3H, t, $^3J_{HH}$=7 Hz, CH_3); 3.69 (2H, s, CH_2); 3.77 (2H, q, $^3J_{HH}$=7 Hz, CH_2); 4.41 (2H, q, $^3J_{HH}$=7.1 Hz, CH_2); 7.42–7.91 (15H, m, 3 Ph). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.92 and 14.06 (2 CH_3); 60.77 and 62.41 (2 OCH_2); 71.02 (CH_2); 82.52 (d, $^1J_{PC}$=113 Hz, P═C); 99.9 (P═C–C═*C*); 128.6–134.4 (Ar); 157.57 (d, $^2J_{PC}$=7 Hz, P═C–*C*); 165.32 (d, $^2J_{PC}$=13 Hz, ester C═O); 168.01 (d, $^3J_{PC}$=17 Hz, ester C═O); 171.47 (ester C═O); 192.41 (ketone C═O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 21.05. MS, *m*/*z* (%): 530 (M^+, 8); 501 (9); 262 (100); 183 (45). Anal. Calcd For $C_{30}H_{27}O_7P$ (530.5) C, 67.92; H, 5.13%. Found: C, 67.9, H, 5.1%.

Diisopropyl 2-[tetrahydrofuran-2, 4-dione]-3-(triphenylphosphoranylidene) butanedioate (3c). Yellow crystals, 0.45 g, mp 150–151°C, yield 80%, IR (KBr) (ν_{max}/cm^{-1}): 1750, 1728, 1660 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.61 (6H, d, $^3J_{HH}$=6 Hz, 2 CH_3); 1.43 (6H, d, $^3J_{HH}$=6 Hz, 2 CH_3); 3.37 (2H, s, CH_2); 4.80 (H, sept., $^3J_{HH}$=6 Hz, CH); 5.34 (H, sept., $^3J_{HH}$=6 Hz, CH); 7.51–7.99 (15H, m, 3 Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 20.90 (2 CH_3); 21.52 (2 CH_3); 68.32 (CH); 70.28 (CH); 71.00 (CH_2); 82.68 (d, $^1J_{PC}$=112 Hz, P═C); 99.90 (d, $^3J_{PC}$=3 Hz, P═C–C═*C*); 128.56–134.24 (Ar); 158.37 (d, $^2J_{PC}$=7 Hz, P═C–*C*); 164.29 (d, $^2J_{PC}$=12 Hz, ester C═O); 167.27 (d, $^3J_{PC}$=17 Hz, ester C═O); 171.34 (ester C═O); 192.41 (ketone C═O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 20.83. MS, *m*/*z* (%): 558 (M^+, 6); 515 (9); 262 (100); 183 (33). Anal. Calcd For $C_{32}H_{31}O_7P$ (558.6) C, 68.81; H, 5.59%. Found: C, 68.8; H, 5.5%.

Preparation of dimethyl 2-oxo-furo[2,3-*b*]-4-(methine triphenylphosphoranylidene)-pyran-2-ene-3,4-dioate (7a). General procedure

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol), triethylamine (0.1 ml, 1 mmol) and 3-chlorotetrahydrofuran-2,4-dione (0.13 g, 1 mmol) in CH_2Cl_2 (5 ml) was added, dropwise, a mixture of methyl propiolate (0.15 ml, 1.5 mmol) in CH_2Cl_2 at −10°C over 5 min. After 24 h stirring at room temperature, the solvent was removed under reduced pressure and the viscous residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using ethyl acetate–hexane (1:1) as eluent. The solvent was removed under reduced pressure and the product was obtained. Yellow crystals, 0.37 g, mp 123–125°C, yield 60%; IR (KBr) (ν_{max}/cm^{-1}): 1708, 1676, and 1620 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.18 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 3.85 (2H, s, CH_2); 5.44 (1H, d, $^2J_{PH}$=18.9 Hz, CH); 7.55–7.90 (15H, m, 3 Ph); 8.1 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 51.98, 52.46 (2 OCH_3); 67.26 (C–CHPPh$_3$); 70.49 (CH_2); 92.65 (C); 111.47 (C–CHO, d, $^3J_{PC}$=90.9 Hz); 120.76 (Ph_3P═CH, d, $^1J_{PC}$=120.76 Hz); 129.8 (C_m, d, $^3J_{PC}$=13.2 Hz); 133.85 (C_o, d, $^2J_{PC}$=10 Hz); 134.12 (C_p, d, $^4J_{PC}$=2.5 Hz); 153.73 (O–C–O); 166.43 (C═O, $^3J_{PC}$=7.1 Hz, ester); 167.80 (C═O, ester), 176.64 (C═O, ketone). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 20.17; MS, *m*/*z* (%): M^+, 528 (2), 262 (45), 185 (20), 183 (100), 108 (70), 77 (40); Anal. Calcd For $C_{30}H_{25}O_7P$ (528.5) C, 68.18; H, 4.77%. Found: C, 67.9; H, 4.6%.

Diethyl 2-oxo-furo[2,3-*b*]-4-(methine triphenylphosphoranylidene)-pyran-2-ene-3,4-dioate (7b). Yellow crystals, 0.42 g, mp 155–157°C, yield 70%; IR (KBr) (ν_{max}/cm^{-1}): 1718, 1674, 1625 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.95 (3H, t, $^3J_{HH}$=7.13 Hz, CH_3); 1.29 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2); 3.53 (2H,q, $^3J_{HH}$=7.13 Hz, CH_2); 3.88 (2H, s, CH_2); 4.20 (2H,q, $^3J_{HH}$ 7.1 Hz, CH_2); 5.49 (1H, q, $^2J_{PH}$=19.52 Hz, CH); 7.50–7.86 (15H, m, 3 C_6H_5); 7.98 (1H, s, CH). ^{13}C NMR (125.8 MHz,

$CDCl_3$): δ_C 14.23, 14.77 ($2CH_3$); 61.13, 62.23 (2 OCH_3); 68.18 (C); 70.81 (CH_2); 92.76 (C); 111.08 (*C*HPPh_3 $^1J_{PC}$=96.0 Hz); 121.45 (C, J_{PC}=92.8 Hz); 130.03 (C_m, $^3J_{PC}$=13.3 Hz); 134.17 (C_o, $^2J_{PC}$=10.82 Hz); 134.27 (C_p, $^4J_{PC}$=2.5 Hz); 154.34 (O–C–O); 166.51 (C═O, $^3J_{PC}$= 7.17 Hz, ester); 167.97 (C═O, ester); 177.06 (C═O, ketone). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ_P 20.17; MS, *m*/*z* (%): M^+, 556 (3), 277 (100), 262 (50), 185 (20), 183 (60), 77 (45); Anal. Calcd For $C_{32}H_{29}O_7P$ (556.6) C, 69.06; H, 5.25%. Found: C, 68.8; H, 5.1%.

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