A Facile Route to Diastereomeric Phosphorus Ylides. Chemoselective Synthesis of Dialkyl (E)-2-[1-(2-Oxocyclopentylidene)ethyl]-2-butenedioates

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Abstract: 2-Acetylcyclopentanone undergoes a smooth reaction with triphenylphosphine and dialkyl acetylenedicarboxylates to produce dialkyl 2-(1-acetyl-2-oxocyclopentyl)-3-(1,1,1-triphenyl-\(\lambda^5\)-phosphanylidene)succinates. These compounds undergo intramolecular Wittig reactions in boiling benzene to produce highly strained spirocyclobutene derivatives, which spontaneously undergo ring-opening reactions to produce dialkyl (E)-2-[1-(2-oxocyclopentylidene)ethyl]-2-butenedioates.

Keywords: 2-Acetylcyclopentanone, phosphorus ylides, spirocompounds, intramolecular Wittig reaction.

Introduction

Phosphorus ylides are reactive compounds which participate in many valuable syntheses of organic products [1-4]. Phosphorus ylides are interesting synthetic targets because of their importance in a variety of industrial, biological and chemical synthetic usages [5-9]. These ylides are usually prepared by treatment of a phosphonium salt with a base, and the phosphonium salts are usually obtained from the phosphine and an alkyl halide and also Michael addition of phosphorus nucleophiles to activated olefins.
In recent years the three-component reactions of triphenylphosphine, electron-deficient derivatives and ZH-acids (Z=C, O, N, S) that leads to phosphorus ylides have been reported by Yavari et al. [10-15]. We here report the reaction of 2-acetylcyclopentanone (acting as a CH-acid) and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine. These reactions lead to diastereomeric phosphorus ylides. These compounds undergo intramolecular Wittig reactions in boiling benzene to produce spirocompounds, which spontaneously undergo ring-opening reactions to produce dialkyl (E)-2-[1-(2-oxopentylidene)ethy]-2-butenedioates (Scheme 1).

Results and Discussion

We have not established a mechanism for the formation of 5a-c experimentally, but a reasonable possibility is indicated in Scheme 2. On the basis of the well established chemistry of trivalent phosphorus nucleophiles [1, 5, 6], it is reasonable to assume that the initial addition of triphenylphosphine to the acetylenic ester and subsequently the protonation of the 1:1 adduct was followed by attack of the carbon moiety of the enolate of CH-acid to the vinylphosphonium cation to generate ylide 3.

Phosphorus ylides 3a-c then undergo smooth reactions in boiling benzene to produce triphenylphosphine oxide and spirocompounds 4a-c. These compounds were unstable and were not isolated, but rather they are spontaneously converted to functionalized 1,3-dienes 5a-c. (Scheme 2).

Compounds 3a-c possess two stereogenic centers, and two diastereomers are expected (I and II) to form (Scheme 3), and indeed two diastereomers were isolated from the reaction mixtures. It should be pointed out that both diastereomeric ylides (I and II) were converted to 1,3-dienes with the same geometry, indicating that the ring opening reactions did not take place as a concerted reaction.
Scheme 2.

\[
\begin{align*}
(\text{Ph})_3\text{P} & \quad + \quad \text{RO}_2\text{C} & \quad \text{CO}_2\text{R} \\
& \quad \text{reflux} \\
\text{H} & \quad \text{O} & \quad \text{O} \quad \text{PPh}_3 \\
\text{H} & \quad \text{O} \quad \text{PPh}_3 \\
\text{H} & \quad \text{O} \quad \text{PPh}_3 \\
\end{align*}
\]

Scheme 3.

Diastereomeric ylides (I and II)

Intramolecular Wittig reaction

benzene reflux

ring opening

5
The structures of the compounds 3a-c were deduced from their elemental analyses, high field $^1$H- and $^{13}$C-NMR as well as IR spectra data. The $^1$H- and $^{13}$C-NMR spectra of diastereomeric ylides 3a-c were consistent with the presence of two geometric isomers. The ylide moiety of these compounds is strongly conjugated to the adjacent carbonyl group and a rotation around the partial double bond in the 3-(E) and 3-(Z) geometric isomers (Figure 1) is relatively slow on the NMR time scale at ambient temperature.

Figure 1.

The geometries of the double bonds in compound 5 were established using $^1$H-NMR data. For the double bond bearing two ester groups, we considered the chemical shift of the vinylic proton. If the vinylic proton is in a cis position relative to the ester group on the adjacent carbon atom, an anisotropy effect is imposed by the carbonyl of the cis ester group which causes a deshielding effect on this proton, so this proton usually appears at a frequency higher than 6.5 ppm [16], as it was clearly observed in our $^1$H-NMR spectra of compounds 5a-c. Therefore, it can be concluded that the vinylic proton is located in the cis position with respect to the vicinal esteric group. We also investigated the stereochemistry of the compound 5 by using a NOE experiment. In the decoupling process of the methyl protons, the NOE difference spectrum did not show a nuclear Overhauser enhancement of the CH$_2$ protons of the cyclopentanone moiety nor the vinylic proton. The irradiation of the CH$_2$ protons also the vinylic proton lead to no enhancement of the intensity of the CH$_3$ protons. On the basis of these results, the geometry for the compound 5 is as indicated in Scheme 3.

Conclusions

In conclusion, the present method may be considered as a practical route for the synthesis of the stable phosphorus ylides and electron deficient 1,3-butadienes. This procedure has advantages of high yield, mild reaction conditions, and simple experimental and work-up conditions.

Experimental

General

Triphenylphosphine, dialkyl acetylenedicarboxylate and 2-acetyl cyclopentanone were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrotermal 9100 apparatus and are uncorrected. $^1$H- and $^{13}$C-NMR spectra were measured with a Bruker DRX-500 AVANCE spectrometer at 500 and 125.8 MHz, respectively.
Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-470 spectrometer.

General procedure for preparation of dialkyl 2-(1-acetyl-2-oxocyclopentyl)-3-[1,1,1-triphenyl-λ5-phosphanylidene]succinates (exemplified by 3a)

A mixture of dimethyl acetylenedicarboxylate (0.245 mL, 2 mmol) in CH2Cl2 (4 mL) was added dropwise at -10 °C over 10 min. to a magnetically stirred solution of 2-acetylcyclopentanone (2, 0.252 g, 2 mmol) and triphenyl phosphine (0.524 g, 2 mmol) in CH2Cl2 (10 mL). The mixture was allowed to stand at room temperature along with stirring for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (Merck silica gel 60, 230-400 mesh) using ethyl acetate-hexane (30:70) as eluent. Two diastereomers were isolated. The solvents were removed under reduced pressure to give ylides 3a-I and 3a-II as white powders.

Dimethyl 2-(1-acetyl-2-oxocyclopentyl)-3-[1,1,1-triphenyl-λ5-phosphanylidene] succinate (3a)

First diastereomer (3a-I): M.p. 126-128.5 °C; yield 50 %; IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 1755, 1730 and 1705 (C=O), 1629 (C=C); MS \(m/z\) (%): 530 (M+, 10), 499 (M–OCH3, 14), 471 (M–CO2Me, 25), 487 (M–CH3CO, 25), 209 [M– (PPh3+CO2Me), 37], 43 (CH3CO+, 100); Anal. calcd. for C31H31O6P (530.56): C, 70.18; H, 5.89%. Found: C 70.06; H, 5.83%; 1H-NMR (CDCl3) 3a-I (Z): \(\delta_H\) 1.42-1.50 (2H, m, CH2), 1.60 (3H, s, CH3), 1.97-2.13 (2H, m, CH2), 2.58-2.82 (2H, m, CH2), 2.92 and 3.70 (6H, 2s, 2OCH3), 3.56 (1H, d, JPH = 18.4 Hz, CH), 7.4-7.7 (15H, m, -Ph); 13C-NMR (CDCl3): \(\delta_C\) 20.12 (CH2), 27.64 (CH3), 29.81 (CH2), 37.31 (CH2), 39.38 (d, JPC = 13.4 Hz, CH), 48.71 and 51.83 (2OCH3), 73.94 (cyclopentanone quaternary carbon), 127.61 (d, JPC = 91.4 Hz, Cipso), 128.58 (d, JPC = 11.7 Hz, Cmeta), 131.9 (Cpara), 133.97 (d, JPC = 9.4 Hz, Cortho), 169.94 (d, JPC = 13.1 Hz, C=O ester), 174.24 (d, JPC = 5.3 Hz, C=O ester), 203.70 and 216.22 (2C=O, ketones).

Second diastereomer (3a-II): M.p. 151-152 °C; yield 45 %; IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 3059 and 2987 (CH), 1751, 1726 and 1689 (C=O), 1629 (C=C); MS \(m/z\) (%): 530 (M+, 8), 471 (M–CO2Me, 18), 487 (M–CH3CO, 30), 268 (M–PPh3, 21), 209 (M– (PPh3+CO2Me), 28), 43 (CH3CO+, 100); Anal. calcd. for C31H31O6P (530.56): C, 70.18; H, 5.89%; Found C 70.05, H 5.78 %; 3a-II (Z) (68 %) 1H-NMR (CDCl3): \(\delta_H\) 1.64 (3H, s, CH3), 1.82-1.95 (2H, m, CH2), 2.09-2.18 (2H, m, CH2), 2.88-2.96 (2H, m, CH2), 2.80 and 3.69 (6H, 2s, 2OCH3), 3.49 (1H, d, JPH = 18.8 Hz, CH), 7.45-7.64 (15H, m, -Ph); 13C-NMR (CDCl3): \(\delta_C\) 20.33 (CH2), 25.45 (CH3), 29.12 (CH2), 39.84 (d, JPC = 121.9 Hz, CH), 40.07.
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Diethyl 2-(1-acetyl-2-oxocyclopentyl)-3-[1,1,1-triphenyl-λ⁵-phosphanylidene] succinate (3b)

First diastereomer (3b-I): M.p. 157.5-159 ºC; yield 53 %; IR (KBr, νmax, cm⁻¹): 1745, 1730 and 1705 (C=O), 1632 (C=C); MS m/z (%): 558 (M +, 7), 530 (M⁺-C₂H₅, 14), 515 (M⁺-CH₃CO, 31), 485 (M⁺-CO₂Et, 18), 296 (M⁺-PPh₃, 20), 223 [M⁺- (PPh₃+CO₂Et), 37], 43 (CH₃CO⁺, 100); Anal. calcd. for C₃₃H₃₅O₆P (530.56); C, 70.96; H, 6.32%; Found: C 70.88; H, 6.25%; 3b-I (Z) (64 %) ¹H-NMR (CDCl₃): δH 1.18 (3H, t, 3JHH = 7 Hz, CH₃), 1.25 (3H, t, 3JHH = 7.2 Hz, CH₃), 1.51-1.55 (2H, m, CH₂), 1.57 (3H, s, CH₃), 1.62 (3H, s, CH₃CO), 2.07-2.12 (2H, m, CH₂), 2.44-2.52 (2H, m, CH₂), 3.37-3.39 (2H, m, OCH₂), 3.47 (1H, d, 3JPH = 19.8 Hz, CH₂CO₂Et), 4.12-4.15 (2H, m, OCH₂), 7.46-7.81 (15H, m, -Ph); ¹³C-NMR (CDCl₃): δC 13.10 and 13.60 (2CH₃), 19.28 and 25.86 (2CH₂), 29.05 (CH₃CO), 37.1 (d, 2JPC = 12.6 Hz, CH₂CO₂Et), 60.97 and 62.15 (2OCH₂), 71.5 (cyclopentanone quaternary carbon), 127.8 (d, 2JPC = 90.8 Hz, C₇p), 129.89 (3JPC=12.4 Hz, Cmeta), 132.13 (2JPC=9.81 Hz, Cortho), 134.83 (Cpara), 165.04 (d, 2JPC=13.1 Hz, C=O ester), 170.72 (d, 3JPC = 6.7 Hz, C=O ester), 203.84 and 215.01 (2C=O, ketones).

Di-tert-butyl 2-(1-acetyl-2-oxocyclopentyl)-3-[1,1,1-triphenyl-λ⁵-phosphanylidene] succinate (3c)

First diastereomer (3c-I): M.p. 149-149.5 ºC; yield 53 %; IR (KBr, νmax, cm⁻¹): 1752, 1733 and 1705 (C=O), 1620 (C=C); MS m/z (%): 614 (M⁺, 5), 571 (M⁺-CH₃CO, 25), 558 (M⁺-C₄H₈, 16), 513 (M⁺-CO₂Bu, 28), 456 [M⁺-(CO₂Bu+CH₃CO), 38], 352 (M⁺-PPh₃, 14), 251 [M⁺- (PPh₃+CO₂Bu), 37], 43 (CH₃CO⁺, 100); Anal. calcd. for C₃₃H₃₅O₆P (614.73): C 72.29, H 7.05 %; Found C 72.15, H 6.95 %; 3c-I (Z) (59 %) ¹H-NMR (CDCl₃): δH 0.84 (9H, s, CMe₃), 1.47 (9H, s, CMe₃), 1.49 (3H, s, CH₃), 1.87-
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1.88 (2H, m, CH2), 2.01-2.06 (2H, m, CH2), 2.78-2.83 (2H, m, CH2), 3.37 (1H, d, \( J_{PH} = 16.8 \) Hz, CH), 7.4-7.55 (15H, m, -Ph); \(^{13}\)C-NMR (CDCl3): \( \delta_C 20.28 \) and 25.83 (2CH2), 28 and 28.44 (2CMe3), 28.21 (CH3), 37.58 (d, \( J_{PC} = 120.79 \) Hz, P=C), 38.76 (CH2), 44.92 (d, \( J_{PC} = 14.28 \) Hz, CH), 74.49 (cyclopentanone quaternary carbon), 80.65 and 81.67 (2CMe3), 125.8 (d, \( J_{PC} = 85.6 \) Hz, Cipso), 128.52 (d, \( J_{PC} = 12.1 \) Hz, Cmeta), 131.96 (Cpara), 132.1 (d, \( J_{PC} = 9.94 \) Hz, Cortho), 169.47 (d, \( J_{PC} = 12.8 \) Hz, C=O ester), 175.73 (d, \( J_{PC} = 6.5 \) Hz, C=O ester), 204.19 and 216.98 (2C=O, ketones).

Second diastereomer; (3c-II): M.p. 157.5-159ºC; yield 42 %; IR (KBr, \( \nu_{max} \), cm\(^{-1} \)): 1748, 1725 and 1695 (C=O), 1612 (C=C); Anal. calcd. for C\(_{37}\)H\(_{43}\)O\(_6\)P (614.72): C 72.29, H 7.05 %; Found C 72.18, H 6.97 %.

Preparation of Dimethyl (E)-2-[1-(2-oxocyclopentylidene)ethyl]-2-butenedioate (5a)

Compound 3a (I or II) was refluxed in benzene for 24 hours. The solvent was removed under reduced pressure and the viscous residue was purified by silica gel column chromatography (Merck silica gel 60, 230-400 mesh) using ethyl acetate-hexane (30:70) as eluent. The solvents were removed under reduced pressure to give the product. White powder; m.p. 67-69 ºC, yield 85 %; IR (KBr, \( \nu_{max} \), cm\(^{-1} \)): 1745, 1735 and 1710 (C=O), 1627 (C=C); \(^{1}\)H-NMR (CDCl3): \( \delta_H 1.37 \) and 1.50 (18H, 2s, 2CMe3), 1.52 (3H, s, CH3CO), 2.05-2.19 (2H, m, CH2), 2.43-2.48 (2H, m, CH2), 2.89-2.98 (2H, m, CH2), 3.30 (1H, d, \( J_{PH} = 21.9 \) Hz, CH), 7.82-8.1 (15H, m, -Ph); \(^{13}\)C-NMR (CDCl3): \( \delta_C 20.40 \) and 24.88 (2CH2), 27.91 and 28.48 (2CMe3), 29.28 (CH3CO), 40.62 (d, \( J_{PC} = 131.33 \) Hz, P=C), 49.39 (d, \( J_{PC} = 13.8 \) Hz, CH), 74.82 (d, \( J_{PC} = 3.5 \) Hz cyclopentanone quaternary carbon), 77.01 and 80.71 (2CMe3), 125.90 (d, \( J_{PC} = 84.8 \) Hz, Cipso), 128.1 (d, \( J_{PC} = 11.8 \) Hz, Cmeta), 131.95 (Cpara), 132.10 (d, \( J_{PC} = 9.4 \) Hz, Cortho), 160.9 (d, \( J_{PC} = 13.1 \) Hz, C=O ester), 173.66 (d, \( J_{PC} = 6.8 \) Hz, C=O ester), 203.12 and 215.98 (2C=O, ketones).

Preparation of Dimethyl (E)-2-[1-(2-oxocyclopentylidene)ethyl]-2-butenedioate (5a)
165.22 (2C=O, esters), 206.29 (C=O, ketone); MS m/z (%): 252 (M+, 21), 237 (M+-Me, 25), 221 (M+-OMe, 34), 193 (M'-CO2Me, 42), 162 [M'-(CO2Me+OMe), 48], 110 (M'-MeO2CCCO2Me, 100); Anal. calcd. for C13H16O5 (252.27): C 61.90, H 6.39 %; Found C 61.77, H 6.30 %. The following compounds were prepared similarly:

**Diethyl (E)-2-[1-(2-oxocyclopentylidene)ethyl]-2-butenedioate (5b).** White powder; m.p. 66-68 ºC; yield 80 %; IR (KBr, νmax, cm⁻¹): 1740, 1730 and 1710 (C=O), 1620 (C=C); ¹H-NMR (CDCl₃): δH 1.25-1.44 (6H, m, 2CH₃), 2 (2H, t, JHH = 7.8 Hz, CH₂), 2.04 (3H, s, CH₃), 2.30-2.40 (2H, t, JHH = 7.7 Hz, CH₂), 2.75-2.77 (2H, m, CH₂), 4.17 (2H, q, JHH = 7.1 Hz, OCH₂), 4.25 (2H, q, JHH = 7.1 Hz, OCH₂), 6.77 (1H, s, CH); ¹³C-NMR (CDCl₃): δC 14.12 and 14.14 (2CH₃), 19.62 and 22.16 (2CH₂), 28.45 (CH₃CO), 39.08 (CH₂), 60.07 and 61.60 (2OCH₂), 125.18, 134.55, 140.1 and 149.92 (olefinic carbons), 164.57 and 164.9 (2C=O, esters), 203.5 (C=O, ketone); MS m/z (%): 280 (M+, 16), 265 (M'-Me, 22), 207 (M'-CO₂Et, 28), 162 [M'-(CO₂Et+OEt), 48], 110 (M'-EtO₂CCCO₂Et, 100); Anal. calcd. for C₁₅H₂₀O₅ (280.32): C 64.27, H 7.19 %; Found C 64.15, H 7.08 %.

**Di-tert-butyl (E)-2-[1-(2-oxocyclopentylidene)ethyl]-2-butenedioate (5c).** White powder; m.p. 64-67 ºC; yield 87 %; IR (KBr, νmax, cm⁻¹): 1738, 1730 and 1715 (C=O), 1618 (C=C); ¹H-NMR (CDCl₃): δH 1.40 and 1.47 (2CMe₃), 1.92 (2H, t, JHH = 7.4 Hz, CH₂), 1.95 (3H, s, CH₃CO), 2.22-2.27 (2H, t, JHH = 7.3 Hz, CH₂), 2.65-2.70 (2H, m, CH₂), 6.54 (1H, s, CH); ¹³C-NMR (CDCl₃): δC 19.62 and 22.44 (2CH₂), 27.92 and 27.98 (2CMe₂), 28.48 (CH₂), 39.10 (CH₂), 81.02 and 81.82 (2CMe₃), 126.60, 133.94, 140.63 and 149.52 (olefinic carbons), 163.86 and 164.43 (2C=O, esters), 205.71 (C=O, ketone); MS m/z (%): 336 (M', 8), 280 (M' - C₄H₈, 22), 263 (M' - O'Bu, 28), 235 (M' - CO₂'Bu, 20), 179 [M'- (CO₂'Bu+C₄H₈), 35], 162 [M'- (CO₂'Bu+O'Bu), 42], 110 (M'-BuO₂CCCO₂'Bu, 54); Anal. calcd. for C₁₉H₂₈O₅ (336.43): C 67.83, H 8.38 %; Found C 67.70, H 8.26 %.

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*Sample Availability:* Available from the authors.

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