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SYNTHESIS OF HIGHLY FUNCTIONALIZED PHOSPHORUS YLIDES BY ONE-POT AND THREE-COMPONENT REACTION

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ABSTRACT

Three-component reaction between dialkyl acetylenedicarboxylate and triphenylphosphine in the presence of NH-acids including 5-fluoroisatin and 5-benzylidene-2-thioxothiazolidin-4-one leads to vinylphosphonium salts which undergo Michael addition with the conjugate base of the NH-acid to produce highly functionalized, salt-free phosphorus ylides in excellent yields.

Keywords: *Phosphorus Ylides, Dialkyl Acetylenedicarboxylates, Triphenylphosphine, NH-acids*

INTRODUCTION

Phosphorus ylides are reactive systems, which take part in many reactions of value in organic synthesis (Engel, 1988; Corbridge, 1995; Cadogan, 1979). Organophosphorus compounds bearing a carbon atom bound directly to a phosphorus atom, are synthetic targets of interest, at least because of their value for a variety of industrial, biological and chemical synthetic uses (Engel, 1988; Corbridge, 1995; Cadogan, 1979). Several methods have been developed for the preparation of phosphorus ylides. These ylides are usually prepared by treatment of an appropriate phosphonium salt with a base; the corresponding phosphonium salts are usually obtained from the phosphine and an alkyl halide (Engel, 1988; Corbridge, 1995). Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated olefins (Engel 1988; Corbridge 1995). Reaction of acetylenic esters with triphenylphosphine in the presence of an organic compound possessing an acidic-hydrogen has been recently reported to produce phosphorus ylides (Yavari and Karimi, 2007; Islami *et al.*, 2009; Alizadeh *et al.*, 2009). In continuation of our work on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids (Anary-Abbasinejad *et al.*, 2007; 2008; Mosslemin *et al.*, 2010), we report herein the results of our study on the reaction between dialkyl acetylenedicarboxylate and triphenylphosphine in the presence of NH-acids including 5-fluoroisatin and 5-benzylidene-2-thioxothiazolidin-4-one.

MATERIALS AND METHODS

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H, ¹³C, ³¹P and ¹⁹F NMR spectra were recorded on BRUKER DRX-400 AVANCE spectrometer in CDCl₃ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General Procedure

To a magnetically stirred solution of 5-fluoroisatin or 5-benzylidene-2-thioxothiazolidin-4-one (1 mmol) and triphenylphosphine (1 mmol) in acetone (15 mL) was added dialkyl acetylenedicarboxylate (1 mmol) acetone in (3 mL) at room temperature over 2 min. The reaction mixture was then allowed to stir for 2 h. The solvent was evaporated at reduced pressure. The residue was precipitated in a solution of diethyl ether-hexane. The solid was filtered and washed with diethyl ether to give the pure product.

Dimethyl 2-(5-fluoro-2,3-dioxo-2,3-dihydroindol-1-yl)-3-triphenyl-λ⁵-phosphany lidene) succinat (3a): Yellow powder; m.p. 137-139° C. IR (KBr) (ν_{max}, cm⁻¹): 1722, 1672, 1643 (C=O). ¹H NMR (400 MHz, CDCl₃): δ 3.07 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.06 (1H, d, ³J_{PH} = 16 Hz), 7.35-7.87 (18H, m,

Research Article

aromatic) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 37.80 (d, $^1J_{\text{PC}} = 128\text{Hz}$, C=P), 49.27, 52.34 (2OCH₃), 59.35 (d, $^2J_{\text{PC}} = 17\text{Hz}$, CH), 126.12 (d, $^1J_{\text{PC}} = 91\text{ Hz}$), 129.74 (d, $^2J_{\text{PC}} = 12\text{Hz}$), 132.29 (d, $^4J_{\text{PC}} = 2\text{Hz}$), 133.88 (d, $^3J_{\text{PC}} = 10\text{Hz}$), 112.44, 125.11, 128.17, 130.22, 130.75 and 158.66 (6C aromatic), 160.59 (C=O), 168.60 (d, $^2J_{\text{PC}} = 12\text{Hz}$ C=O), 172.44 (d, $^3J_{\text{PC}} = 17\text{Hz}$ C=O), 181.38 (C=O) ppm. ^{31}P NMR: δ 23.48 ppm. ^{19}F NMR: δ -119.72 ppm. Anal. Calcd for $\text{C}_{32}\text{H}_{25}\text{FNO}_6\text{P}$: C, 67.49; H, 4.42; N, 2.46. Found: C, 67.28; H, 4.33; N, 2.60 %. MS, m/z (%): 569 (M^+ , 11).

Diethyl 2-(5-fluoro-2,3-dioxo-2,3-dihydroindol-1-yl)-3-triphenyl- λ^5 -phosphanylidene) succinat (3b):

Yellow powder; m.p. 132-134° C. IR (KBr) (ν_{max} , cm^{-1}): 1732, 1661, 1584 (C=O). ^1H NMR (400 MHz, CDCl_3): δ 1.24 (3H, d $^3J_{\text{HH}} = 7\text{Hz}$, CH₃), 1.34 (3H, d $^3J_{\text{HH}} = 7\text{Hz}$, CH₃), 4.14 (2H, q $^3J_{\text{HH}} = 7\text{Hz}$, OCH₂), 4.30 (2H, q $^3J_{\text{HH}} = 7\text{Hz}$, OCH₂), 4.99 (1H, d, $^3J_{\text{PH}} = 16\text{ Hz}$), 7.37-7.99 (18H, m, aromatic). ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 14.30 and 14.72 (2CH₃), 40.46 (d, $^1J_{\text{PC}} = 128\text{Hz}$, C=P), 58.50, 62.00 (2OCH₂), 58.88 (d, $^2J_{\text{PC}} = 17\text{Hz}$, CH), 126.52 (d, $^1J_{\text{PC}} = 91\text{Hz}$), 129.06 (d, $^2J_{\text{PC}} = 12\text{ Hz}$), 132.59 (d, $^4J_{\text{PC}} = 2\text{ Hz}$), 134.28 (d, $^3J_{\text{PC}} = 10\text{ Hz}$), 112.67, 125.26, 128.21, 130.30, 130.85 and 158.61 (6C aromatic), 160.55 (C=O), 168.40 (d, $^2J_{\text{PC}} = 12\text{Hz}$ C=O), 171.73 (d, $^3J_{\text{PC}} = 17\text{Hz}$ C=O), 181.46 (C=O) ppm. ^{31}P NMR: δ 23.11 ppm. ^{19}F NMR: δ -119.48 ppm. Anal. Calcd for $\text{C}_{34}\text{H}_{29}\text{FNO}_6\text{P}$: C, 68.34; H, 4.89; N, 2.34. Found: C, 68.50; H, 4.78; N, 2.52 %. MS, m/z (%): 597 (M^+ , 5).

Dimethyl 2-(5-benzylidene-4-oxo-2-thioxothiazolidin-3-yl)-3-triphenyl- λ^5 -phosphanylidene) succinat (5a):

Yellow powder; m.p. 180-182° C. IR (KBr) (ν_{max} , cm^{-1}): 1757, 1735, 1675 (C=O). ^1H NMR (400 MHz, CDCl_3): δ 3.34 (3H, s, OCH₃), 3.45 (3H, s, OCH₃), 6.31 (1H, d, $^3J_{\text{PH}} = 16\text{ Hz}$), 7.32-8.25 (20H, m, aromatic), 8.63 (1H, s, =CH). ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 40.10 (d, $^1J_{\text{PC}} = 128\text{Hz}$ C=P), 49.90, 53.16 (2OCH₃), 59.60 (d, $^2J_{\text{PC}} = 17\text{Hz}$, CH), 126.70 (d, $^1J_{\text{PC}} = 91\text{Hz}$), 128.90 (d, $^2J_{\text{PC}} = 12\text{Hz}$), 132.46 (d, $^4J_{\text{PC}} = 2\text{Hz}$), 134.28 (d, $^3J_{\text{PC}} = 10\text{Hz}$), 127.45, 128.56, 128.82, 132.63, 134.46 and 164.26 (aromatic), 168.27 (d, $^2J_{\text{PC}} = 12\text{Hz}$ C=O), 171.38 (d, $^3J_{\text{PC}} = 17\text{Hz}$ C=O), 174.38 (C=O), 201.63 (C=S).ppm. ^{31}P NMR: δ 23.84 ppm. Anal. Calcd for $\text{C}_{34}\text{H}_{28}\text{NO}_5\text{PS}_2$: C, 65.27; H, 4.51; N, 2.24. Found: C, 65.38; H, 4.46; N, 2.15 %. MS, m/z (%): 625 (M^+ , 7).

Diethyl 2-(5-benzylidene-4-oxo-2-thioxothiazolidin-3-yl)-3-triphenyl- λ^5 -phosphanylidene) succinat (5b):

Yellow powder; m.p. 169-171° C. IR (KBr) (ν_{max} , cm^{-1}): 1737, 1645, 1629 (C=O). ^1H NMR (400 MHz, CDCl_3): δ 0.35 (3H, d $^3J_{\text{HH}} = 7\text{Hz}$, CH₃), 1.32 (3H, d $^3J_{\text{HH}} = 7\text{Hz}$, CH₃), 3.58 (2H, q $^3J_{\text{HH}} = 7\text{Hz}$, OCH₂), 4.17 (2H, q $^3J_{\text{HH}} = 7\text{Hz}$, OCH₂), 4.99 (1H, d, $^3J_{\text{PH}} = 16\text{ Hz}$), 7.37-8.22 (20H, m, aromatic), 8.97(1H, s, =CH). ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 14.25 and 14.78 (2CH₃), 40.49 (d, $^1J_{\text{PC}} = 128\text{Hz}$, C=P), 52.30, 62.55 (2OCH₂), 58.36 (d, $^2J_{\text{PC}} = 17\text{Hz}$, CH), 126.45 (d, $^1J_{\text{PC}} = 91\text{Hz}$), 129.13 (d, $^2J_{\text{PC}} = 12\text{ Hz}$), 132.50 (d, $^4J_{\text{PC}} = 2\text{ Hz}$), 134.38 (d, $^3J_{\text{PC}} = 10\text{ Hz}$), 127.62, 128.30, 128.85, 129.05, 132.77 and 134.10 (aromatic), 168.86 (d, $^2J_{\text{PC}} = 12\text{Hz}$ C=O), 171.63 (d, $^3J_{\text{PC}} = 17\text{Hz}$ C=O), 174.25 (C=O), 201.55 (C=S).ppm. ^{31}P NMR: δ 23.77 ppm. Anal. Calcd for $\text{C}_{36}\text{H}_{32}\text{NO}_5\text{PS}_2$: C, 66.14; H, 4.93; N, 2.14. Found: C, 65.93; H, 5.05; N, 2.30 %. MS, m/z (%): 653 (M^+ , 4).

RESULTS AND DISCUSSION

The reaction of the dialkyl acetylenedicarboxylate **2** and triphenylphosphine in the presence of NH-acids including 5-fluoroisatin **1** and 5-benzylidene-2-thioxothiazolidin-4-one **4** leads to the corresponding ylides **3** and **5** in good yields (Figure 1).

Research Article

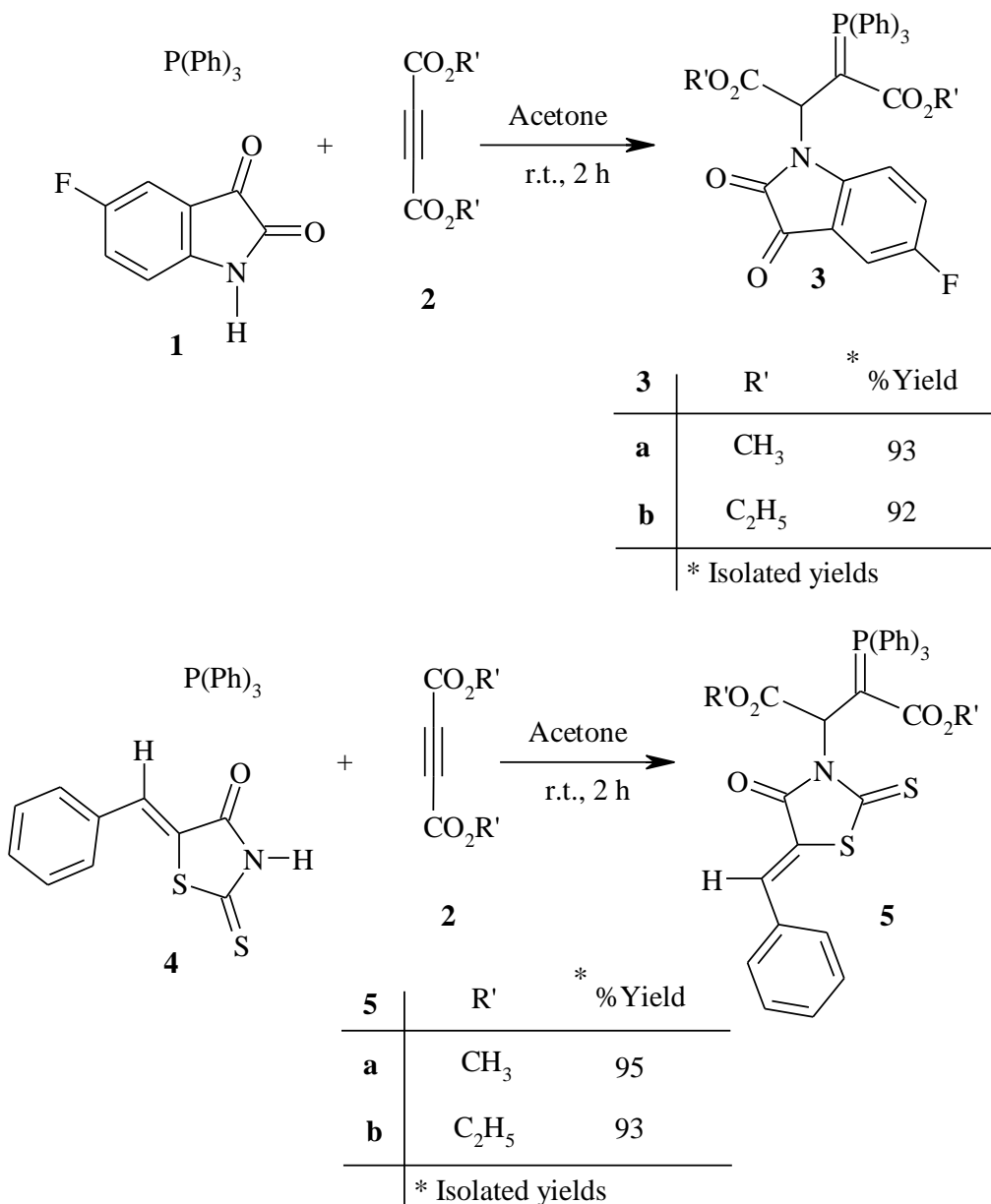


Figure 1: Condensation of dialkyl acetylenedicarboxylate and triphenylphosphine in the presence of NH-acids including 5-fluoroisatin and 5-benzylidene-2-thioxothiazolidin-4-one

The products **3a,b** and **5a,b** were all new compounds. Their structures were deduced from their elemental analyses and spectral data.

The ¹H NMR spectrum of **3a** exhibits two sharp lines at $\delta = 3.07$ and 3.85 ppm for the protons of two methoxy groups and a doubled signal for the methine proton at 6.06 ppm ($^3J_{HP} = 16\text{Hz}$). Aromatic protons resonate between 7.35 and 7.87 ppm as multiplets. ¹³C NMR spectra of compound **3a** shows 18 distinct signals, which is consistent with the proposed structure. The ³¹P NMR spectrum of compound **3a** consists of one signal at 23.48 ppm. This shift is similar to those observed for other stable phosphorus ylides (Tebby, 1987; Vedejs and Snoble, 1973). The structural assignments made on the basis of the NMR spectra of compounds **3a,b** and **5a,b** are supported by their IR spectra. The carbonyl groups exhibited

Research Article

strong absorption bands at 1722, 1672 and 1643 cm^{-1} . The ^{19}F NMR spectrum of compound **3a** consists of one signal at -119.72 ppm.

It is reasonable to assume that ylide **3** results from the initial addition of triphenylphosphine to acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acidic 5-fluoroisatin **1** or 5-benzylidene-2-thioxothiazolidin-4-one **4**. The positively charged ion **6** is then attacked by anion **7** to form the phosphorane **3** (Figure 2).

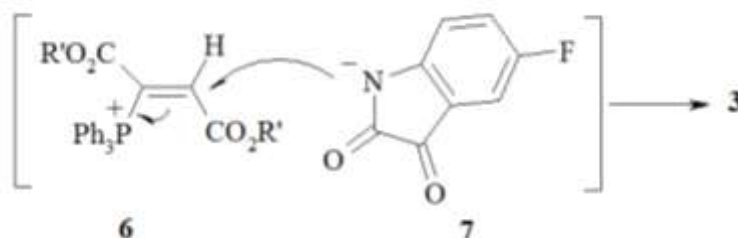


Figure 2: Suggested mechanism for formation of compound **3** or **5**

In summary simple, one-pot and three-component reaction between dialkyl acetylenedicarboxylate and triphenylphosphine in the presence of NH-acids including 5-fluoroisatin and 5-benzylidene-2-thioxothiazolidin-4-one derivatives leads to highly functionalized, salt-free phosphorus ylides in excellent yields. The present method carries the advantage that the reaction is performed under neutral conditions and starting materials can be mixed without any activation or modification.

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Research Article

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