

A synthesis of isatin phosphonate from the reaction of aniline with activated acetylenic compounds in the presence of phosphites

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Abstract: The reaction of activated acetylenic compounds with trialkyl(aryl) phosphites in the presence of aniline and diethyl oxalate leads to stable phosphonate derivatives in excellent yields. The reaction workup is easy and the products can be easily separated from the reaction mixture.

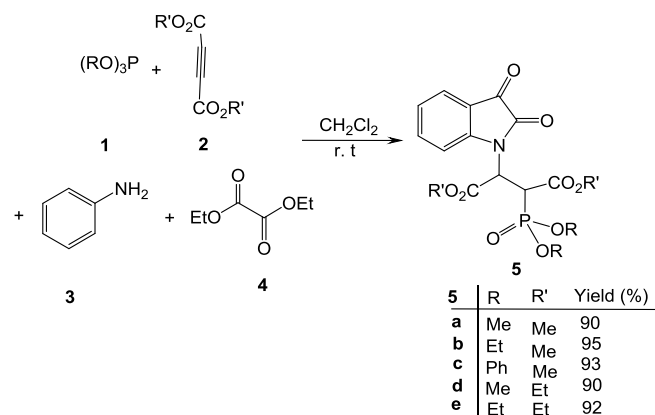
Keywords: Acetylenic esters, Phosphites, Phosphonates, Isatin, Three-component reaction.

Introduction

Organophosphorus compounds are synthetic targets of interest, not least because of their value for a variety of industrial, biological, and chemical synthetic uses [1-6]. 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 [7-9]. As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds [3]. There are many studies on the reaction between trivalent phosphorus nucleophiles and α,β -unsaturated carbonyl compounds in the presence of a proton source such as alcohol or phenol [10-12]. We report the reaction of propiolates with a trivalent phosphorus nucleophile such as trimethyl, triethyl, or triphenyl phosphite in the presence of various heterocyclic N-H acids.

The reaction of trialkyl(aryl) phosphites **1** and propiolates **2** in the presence of aniline **3** and diethyl

oxalate **4**, proceeds smoothly in CH_2Cl_2 at ambient temperature to produce phosphonate derivatives **5** in 90-95% yields (Scheme 1).



Scheme 1: Synthesis of phosphonate derivatives **5**.

Results and discussion

The reaction of trialkyl(aryl) phosphites **1** and propiolates **2** in the presence of aniline **3** and diethyl oxalate **4**, proceeds smoothly in CH_2Cl_2 at ambient temperature to produce phosphonate derivatives **5** in good yields (Scheme 1). The structures of compounds **5a–5e** as 1:1:1 adducts were apparent from their mass spectra, which displayed, in each case, the molecular

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ion peak at appropriate m/z values. The ^1H - and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^1H NMR spectrum of **5a** exhibited two doublets readily recognized as arising from the two diastereotopic methoxy ($\delta = 2.85$ ppm, $^3J_{\text{HP}} = 11$ Hz and $\delta = 3.67$ ppm, $^3J_{\text{HP}} = 11$ Hz) groups. The two singlets at $\delta = 3.71$ and 3.82 ppm belong to the ester methoxy protons. The

proton-decoupled ^{13}C NMR spectrum of **5a** showed sixteen distinct resonances in agreement with the proposed structure. Observation of $^3J_{\text{HH}}$ 13 Hz for the vicinal methine protons in **5a** indicates the dominance of the *anti* arrangement. Since compound **5a** possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangement are possible (Scheme 2).

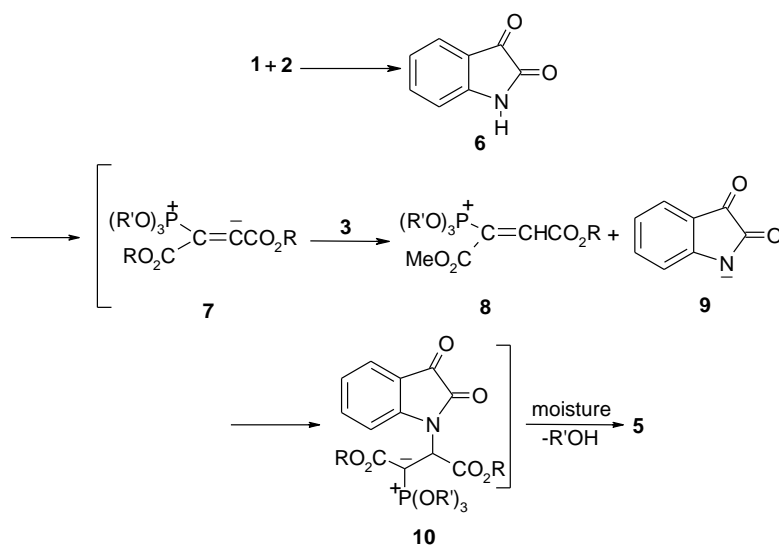


Scheme 2: Two diastereomers with *anti* HCCH arrangement of **5**.

The observation of $^3J_{\text{CP}} = 24$ Hz for CO_2Me group in agreement with the (2*R*, 3*S*) or (2*S*, 3*R*) diastereoisomer. Thus, the reaction is diastereoselective.

Although we have not established the mechanism of the reaction between trialkyl(aryl) phosphites and activated acetylenic compounds in the presence of aniline and diethyl oxalate in an experimental manner,

a possible explanation is proposed in Scheme 3. The first step may involve addition of trialkyl(aryl) phosphites to the acetylenic ester and formation [13] of the 1:1 adducts **5** and its subsequent protonation by isatin that are generated *in situ*. Then, the positively charged ion **8** is attacked by the anion of the NH-acid **9** to produce **5** (Scheme 3).



Scheme 3: Proposed mechanism for generation of **5**.

Conclusion

In summary, the reaction of activated acetylenic compounds with trialkyl(aryl) phosphites in the presence of aniline and diethyl oxalate, provides a simple one-pot synthesis of stable dialkyl(aryl)

phosphorylsuccinates of potential synthetic and pharmaceutical 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

General.

Compounds **1-3** were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^1H -, ^{13}C -, and ^{31}P NMR spectra: Bruker DRX-500 AVANCE instrument; in CDCl_3 at 500.1, 125.7, and 202.4 MHz, respectively; δ 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.

General Procedure for the Preparation of Compounds **5**:

To a stirred solution of **2** (2 mmol) and **3** (2 mmol) in anhyd. CH_2Cl_2 (10 cm^3) was added drop-wise a mixture of **1** (2 mmol) in CH_2Cl_2 (5 cm^3) at -5° over 10 min. The mixture was then allowed to warm to rt, and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2 ; n -hexane/AcOEt 4:1) to afford the pure adducts.

Dimethyl 2-(dimethoxyphosphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (**5a**, $\text{C}_{16}\text{H}_{18}\text{NO}_9\text{P}$):

Orange powder, mp 124-126°C; yield 0.71 g, 89%; IR (KBr): $\bar{\nu} = 1725, 1610 \text{ cm}^{-1}$; ^1H NMR: 2.85 (d, $^3J_{\text{HP}} = 11.0$, OMe), 3.67 (d, $^3J_{\text{HP}} = 11.0$, OMe), 3.71 (s, OMe), 3.82 (s, OMe), 4.30 (1 H, dd, $^3J_{\text{HH}} = 13.0$, $^2J_{\text{HP}} = 21.4$, CH), 5.69 (dd, $^3J_{\text{HH}} = 13.0$, $^3J_{\text{HP}} = 9.9$, CH), 7.21 (t, $^3J_{\text{HH}} = 7.2$, 2 CH), 7.51 (t, $^3J_{\text{HH}} = 7.5$, CH), 7.54 (d, $^3J_{\text{HH}} = 7.5$, CH) ppm; ^{13}C NMR: 44.5 (d, $^1J_{\text{CP}} = 131.9$, CH), 51.9 (d, $^2J_{\text{CP}} = 7.0$, CH), 52.7 (d, $^2J_{\text{PC}} = 7$, OMe), 53.9 (d, $^2J_{\text{PC}} = 7$, OMe), 53.1 (OMe), 53.3 (OMe), 111.3 (2 CH), 117.9 (C), 124.0 (CH), 125.2 (C), 137.9 (CH), 160.9 (C=O), 166.5 (d, $^2J_{\text{CP}} = 13.2$, C=O), 170.5 (d, $^3J_{\text{CP}} = 4.0$, C=O), 181.7 (C=O) ppm; ^{31}P NMR: 11.65 ppm; EI-MS: 399 (M^+ , 15), 368 (62), 290 (100), 253 (38), 146 (88), 109 (86), 31 (56).

Dimethyl 2-(diethoxyphosphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (**5b**, $\text{C}_{18}\text{H}_{22}\text{NO}_9\text{P}$):

Yellow powder, mp 127-129°C; yield 0.80 g, (94%); IR (KBr): $\bar{\nu} = 1730, 1602 \text{ cm}^{-1}$; ^1H NMR: 1.13 (t, $^3J_{\text{HH}} = 7.1$, Me), 1.15 (t, $^3J_{\text{HH}} = 7.1$, Me), 3.71 (s, OMe), 3.85 (s, OMe), 3.93 (m, OCH_2), 3.97 (m, OCH_2), 4.28 (dd, $^3J_{\text{HH}} = 12.2$, $^2J_{\text{HP}} = 21.6$, CH), 5.74 (dd, $^3J_{\text{HH}} = 12.2$, $^3J_{\text{HP}} = 9.6$, CH), 7.06 (d, $^3J_{\text{HH}} = 7.5$, CH), 7.14 (t, $^3J_{\text{HH}} =$

7.5, CH), 7.60 (t, $^3J_{\text{HH}} = 7.6$, CH), 7.64 (d, $^3J_{\text{HH}} = 7.5$, CH) ppm; ^{13}C NMR: 15.9 (d, $^3J_{\text{CP}} = 6.1$, Me), 16.1 (d, $^3J_{\text{CP}} = 6.0$, Me), 43.8 (d, $^1J_{\text{CP}} = 130.9$, CH), 52.7 (d, $^2J_{\text{CP}} = 7.0$, CH), 53.6 (OMe), 53.1 (OMe), 63.5 (d, $^2J_{\text{CP}} = 7.1$, OCH_2), 63.6 (d, $^2J_{\text{CP}} = 7.1$, OCH_2), 110.9 (2 CH), 118.1 (C), 123.9 (CH), 125.5 (C), 138.2 (CH), 160.1 (C=O), 167.5 (d, $^2J_{\text{CP}} = 14.2$, C=O), 170.1 (d, $^3J_{\text{CP}} = 10.1$, C=O), 181.9 (C=O) ppm; ^{31}P NMR: 17.28. EI-MS: 427 (M^+ , 5), 395 (52), 340 (100).

Dimethyl 2-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-3-(diphenoxyphosphoryl)-succinates (**5c**, $\text{C}_{26}\text{H}_{22}\text{NO}_9\text{P}$):

Yellow crystals, mp 132-134°C; yield 0.96 g, 92%; IR (KBr): $\bar{\nu} = 1729, 1603 \text{ cm}^{-1}$; ^1H NMR: 3.72 (s, OMe), 3.85 (s, OMe), 4.62 (dd, $^3J_{\text{HH}} = 12.0$, $^2J_{\text{HP}} = 21.1$, CH), 5.51 (dd, $^3J_{\text{HH}} = 12.1$, $^3J_{\text{HP}} = 9.2$, CH), 6.87 (d, $^3J_{\text{HH}} = 7.6$, 2 CH), 6.93 (d, $^3J_{\text{HH}} = 7.9$, 2 CH), 7.11 (m, 6 CH), 7.21 (d, $^3J_{\text{HH}} = 7.8$, CH), 7.52 (t, $^3J_{\text{HH}} = 7.8$, 2 CH), 7.54 (d, $^3J_{\text{HH}} = 6.9$, CH) ppm; ^{13}C NMR: 44.9 (d, $^1J_{\text{CP}} = 133.1$, CH), 52.7 (d, $^2J_{\text{CP}} = 7.2$, CH), 53.4 (OMe), 53.7 (OMe), 111.1 (2 CH), 118.2 (C), 120.0 (d, $^3J_{\text{CP}} = 4.7$, 2 CH_{ortho}), 120.1 (d, $^3J_{\text{CP}} = 4.7$, 2 CH_{ortho}), 125.5 (C), 124.1 (CH), 125.6 (CH_{para}), 125.7 (CH_{para}), 138.4 (CH), 129.8 (m, 4 CH_{meta}), 149.7 (m, 2 C_{ipso}), 166.6 (d, $^2J_{\text{CP}} = 21.0$, C=O), 158.8 (C=O), 167.7 (d, $^3J_{\text{CP}} = 4.7$, C=O), 181.3 (C=O) ppm; ^{31}P NMR: 10.20 ppm; EI-MS: 523 (M^+ , 5), 430 (54), 376 (54), 285 (100), 147 (92), 92 (56), 77 (92).

Diethyl 2-(dimethoxyphosphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (**5d**, $\text{C}_{22}\text{H}_{30}\text{NO}_9\text{P}$):

Orange powder, mp 158-160°C; yield 0.86 g, 89%; IR (KBr): $\bar{\nu} = 1724, 1608 \text{ cm}^{-1}$; ^1H NMR: 1.20 (s, CMe_3), 1.35 (s, CMe_3), 2.86 (d, $^3J_{\text{HP}} = 10.9$, OMe), 3.66 (d, $^3J_{\text{HP}} = 10.5$, OMe), 4.35 (dd, $^3J_{\text{HH}} = 12.2$, $^2J_{\text{HP}} = 21.3$, CH), 5.67 (dd, $^3J_{\text{HH}} = 12.1$, $^3J_{\text{HP}} = 9.7$, CH), 7.11 (d, $^3J_{\text{HH}} = 7.3$, CH), 7.20 (t, $^3J_{\text{HH}} = 7.3$, CH), 7.58 (t, $^3J_{\text{HH}} = 7.4$, CH), 7.54 (d, $^3J_{\text{HH}} = 7.4$, CH) ppm; ^{13}C NMR: 27.6 (CMe_3), 27.4 (CMe_3), 44.6 (d, $^1J_{\text{CP}} = 132.8$, CH), 52.1 (d, $^2J_{\text{CP}} = 7.1$, CH), 52.4 (d, $^2J_{\text{PC}} = 7.0$, OMe), 53.9 (d, $^2J_{\text{PC}} = 7.1$, OMe), 84.7 (CMe_3), 85.2 (CMe_3), 111.3 (2 CH), 116.9 (C), 123.6 (CH), 124.9 (C), 136.8 (CH), 162.1 (C=O), 167.3 (d, $^2J_{\text{CP}} = 21.3$, C=O), 171.2 (d, $^3J_{\text{CP}} = 9.1$, C=O), 182.3 (C=O) ppm; ^{31}P NMR: 11.67 ppm; EI-MS: 483 (M^+ , 5), 452 (52), 374 (100), 337 (38), 146 (88), 109 (82), 73 (62), 57 (56), 31 (54).

Diethyl 2-(diethoxyphosphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (5e, C₂₄H₃₄NO₉P):

Yellow crystals, mp 136-138°C; yield 0.91 g, 88%; IR (KBr): $\bar{\nu}$ = 1735, 1615 cm⁻¹; ¹H NMR: 1.18 (t, ³J_{HH} = 6.7, Me), 1.21 (t, ³J_{HH} = 6.7, Me), 1.25 (s, CMe₃), 1.30 (s, CMe₃), 3.92 (m, OCH₂), 4.01 (m, OCH₂), 4.25 (dd, ³J_{HH} = 12.0, ²J_{HP} = 21.0, CH), 5.56 (dd, ³J_{HH} = 11.9, ³J_{HP} = 9.5, CH), 6.93 (d, ³J_{HH} = 7.9, CH), 7.11 (t, ³J_{HH} = 7.5, CH), 7.55 (t, ³J_{HH} = 7.7, CH), 7.59 (d, ³J_{HH} = 7.4, CH) ppm; ¹³C NMR: 16.2 (d, ³J_{CP} = 6.2, Me), 16.6 (d, ³J_{CP} = 6.0, Me), 27.2 (CMe₃), 27.9 (CMe₃), 46.2 (d, ¹J_{CP} = 130.8, CH), 52.5 (d, ²J_{CP} = 6.9, CH), 63.9 (d, ²J_{PC} = 7.3, OMe), 64.4 (d, ²J_{PC} = 7.2, OMe), 83.2 (CMe₃), 84.3 (CMe₃), 110.5 (2 CH), 117.9 (C), 123.8 (CH), 124.5 (C), 138.3 (CH), 157.9 (C=O), 166.9 (d, ²J_{CP} = 21.1, C=O), 169.0 (d, ³J_{CP} = 14.0, C=O), 182.1 (C=O) ppm; ³¹P NMR: 19.04 ppm; EI-MS: 511 (M⁺, 10), 418 (52), 365 (92), 278 (68), 233 (76), 146 (88), 93 (100), 73 (62), 57 (56).

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