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Green synthesis and investigation of antioxidant ability of new phosphonate derivatives

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Abstract: The reaction of activated acetylenic compounds, trialkyl(aryl) phosphites, phthalaldehyde and ammonium acetate with *in situe* generated isatin in acetonitrile at room temperature leads to stable isatin phosphonate derivatives in good yield.

Keywords: Acetylenic esters, Phosphites, Phosphonates, Isatin, Five component reaction.

Introduction

Employing of green method is to find out procedure for saving resources and decrease prices. Use of ecologically solvents instead of toxic solvents and employing of moderate conditions and cheap reagents are the most attractive methods to expand a simple and green synthesis of organic compounds [1, 2]. The important procedure for producing complex molecules from simple starting materials is multicomponent reactions (MCRs). The compounds that were produced by this method are attractive for medicinal and synthetic chemists. 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].

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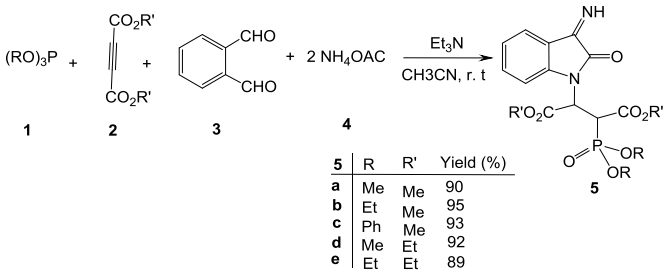
As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds [3]. There are many studies on the reaction between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds in the presence of a proton source such as alcohol or phenol [10-12]. 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 isatin that was produced *in situe* from the reaction of phthalaldehyde and ammonium acetate proceeds smoothly in CH_3CN at ambient temperature to produce phosphonate derivatives **4** in 88-95% yields (Scheme **1**).

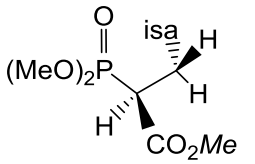


5	R	R'	Yield (%)
a	Me	Me	90
b	Et	Me	95
c	Ph	Me	93
d	Me	Et	92
e	Et	Et	89

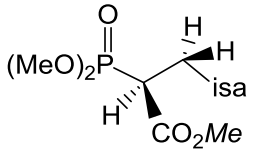
Scheme 1: Synthesis of isatin phosphonate derivatives **5**

Results and discussion

The reactions were carried out by mixing the acetylenic ester **2** with trialkyl or aryle phosphite **3**, then the mixture of phthalaldehyde and ammonium acetate was added slowly. The reactions were complete within 24 hr. The structures of compounds **5a**–**5e** as 1:1:1 adducts 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 **5a** exhibited two doublets readily recognized as arising from the two diastereotopic methoxy (δ = 2.85 ppm, $^{3}J_{HP}$ = 11 Hz and δ = 3.67 ppm, $^{3}J_{HP}$ = 11 Hz) groups. The two singlets at δ = 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 $^{3}J_{HH}$ 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 (Figure **1**).



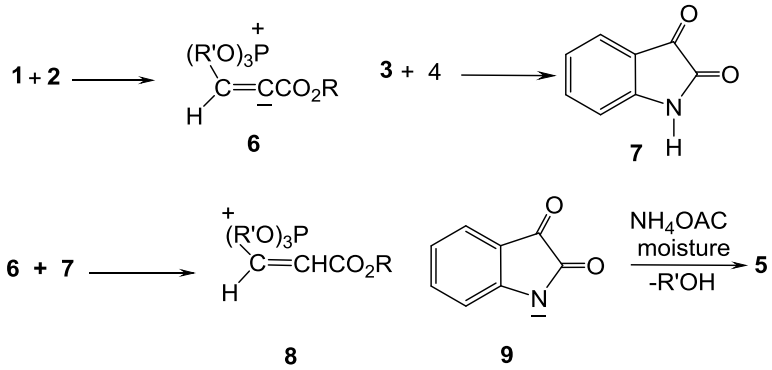
(2*S*, 3*R*)-**5a** or (2*R*, 3*S*)-**5a**



(2*S*, 3*S*)-**5a** or (2*R*, 3*R*)-**5a**

Figure 1: Two diastereomers with *anti* HCCH arrangement of **5**

The observation of $^{3}J_{CP}$ = 24 Hz for *C*O_2Me group in agreement with the (2*R*, 3*S*) or (2*S*, 3*R*) diastereoisomer and the reaction is diastereoselective. Although we have not established the mechanism of the reaction between trialkyl(aryl) phosphites and propiolate in the presence of *insitu* produced isatin in an experimental manner, a possible explanation is proposed in Scheme **2**. The first step may involve addition of trialkyl(aryl) phosphits **1** to the acetylenic ester **2** and formation [13] of the 1:1 adducts **6** and its subsequent protonation by isatin that was produced from the raction of phthalaldehyde **3** and ammonium acetate **4**. Then, the positively charged ion **6** is attacked by the anion of the NH-acid **7** to produce **4** (Scheme **2**).



Scheme 2: Proposed mechanism for generation of **5**

Conclusion

In summary, the reaction of activated acetylenic compounds with trialkyl(aryl) phosphites in the presence of isatin that is produced in situ from the reaction of phthalaldehyde and ammonium acetate , provides a simple one-pot synthesis of stable isatin phosphonate with 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. All of chemicals were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. 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, respectively; □ 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 **1** (2 mmol) and **2**(2 mmol) in CH_3CN (5 cm^3) was added dropwise a mixture of **1** (2 mmol) and **2** (2 mmol) in CH_3CN (5 cm^3) at room temperature. The mixture was then allowed to stirred for 5 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-(dimethoxyphsphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (5a)

Orange powder, mp 124-126°C; yield 0.71 g, 89%; IR (KBr): $\bar{\nu}$ = 1725, 1610 cm^{-1}; ^{1}H NMR: 2.85 (d, $^{3}J_{HP}$ = 11.0, OMe), 3.67 (d, $^{3}J_{HP}$ = 11.0, OMe), 3.71 (s, OMe), 3.82 (s, OMe), 4.30 (1 H, dd, $^{3}J_{HH}$ = 13.0, $^{2}J_{HP}$ = 21.4, CH), 5.69 (dd, $^{3}J_{HH}$ = 13.0, $^{3}J_{HP}$ = 9.9, CH), 7.21 (t, $^{3}J_{HH}$ = 7.2, 2 CH), 7.51 (t, $^{3}J_{HH}$ = 7.5, CH), 7.54 (d, $^{3}J_{HH}$ = 7.5, CH) ppm; ^{13}C NMR: 44.5 (d, $^{1}J_{CP}$ = 131.9, CH), 51.9 (d, $^{2}J_{CP}$ = 7.0, CH), 52.7 (d, $^{2}J_{PC}$ = 7, OMe), 53.9 (d, $^{2}J_{PC}$ = 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, $^{2}J_{CP}$ = 13.2, C=O), 170.5 (d, $^{3}J_{CP}$ = 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-(diethoxyphsphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (**5b)**

Yellow powder, mp 127-129°C; yield 0.80 g, (94%); IR (KBr): $\bar{\nu}$ = 1730, 1602 cm^{-1}; ^{1}H NMR: 1.13 (t, $^{3}J_{HH}$ = 7.1, Me), 1.15 (t, $^{3}J_{HH}$ = 7.1, Me), 3.71(s, OMe), 3.85 (s, OMe), 3.93 (m, OCH_2), 3.97 (m, OCH_2), 4.28 (dd, $^{3}J_{HH}$ = 12.2, $^{2}J_{HP}$ = 21.6, CH), 5.74 (dd, $^{3}J_{HH}$ = 12.2, $^{3}J_{HP}$ = 9.6, CH), 7.06 (d, $^{3}J_{HH}$ = 7.5, CH), 7.14 (t, $^{3}J_{HH}$ = 7.5, CH), 7.60 (t, $^{3}J_{HH}$ = 7.6, CH), 7.64 (d, $^{3}J_{HH}$ = 7.5, CH) ppm; ^{13}C NMR: 15.9 (d, $^{3}J_{CP}$ = 6.1, Me), 16.1 (d, $^{3}J_{CP}$ = 6.0, Me), 43.8 (d, $^{1}J_{CP}$ = 130.9, CH), 52.7 (d, $^{2}J_{CP}$ = 7.0, CH), 53.6 (OMe), 53.1 (OMe), 63.5 (d, $^{2}J_{CP}$ = 7.1, OCH_2), 63.6 (d, $^{2}J_{CP}$ = 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*, $^{2}J_{CP}$ = 14.2, C=O), 170.1 (*d*, $^{3}J_{CP}$ = 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-(diphenoxyphsphoryl)-succinates (**5c)**

Yellow crystals, mp 132-134°C; yield 0.96 g, 92%; IR (KBr): $\bar{\nu}$ = 1729, 1603 cm^{-1}; ^{1}H NMR: 3.72 (s, OMe), 3.85 (s, OMe), 4.62 (dd, $^{3}J_{HH}$ = 12.0, $^{2}J_{HP}$ = 21.1, CH), 5.51 (dd, $^{3}J_{HH}$ = 12.1, $^{3}J_{HP}$ = 9.2, CH), 6.87 (d, $^{3}J_{HH}$ = 7.6, 2 CH), 6.93 (d, $^{3}J_{HH}$ = 7.9, 2 CH), 7.11 (m, 6 CH), 7.21 (d, $^{3}J_{HH}$ = 7.8, CH), 7.52 (t, $^{3}J_{HH}$ = 7.8, 2 CH), 7.54 (d, $^{3}J_{HH}$ = 6.9, CH) ppm; ^{13}C NMR: 44.9 (*d*, $^{1}J_{CP}$ = 133.1, CH), 52.7 (*d*, $^{2}J_{CP}$ = 7.2, CH), 53.4 (OMe) , 53.7 (OMe), 111.1 (2 CH), 118.2 (C), 120.0 (d, $^{3}J_{CP}$ = 4.7, 2 CH_{ortho}), 120.1 (d, $^{3}J_{CP}$ = 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*, $^{2}J_{CP}$ = 21.0, C=O), 158.8 (C=O), 167.7 (*d*, $^{3}J_{CP}$ = 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-(dimethoxyphsphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (5d)

Orange powder, mp 158-160°C; yield 0.86 g, 89%; IR (KBr): $\bar{\nu}$ = 1724, 1608 cm^{-1}; ^{1}H NMR: 1.20 (*s*, CMe_3), 1.35 (*s*, CMe_3), 2.86 (d, $^{3}J_{HP}$ = 10.9, OMe), 3.66 (d, $^{3}J_{HP}$ = 10.5, OMe), 4.35 (dd, $^{3}J_{HH}$ = 12.2, $^{2}J_{HP}$ = 21.3, CH), 5.67 (dd, $^{3}J_{HH}$ = 12.1, $^{3}J_{HP}$ = 9.7, CH), 7.11 (d, $^{3}J_{HH}$ = 7.3, CH), 7.20 (t, $^{3}J_{HH}$ = 7.3, CH), 7.58 (t, $^{3}J_{HH}$ = 7.4, CH), 7.54 (d, $^{3}J_{HH}$ = 7.4, CH) ppm; ^{13}C NMR: 27.6 (CMe_3), 27.4 (CMe_3), 44.6 (d, $^{1}J_{CP}$ = 132.8, CH), 52.1 (d, $^{2}J_{CP}$ = 7.1, CH), 52.4 (d, $^{2}J_{PC}$ = 7.0, OMe), 53.9 (d, $^{2}J_{PC}$ = 7.1, OMe), 84.7 (*C*Me_3), 85.2 (*C*Me_3), 111.3 (2 CH), 116.9 (C), 123.6 (CH), 124.9 (C), 136.8 (CH), 162.1 (C=O), 167.3 (d, $^{2}J_{CP}$ = 21.3, C=O), 171.2 (d, $^{3}J_{CP}$ = 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-(diethoxyphsphoryl)-3-(2,3-dioxo-2,3-dihydro-(1H)-indol-1-yl)-succinates (**5e)**
Yellow crystals, mp 136-138°C; yield 0.91 g, 88%; IR (KBr): $\overline{V}$ = 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, CMe_3), 1.30 (s, CMe_3), 3.92 (m, OCH_2), 4.01 (m, OCH_2), 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; ^{13}C NMR: 16.2 (d, $^3J_{CP}$ = 6.2, Me), 16.6 (d, $^3J_{CP}$ = 6.0, Me), 27.2 (CMe_3), 27.9 (CMe_3), 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 (CMe_3), 84.3 (CMe_3), 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; ^{31}P 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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