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A synthesis of phosphonate derivatives using multicomponent reaction of oxalyl chloride

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Abstract: In this research, phosphonate derivatives were produced from the reaction of aniline, oxalylchloride, malononitrile, activated acetylenic compounds and trialkyl(aryl) phosphites in water at room temperature in excellent yields.

Keywords: Acetylenic esters, oxalylchloride, Phosphonates, Aniline, Five-component reaction.

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial,[1] antimicrobial,[2] antitumor,[3] anticancer, [4] antidepressant,[5] antiviral,[6] antidiabetic,[7] anti-inflammatory [8] and anti-HIV. [9] Moreover, they also contribute in the feld of material science, [10] dyes and pigment science [11] as well as agrochemistry [12]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [13, 14]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [15–17].

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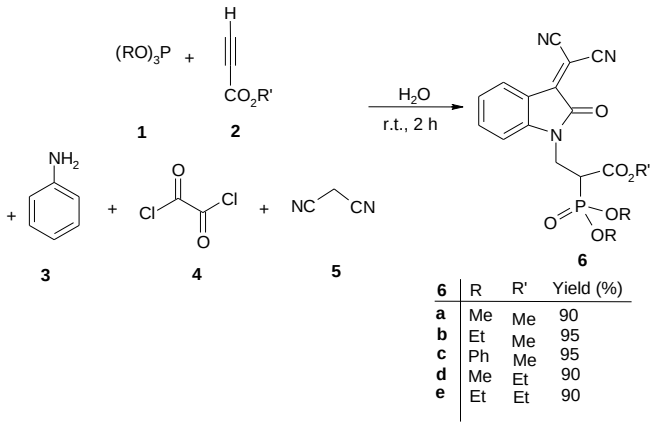
Organophosphorus compounds are synthetic targets of interest, not least because of their value for a variety of industrial, biological, and chemical synthetic uses [18-24]. The physical properties and chemical reactivity of phosphate esters interlinks many areas in chemistry and biology. Introduction of a phosphate monoester into a molecule such as a drug candidate enhances the water solubility, hence altering its bioavailability [25-27]. As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds [27]. 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 [28-29].The reaction of aniline **1**, oxalylchloride **2**, malononitrile **3**, activated acetylenic compounds **4** and trialkyl(aryl) phosphites **5** proceeds smoothly in water at room temperature to produce phosphonate derivatives **6** in 90-95% yields (Scheme **1**).



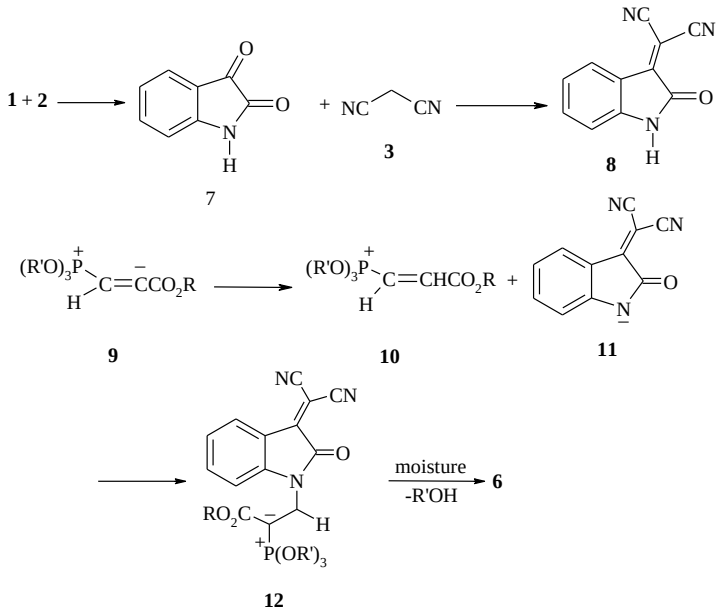
6	R	R'	Yield (%)
a	Me	Me	90
b	Et	Me	95
c	Ph	Me	95
d	Me	Et	90
e	Et	Et	90

Scheme 1: Synthesis of phosphonate derivatives **6**

Results and discussion

The reaction of aniline **1**, oxalylchloride **2**, malononitrile **3**, activated acetylenic compounds **4** and trialkyl(aryl) phosphites **5** proceeds smoothly in water at room temperature to produce phosphonate derivatives **6** in 90-95% yields (Scheme **1**). The structures of compounds **6a**–**6e** 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 **6a** 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 **6a** showed sixteen distinct resonances in agreement with the proposed structure. Observation of $^{3}J_{HH}$ 13 Hz for the vicinal methine protons in **6a** indicates the dominance of the *anti* arrangement. Since compound **6a** possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangement are possible. The observation of $^{3}J_{CP}$ = 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 propiolate in the presence of intermediate which is produced from the isatin **7** with malononitrile **3** in an experimental manner, a possible explanation is proposed in Scheme **2**. The first step may involve addition of trialkyl(aryl) phosphits to the acetylenic ester and formation of the 1:1 adducts **9** and its subsequent protonation by isatin. Then, the positively charged ion **10** is attacked by the anion of the NH-acid **11** to produce **6** (Scheme **2**).



Scheme 2: Proposed mechanism for generation of **6**

Conclusion

In summary, the reaction of aniline **1**, oxalylchloride **2**, malononitrile **3**, activated acetylenic compounds **4** and trialkyl(aryl) phosphites **5** proceeds smoothly in water at room temperature to produce phosphonate derivatives **6** in excellent yields. 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 compounds 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 **6**

To a stirred solution of aniline **1** (2 mmol), oxalylchloride **2** (2 mmol), under solvent-free conditions. After 30 min malononitrile **3** (2 mmol) was added drop-wise to previous mixture. The mixture was then allowed to warm to rt, and stirred for 30 min. Then activated acetylenic compounds **4** (2 mmol) and phosphite **5** (2 mmol) was added and final mixture was stirred for 2 h. after completion of the reaction, water (5 mL) was poured to mixture of reactions and the precipitate was separated by filtration and 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 (**6a**, $C_{16}H_{18}NO_9P$):

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 (**6b,** $C_{18}H_{22}NO_9P$):

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, $^3J_{HH}$ = 12.2, $^2J_{HP}$ = 21.6, CH), 5.74 (dd, $^3J_{HH}$ = 12.2, $^3J_{HP}$ = 9.6, CH), 7.06 (d, $^3J_{HH}$ = 7.5, CH), 7.14 (t, $^3J_{HH}$ = 7.5, CH), 7.60 (t, $^3J_{HH}$ = 7.6, CH), 7.64 (d, $^3J_{HH}$ = 7.5, CH) ppm; ^{13}C NMR: 15.9 (d, $^3J_{CP}$ = 6.1, Me), 16.1 (d, $^3J_{CP}$ = 6.0, Me), 43.8 (d, $^1J_{CP}$ = 130.9, CH), 52.7 (d, $^2J_{CP}$ = 7.0, CH), 53.6 (OMe), 53.1 (OMe), 63.5 (d, $^2J_{CP}$ = 7.1, OCH_2), 63.6 (d, $^2J_{CP}$ = 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*, $^2J_{CP}$ = 14.2, C=O), 170.1 (*d*, $^3J_{CP}$ = 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 (**6c,** $C_{26}H_{22}NO_9P$):

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, $^3J_{HH}$ = 12.0, $^2J_{HP}$ = 21.1, CH), 5.51 (dd, $^3J_{HH}$ = 12.1, $^3J_{HP}$ = 9.2, CH), 6.87 (d, $^3J_{HH}$ = 7.6, 2 CH), 6.93 (d, $^3J_{HH}$ = 7.9, 2 CH), 7.11 (m, 6 CH), 7.21 (d, $^3J_{HH}$ = 7.8, CH), 7.52 (t, $^3J_{HH}$ = 7.8, 2 CH), 7.54 (d, $^3J_{HH}$ = 6.9, CH) ppm; ^{13}C NMR: 44.9 (*d*, $^1J_{CP}$ = 133.1, CH), 52.7 (*d*, $^2J_{CP}$ = 7.2, CH), 53.4 (OMe) , 53.7 (OMe), 111.1 (2 CH), 118.2 (C), 120.0 (d, $^3J_{CP}$ = 4.7, 2 CH_{ortho}), 120.1 (d, $^3J_{CP}$ = 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*, $^2J_{CP}$ = 21.0, C=O), 158.8 (C=O), 167.7 (*d*, $^3J_{CP}$ = 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 **(6d,** $C_{22}H_{30}NO_9P$):

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, $^3J_{HP}$ = 10.9, OMe), 3.66 (d, $^3J_{HP}$ = 10.5, OMe), 4.35 (dd, $^3J_{HH}$ = 12.2, $^2J_{HP}$ = 21.3, CH), 5.67 (dd, $^3J_{HH}$ = 12.1, $^3J_{HP}$ = 9.7, CH), 7.11 (d, $^3J_{HH}$ = 7.3, CH), 7.20 (t, $^3J_{HH}$ = 7.3, CH), 7.58 (t, $^3J_{HH}$ = 7.4, CH), 7.54 (d, $^3J_{HH}$ = 7.4, CH) ppm; ^{13}C NMR: 27.6 (CMe_3), 27.4 (CMe_3), 44.6 (d, $^1J_{CP}$ = 132.8, CH), 52.1 (d, $^2J_{CP}$ = 7.1, CH), 52.4 (d, $^2J_{PC}$ = 7.0, OMe), 53.9 (d, $^2J_{PC}$ = 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, $^2J_{CP}$ = 21.3, C=O), 171.2 (d, $^3J_{CP}$ = 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 (**6e,** $C_{24}H_{34}NO_9P$):

Yellow crystals, mp 136-138°C; yield 0.91 g, 88%; IR (KBr): $\bar{\nu}$ = 1735, 1615 cm^{-1}; ^{1}H 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 (*C*Me_3), 84.3 (*C*Me_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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