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Catalyst free synthesis of new alfa-amino phosphonates by three component reaction of diphenylphosphite, activated acetylenes and thiazole

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Abstract: A three-component and non-catalized synthesis of *α*-aminophosphonates *via* the reaction of thiazole with activated acetylenes in moderate to good yields are described.

Keywords: Diphenyl phosphite, Activated acetylene, Thiazole, *α*-Aminophosphon, *α*-Mercaptophosphonate.

Introduction

One of the most challenging tasks in organic synthesis is the efficient preparation of complex molecules starting from easily available raw materials. Approaches towards the synthesis of optically active or racemic α-aminophosphonates have been intensely investigated over the last few decades [1,2]. Because α-aminophosphonates are structural mimics of α-amino acids, some of these compounds exhibit very high potency in inhibiting enzymes that are involved in the metabolism of the corresponding amino acids. These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticide [3-6] with some of them being commercialized [7]. Therefore Extensive efforts have been made to introduce convenient and efficient methods for the synthesis of phosphonates [11-13].

As part of our group current studies on the synthesis of alkyl phosphonates, and α- aminophosphonates [14-19]. Herein we report the results of our studies involving the reactions of Thiazole (**1**) activared acetylens (**2**) and Diphenylphosphite (**3**) which constitute a synthesis of diphenyl a-amino phosphonates **4** (Scheme **1**).

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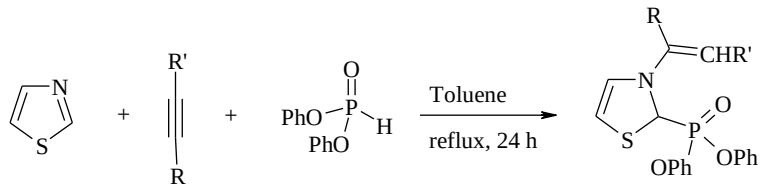
Results and discussion

The reaction of thiazole (**1)** and activated acetylenes **2** in the presence of diphenyl phosphite (**3)**, proceeded smoothly at reflux and was complete within 24 h. (Scheme **1**). The structures of compounds **4a-4C** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C and ^{31}P NMR spectral data. For example, the 1H NMR spectrum of 4a exhibited signals for MeO (δ 3.65 and 3.74), CH (δ 6.10), and vinylic (δ 5.94, 6.45, and 6.62), along with multiplets for the aromatic H-atoms.The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 17 distinct resonances that confirms the proposed structure. The ^{1}H-decoupled ^{31}P NMR spectrum of **3a** showed resonance at (δ 8.4 ppm) for the. The IR spectrum of **3a** displayed aliphatic, aromatic and P=O bands (2925, 1727, 1720, 1488, 1475, 1250, 940, 770 cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra of **4b-3C** are similar to those for **4a** except for the amide moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme **2**).

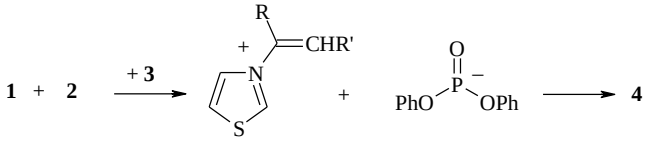
Presumably, the zwitterionic intermediate **5** formed from thiazole and activated acetylenes [20-22], is protonated by **3** to furnish intermediate **5**, which is attacked by **6** to produce **4.**



1 **2** **3**

4	R	R'	Yield %
a	CO_2Me	CO_2Me	60
b	CO_2Et	CO_2Et	53
c	$CO_2{}^tBu$	$CO_2{}^tBu$	42
d	H	CO_2Me	0

Scheme 1: Synthesis of hydrogen phosphonate derivatives.



5 **6**

Scheme 2: Proposed mechanism for the formation of products.

Conclusion

In summary, we report a synthesis of dialkyl 2-[2-(diphenoxyphosphoryl)-1,3-thiazol-3(2*H*)-yl]-2-butenedioate derivatives in moderate to good yields. The present procedure has the advantage that the reactants can be mixed without any prior activation or modification. The simplicity of the present procedure makes it interesting approaches.

Experimental

General procedure:

Compounds 1, 2 and 3 were obtained from Fluka or Merck and were used without further purification. M.p. Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C-, ^{31}P- NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500, 125 and 200.8 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

Typical procedure for preparation of (4):

To a stirred mixture of 0.47 g of diphenylphosphite (2 mmol) and activated acetylenes 2 (2 mmol) in toluene (5 cc) was added 0.172 g of thiazole (2 mmol) at rt. Then the reaction mixture refluxed for 24 hours, the solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using *n*-hexane–EtOAc (8:1) mixture as eluent to get pure product **4**.

Data:

Dimethyl 2-[2-(diphenoxyphosphoryl)-1,3-thiazol-3(2H)-yl]-2-butenedioate (4a):

White powder, mp 123-125 °C, yield 0.27 g (60%). IR (KBr) (ν_{max}/ cm^{-1}): 2925, 1727 (C=O), 1720 (C=O), 1488, 1475, 1250 (P=O), 940, 770. Anal. Calcd for $C_{21}H_{20}NO_7PS$ (461.42): C, 54.66; H, 4.37; N, 3.04%. Found: C, 54.85; H, 4.46; N, 3.12%. ^{1}H-NMR: δ = 3.65 (3 H, s, OMe), 3.74 (3 H, s, OMe), 5.94 (1 H, s, CH), 6.10 (1 H, d, $^2J_{PH}$ =11.2, CH), 6.45 (1 H, d, $^3J_{HH}$ =3.8, CH), 6.62 (1 H, d, $^3J_{HH}$ =3.8, CH), 7.03-7.07 (2 H, m, 2 CH), 7.10-7.14 (3 H, m, 3 CH), 7.22-7.27 (5 H, m, 5 CH). ^{13}C-NMR: δ = 53.6 (OMe), 54.3 (OMe), 65.7 (d, $^1J_{PC}$ = 171.3, P-CH), 95.5 (CH), 114.5 (CH), 116.9 (CH), 120.3 (d, $^3J_{CP}$ = 4.4, 2 CH), 120.9 (d, $^3J_{CP}$ = 4.3, 2 CH), 125.7 (d, $^4J_{CP}$= 4.1, 2 CH), 126.4 (CH), 128.4 (CH), 129.7 (2 CH), 144.1 (C), 150.0 (d, $^2J_{CP}$ = 10.5, C), 150.6 (d, $^2J_{CP}$ = 9.9, C), 163.6 (C=O), 164.4 (C=O). ^{3l}P NMR: δ =8.4.

Diethyl 2-[2-(diphenoxyphosphoryl)-1,3-thiazol-3(2H)-yl]-2-butenedioate (4b):

White powder, Mp 124-126 °C, yield 0.29 g (53%). IR (KBr) (ν_{max}/ cm^{-1}): 2918, 1726 (C=O), 1640 (C=O), 1580, 1478, 1223 (P=O), 984, 751. Anal. Calcd for $C_{23}H_{24}NO_7PS$ (489.47): C, 56.44; H, 4.94; N, 2.86%. Found: C, 56.74; H, 4.86; N, 3.01%. ^{1}H-NMR: δ = 0.95 (3 H, t, $^3J_{HH}$ = 7.6, CH_3), 1.12 (3 H, t, $^3J_{HH}$ = 7.8, Me), 3.79 (2 H, q,$^3J_{HH}$ = 7.8, OCH_2), 4.03 (2 H, q, $^3J_{HH}$ = 7.6, OCH_2), 6.48 (1 H, s, CH), 6.24 (1 H, d, $^2J_{PH}$ =10.7, CH), 6.67 (1 H, d, $^3J_{HH}$ =5.5, CH), 6.89 (1 H, d, $^3J_{HH}$ =5.5, CH), 7.13-7.18 (2 H, m, 2 CH), 7.20-7.23 (3 H, m, 3 CH), 7.27-7.33 (5 H, m, 5 CH). ^{13}C-NMR: δ = 14.2 (CH_3), 15.1 (CH_3), 62.4 (OCH_2), 63.4 (OCH_2), 68.6 (d, $^1J_{PC}$ = 174.9, P-CH), 95.7 (CH), 113.3 (CH), 115.7 (CH), 121.1 (d, $^3J_{CP}$ = 4.3, 2 CH), 121.8 (d, $^3J_{CP}$ = 4.7, 2 CH), 126.1 (d, $^4J_{CP}$= 4.4, 2 CH), 126.5 (CH), 127.7 (CH), 129.4 (2 CH), 146.2 (C), 151.2 (d, $^2J_{CP}$ = 10.5, C), 151.9 (d, $^2J_{CP}$ = 9.9, C), 164.5 (C=O), 165.8 (C=O)**.** ^{3l}P NMR: δ = 11.3.

Di(t-butyl) 2-[2-(diphenoxyphosphoryl)-1,3-thiazol-3(2H)-yl]-2-butenedioate (4c):

White powder, Mp 130-133 °C, yield 0.23 g (42%). IR (KBr) (ν_{max}/ cm^{-1}): 2945, 1729 (C=O), 1723 (C=O), 1515, 1486, 1262 (P=O), 953, 774. Anal. Calcd for $C_{27}H_{22}NO_7PS$ (545.58): C, 59.44; H, 5.91; N, 2.57%. Found: C, 59.62; H, 5.85; N, 2.01%. ^{1}H-NMR: δ = 1.33 (9 H, s, Me_3C), 1.61 (9 H, s, Me_3C), 6.30 (1 H, d, $^2J_{PH}$= 13.4, CH), 6.39 (1 H, s, CH), 6.54 (1 H, d, $^3J_{HH}$ =5.7, CH), 6.63 (1 H, d, $^3J_{HH}$ =5.7, CH), 7.19-7.22 (2 H, m, 2 CH), 7.25-7.27 (3 H, m, 3 CH), 7.30-7.36 (5 H, m, 5 CH). ^{13}C-NMR: δ =26.2 (Me_3C), 28.5 (Me_3C), 64.4 (d, $^1J_{PC}$ = 172.2, P-CH), 82.3 (O*C*Me$_3$), 83.5 (*OC*Me$_3$), 99.3 (CH), 111.7 (CH), 116.4 (CH), 120.1 (d, $^3J_{CP}$ = 4.2, 2 CH), 121.4 (d, $^3J_{CP}$ = 4.6, 2 CH), 126.5 (d, $^4J_{CP}$= 4.4, 2 CH), 127.2 (CH), 127.7 (CH), 129.3 (2 CH), 146.6 (C), 151.7 (d, $^2J_{CP}$ = 11.3, C), 152.4 (d, $^2J_{CP}$ = 9.7, C), 161.8 (C=O), 163.7 (C=O)**.** ^{3l}P NMR: δ = 14.2.

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