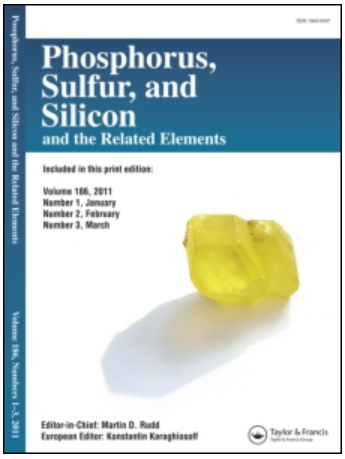

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Tavakolinejad-Kermani, Esmat , Saidi, Kazem and Islami, Mohammad Reza(2005) 'New Synthesis of Acetaminophen Derivatives Containing a Phosphorus Atom', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 8, 1879 — 1884
To link to this Article: DOI: 10.1080/104265090889594
URL: http://dx.doi.org/10.1080/104265090889594

Phosphorus, Sulfur, and Silicon, 180:1879–1884, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090889594

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New Synthesis of Acetaminophen Derivatives Containing a Phosphorus Atom

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Two derivatives of acetaminophen have been efficiently prepared from 4-aminophenol via a two-step procedure involving acetylation of OH and NH_2 groups and then the reaction of the acetylated compounds with diakyl acetylenedicarboxylate in the presence of triphenylphosphine. The products were obtained in good yields.

Keywords Acetaminophen; acetylenic esters; phosphorus compounds

INTRODUCTION

4-Aminophenol and its derivatives have attracted considerable attention in recent years. They were reported to posses antibacterial activity as polymers with styrene[1] and nonlinear optical properties as salts with H_3PO_4.[2] Acetaminophen is a derivative of 4-aminophenol that has been widely used as antipyretic and calmative[3] agent. Although these compounds have received considerable attention, the closely related highly functionalized acetaminophen derivatives are unknown to our knowledge. Recently, our interest focused on the functionalized stable phosphorus ylides that could be transformed into versatile compounds.[4–6] In this article we wish to report the results of our continuing studies on the synthesis of substituted acetaminophens using acetylenic esters, triphenylphosphine, and (4-acetylamino) phenyl acetate **2**. Dialkyl acetylenedicarbonylate **1** reacts with triphenylphosphine in the

Received July 29, 2004; accepted September 7, 2004.
The authors express appreciation to Shahid Bahonar University of Kerman, Faculty Research Committee, for its support of this investigation.
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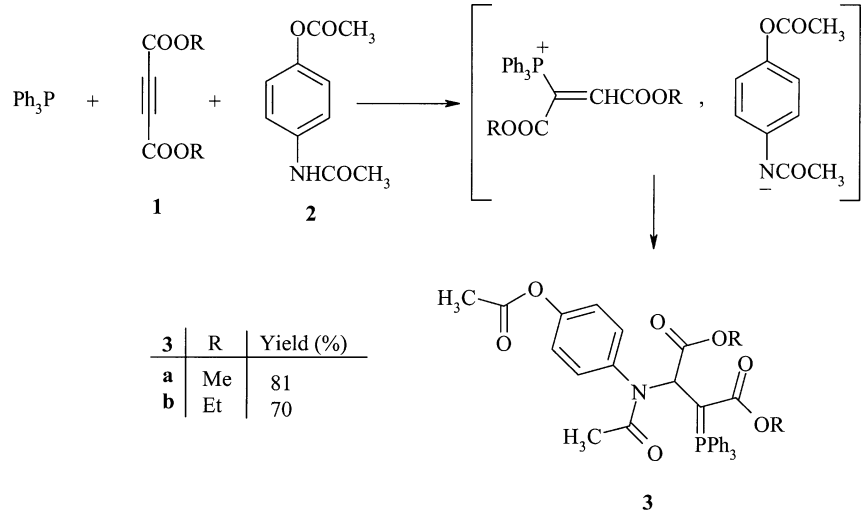
presence of **2** in the mixture of ethyl acetate-hexane (6:1) as a solvent at ambient temperature for 1 h to give acetaminophens **3** containing an ylide moiety in good yields.

RESULTS AND DISCUSSION

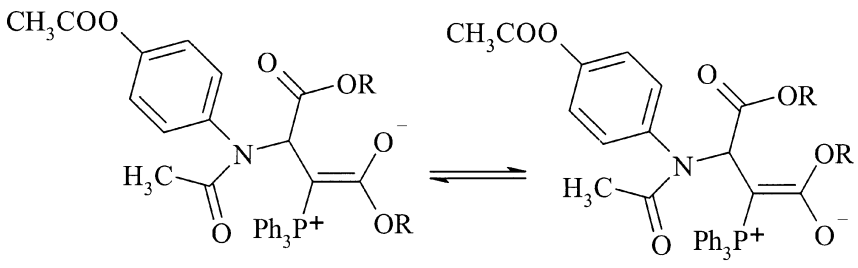
On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[7–10] it is reasonable to assume that compounds **3a–b** are formed by the initial addition of triphenylphosphine to the acetylenic esters with subsequent protonation of the 1:1 adduct by the NH-acid **2**. Then the positively-charged ion is attacked by the nitrogen atom of the conjugated base of the NH-acid to form acetaminophens **3** (Scheme 1).



3	R	Yield (%)
a	Me	81
b	Et	70

SCHEME 1

The structures of compounds **3a–b** were deduced from their high-field of ^{1}H, ^{13}C NMR and IR spectral data. The nature of these compounds as 1:1:1 adducts were apparent from their mass spectra which displayed fairly weak molecular ion peaks at m/z = 597 and 625, respectively. Initial fragmentations involve loss of the complete side chain or partial loss of the side chains and scission of the ring system. The ^{1}H and ^{13}C NMR spectroscopic data for compounds **3a–b** exhibit a mixture of two rotational isomers (Scheme 2). The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in **3-(E)** and **3-(Z)** geometrical isomer, which is low on the NMR time scale at ambient temperature.



3-(Z) **3-(E)**

SCHEME 2

Rotamer forms in ylides have been previously established and reported in the literature.[11–13]

The ^{1}H NMR spectrum of **3a** showed 4 sharp lines ($\delta =$ 2.83, 3.06, 3.72, and 3.80 ppm) due to the methoxy protons, along with signals for methine protons at $\delta = 5.20$ and 5.27 ppm, which appear as two doublets ($^{3}J_{PH} = 18.5$ Hz) and ($^{3}J_{PH} = 20$ Hz), respectively, for the major and minor geometrical isomers. The aromatic region appeared as a multiplet at $\delta = 7.1$–7.7 ppm. The ^{13}C NMR spectrum of **3a** is in agreement with the mixture of two rotamers. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of the compounds **3a–b**, it helps to obtain some valuable information by long range spin–spin coupling constants of ^{31}P with ^{1}H and ^{13}C nuclei.

The ^{1}H and ^{13}C NMR spectroscopic data for compound **3b** are similar to those of **3a**, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts. The structural assignments made for phophoranes **3a–b** on the basis of the ^{1}H and ^{13}C NMR spectra were supported by their IR spectra. The band at 3379 cm^{-1}, which is due to the N—H amide group in acetylated acetaminophen; disappeared in the ylide structures. The carbonyl region of the spectrum exhibited absorption bands for each compound. Of special interest is the ester absorption at 1785–1617 cm^{-1} for these compounds. Conjugation with the negative charge appears to be a plausible factor in the reduction of the wave number of one carbonyl absorption band.

CONCLUSION

It has been shown that the condensation of triphenylphosphine with dialkyl acetylendicarboxylates in the presence of (4-acetylamino) phenyl

acetate efficiently occurs, providing a convenient and rapid synthesis of acetaminophen derivatives containing an ylide moiety.

EXPERIMENTAL

Dialkyl acetylenedicarboxylates and 4-aminophenol were obtained from Merck Chemical Co. and were used without further purification. Acetylated acetaminophen was prepared according to the reported procedure.[14] Melting points were obtained on a Gallenkamp melting point apparatus and were uncorrected. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were reported on a BRUKER DRX-500 AVANCE spectromer at 500 and 125.77 MHz, respectively.

Dimethyl-2-[acetyl-4(acetyloxy)anilino]-3-triphenylphosphoranylidene Succinate 3a

At ambient temperature dimethyl acetylenedicarboxylate (2 mmol, 0.24 mL) was added dropwise to a magnetically stirred solution of triphenylphosphine (2 mmol, 0.53 g) and acetylated acetaminophen (2 mmol, 0.3 g) in a 10-mL mixture of ethyl acetate-hexane (6:1). After the addition was complete (approximately 5 min) the mixture was stirred for 3 h and then filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a white powder. (0.98 g, m.p. 174–176°C, yield 81%); IR (KBr) (υ_{max}, cm^{-1}): 1765; 1666, and 1617 (C=O). MS, m/z (%): 597 (M^+, 3), 278 (27), 277 (70), 262 (100), 183 (97), 77 (27), 43 (62).

Major isomer, **3a**-(Z) (64%), H NMR: δ 1.70 (3H, s, CH_3), 2.30 (3H, s, CH_3,), 3.03 and 3.74 (6H, 2s, $2OCH_3$), 5.27 (1H, d, $^{3}J_{PH}$ 20 Hz), 7.10–7.70 (38H, m, arm)," ^{13}C NMR: δ 21.11 and 23.30 ($2CH_3$), 41.12 (d, $^{1}J_{PC}$ 126.7 Hz, P=C), 49.41, 52.30 ($2OCH_3$), 58.86 (d, $^{2}J_{PC}$ 17.2 Hz, P=C–CH), 120.33 and 121.15 (CH), 137.94 and 150.05 (C), 126.47 (d, $^{1}J_{PC}$ 91.1 Hz, C^{ipso}), 128.82 (d, $^{3}J_{PC}$ 12.1 Hz, C^{meta}), 133.73 (d, $^{4}J_{PC}$ 2.6 Hz, C^{para}), 133.73 (d, $^{2}J_{PC}$ 9.6 Hz, C^{ortho}), 168.96, 169.17, 169.78, 169.87 (4C=O)*, 169.00 (d, $^{2}J_{PC}$ 13.5 Hz, C=O), 170.00 (d, $^{3}J_{PC}$ 12.5 Hz).

Minor isomer, **3a**-(**E**) (36%), ^{1}H NMR: δ 2.32 (3H, s, CH_3), 2.82 (3H, s, CH_3), 3.80. (6H, 2s, $2OCH_3$), 5.19 (1H, d, $^{3}J_{PH}$ 18.5 Hz). ^{13}C NMR: δ 21.11, 23.45 (2 CH^3), 38.57 (d, $^{1}J_{PC}$ 125.4 Hz, P=C), 48.78, 52.37 ($2OCH_3$), 60.12 (d, $^{2}J_{PC}$, 16.5 Hz, P=C–CH), 120.47, 121.67 (CH), 138.40, 149.76 (C), 127.14 (d, $^{1}J_{PC}$ 91 Hz, C^{ipso}), 128.50 (d, $^{3}J_{PC}$ 12.50 Hz,

C^{meta}), 131.94 (d, $^4J_{PC}$ 2.6 Hz, C^{para}), 133.58 (d, $^2J_{PC}$ 9.6 Hz, C^{ortho}), 168.60 (d, ^{2}Jpc 13.5 Hz, C=O), 173.19 (d, $^3J_{PC}$ 13.00 Hz, C=O).

Diethyl-2-[acetyl-4-(acetyloxy)anilino]-3-triphenylphosphoranylidine Succinate 3b

(0.87 g, m.p. 180–181°C, yield 70%); IR (KBr) (υ_{max}, cm^{-1}): 1756, 1645 and 1617 (C=O). MS, m/z (%): 625 M^+, 2), 278 (26), 277 (80), 262 (100), 183 (98), 77 (26), 43 (62).

Major isomer, **3b**-(E) (53.6%), ^{1}H NMR: δ 0.31 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_3), 1.34 (3H, t, $^3J_{HH}$ 6.6 Hz, CH_3), 3.30–3.70 (4H, m, $2CH_2$), 5.20 (1H, d, $^3J_{PH}$ 18.9 Hz, P=C–CH), 7.45–7.71 (38 H, m, arom)*, ^{13}C NMR: δ 13.78 and 14.26 (2 CH_3), 38.43 (d, $^1J_{PC}$ 125 Hz, P=C), 57.85 and 61.20 (2 OCH_2), 120.17, 120.45, 121.20, and 121.30 (CH)*, 127.30 (d, $^1J_{PC}$ 91.37 Hz, C^{ipso}), 128.40 (d, $^3J_{PC}$ 11.7 Hz, C^{meta}), 131.90 (C^{para}) 132.28 (CH), 133.55 (d, $^3J_{PC}$ 8.9 Hz, C^{ortho}), 137.89, 138.35, 149.67, 149.96 (C)*, 167.95 (d, $^2J_{PC}$ 13.2 Hz, C=O), 168.86, 169.04, 169.70 and 169.92 (4C=O)*, 172.37 (d, $^3J_{PG}$ 12.1 Hz, C=O).

Minor isomer, **3b**-(Z) (46.4%) ^{1}H NMR: δ 0.90 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_3), 1.7 (3H, t, $^3J_{H,H}$ 6.6 Hz, CH_3) 2.32 (3H, s, CH_3)*, 2.37 (3H, s, CH_3)*, 4.9–4.37 (4H, m, $2CH_2$)*, 5.31 (1H, d, $^3J_{PH}$ 19 Hz, P=C–H), ^{13}C NMR: δ 14.14 and 14.38 ($2CH_3$), 40.88 (d, $^1J_{PC}$ 33 Hz, P=C), 57.34 and 60.80 (2 OCH_2), 126.5 (d, $^1J_{PC}$ 79.5 Hz, C^{ipso}), 128.61 (d, $^3J_{PC}$ 11.2 Hz, C^{meta}), 132.0 (C^{para}), 133.65 (d, $^3J_{PC}$ 8.87 Hz, C^{ortho}), 169.65 (d, $^2J_{PC}$ 13.7 Hz, C=O), 172.16 (d, $^3J_{PC}$ 12.2 Hz, C=O).

REFERENCES

[1] J. H. Jeong, Y. S. Byoun, and Y. S. Lee, *Reactive and Functional Polymer*, **50,** 257 (2002).

[2] T. Gowiak, S. Debrus, M. May, A. J. Barners, and H. J. Ratajczake, *Molecular Structure*, **77,** 596 (2001).

[3] L. F. Preascott, *A Critical Biblographic Review*. London, Taylor & Francis (1996).

[4] M. R. Islami, Z. Hassani, H. Sheibani, B. Abdolahzadeh, and N. Etminan, *Tetrahedron*, **59,** 4993 (2003).

[5] M. R. Islami, Z. Hassani, and K. Saidi, *Synth. Comm*., **33,** 65 (2003).

[6] M. R. Islami, Z. Hassani, and H. Sheibani, *Phosphorus, Sulfur, and Silicon*, **177,** 2547 (2002).

[7] B. E. Maryano and A. B. Reitz, *Chem. Rev*., **89,** 863 (1989).

[8] H. J. Bestmann and O. Vostrowsky, *Topics Curr. Chem*., **109,** 86 (1983).

[9] E. Zbiral, *Synthesis*, 775 (1974).

[10] K. B. Becker, *Tetrahedron*, **36,** 1717 (1980).

*For two rotamers.

[11] H. J. Bestmann and J. P. Snyder, *J. Am. Chem. Soc*., **89,** 3963 (1967).
[12] D. L. Hooper and S. Garagan, *J. Org. Chem*. **59,** 1126 (1994).
[13] H. J. Bestmann, G. Joachim, T. Lengyel, J. F. Oth, R. Merenyi, and H. Weitkamp, *Tetrahedron. Lett*., 3355 (1966).
[14] R. Kent and S. M. McElvain, *Org. Synth. Coll III*. New York: Wiley and Sons (1955).