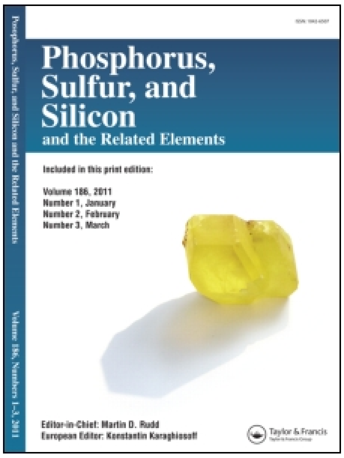

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Simple Synthesis of Stable Phosphorus Ylides Derived from Imidazolidine-2-Thione. Efficient One-Pot Synthesis of α-Amino Esters with β-Phosphorus Substituents

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Simple Synthesis of Stable Phosphorus Ylides Derived from Imidazolidine-2-Thione. Efficient One-Pot Synthesis of α-Amino Esters with β-Phosphorus Substituents

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Crystalline phosphorus ylides are obtained in nearly quantitative yields from the addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates, and imidazolidine-2-thione. A dynamic NMR effect is observed in the ^1H NMR spectrum of the stabilized ylide obtained from dimethyl acetylenedicarboxylate ($\Delta G^{\neq} = 66.6$ kJmol^{-1}) and is attributed to restricted rotation around the carbon–carbon partial double bond resulting from the conjugation of the ylide moiety with the adjacent carbonyl group.

Keywords Acetylenic esters; amino esters; imidazolidine-2-thione; stable phosphorus ylides; triphenylphosphine

INTRODUCTION

Phosphorus ylides are reactive intermediates, which take part in many valuable reactions in organic synthesis.[1–12] Several methods have been developed for the preparation of phosphorus ylides. These ylides usually are prepared by the treatment of a phosphonium salt with a

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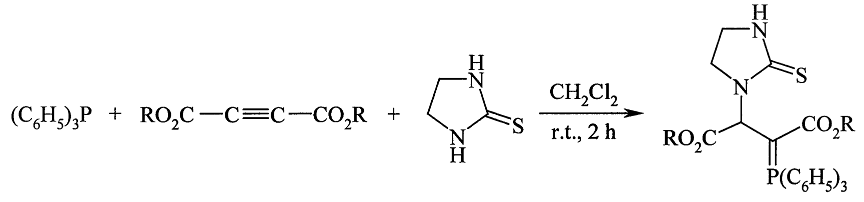
base, and phosphonium salts usually are prepared from the phosphine and an alkyl halide.[1–3] Phosphonium salts also are prepared by the Michael addition of phosphorus nucleophiles to activated olefins among other methods.[1] We report here an efficient synthetic route to phosphorus ylides using triphenylphosphine, dialkyl acetylenedicarboxylates, and imidazolidine-2-thione. Thus, reaction of triphenylphosphine with dialkyl acetylenedicarboxylates **1** in the presence of imidazolidine-2-thione **2** leads to the corresponding stable sulfur-containing phosphorus ylides **3** in nearly quantitative yields (Scheme 1).



1 **2** **3**

1, 3	R	% Yield of **3**
a	CH_3	99
b	CH_2CH_3	98
c	$CH(CH_3)_2$	98
d	$C(CH_3)_3$	96

SCHEME 1

RESULTS AND DISCUSSION

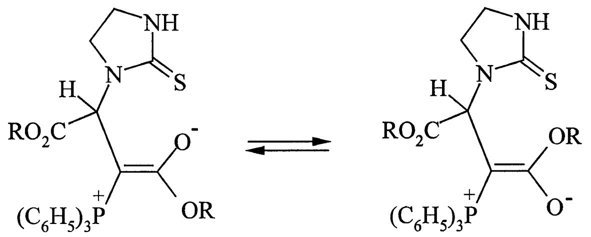
The reaction of triphenylphosphine with dialkyl acetylenedicarboxylates in the presence of imidazolidine-2-thione proceeded spontaneously at room temperature in dichloromethane, and was finished within 2 h. ^1H and ^{13}C NMR spectra of the crude product clearly indicated the formation of phosphorane **3**. Any product other than **3** could not be detected by NMR spectroscopy.

The structures of compounds **3a–d** were deduced from their elemental analyses and their high-field ^1H, ^{13}C, ^{31}P NMR, and IR spectral data. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed molecular ion peaks at m/z = 506, 534, 562, and 590, respectively. Initial fragmentations involve loss from or complete loss of the side chains and a scission of the heterocyclic ring system.

The ^1H, ^{13}C, and ^{31}P NMR spectra of ylides **3a–d** are consistent with the presence of two isomers. Selected ^1H, ^{13}C, and ^{31}P NMR chemical shifts and coupling constants in the major (M) and minor (m) geometrical isomers of compounds **3a–d** are shown in Table I. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and the rotation about the partial double bond in **3**-(*E*) and **3**-(*Z*) geometrical isomers is slow on the NMR timescale at ambient temperature.

The most noteworthy feature of the ^1H NMR spectrum of **3a** in $CDCl_3$ at room temperature (25°C) is the methoxy region, which exhibits two singlets ($\delta = 3.73$ and 3.76 ppm) for the CO_2CH_3 groups of (*E*)-**3a** and (*Z*)-**3a** and two singlets ($\delta = 3.08$ and 3.51) for the methoxy groups. Near 5°C, the fairly sharp lines become sharper. The ^1H NMR spectrum of **3a** was examined in 1,2-dichlorobenzene. at 5°C, the spectrum is

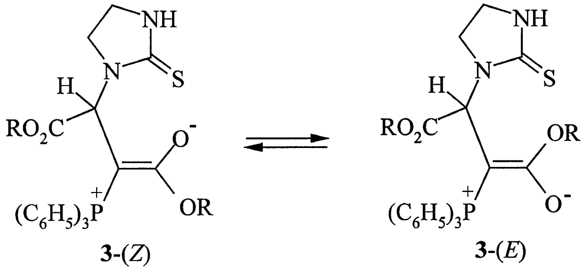
TABLE I Selected ^1H, ^{13}C, and ^{31}P NMR Chemical Shifts (δ in ppm) and Coupling Constants (*J* in Hz) for H-2, CO_2R, COR, C-2, C-3, and P in the Major (M) and Minor (m) Geometrical Isomers of Compounds 3a–d



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

Compound	Isomer (%)	^1H NMR spectroscopic data			^{13}C NMR spectroscopic data		
		H-2 ($^3J_{PH}$)	OR	CO_2R	C-2 ($^2J_{PC}$)	C-3 ($^1J_{PC}$)	^{31}P
3a	M (69.7)	5.20 (17.5)	3.08	3.76	58.79 (17.6)	40.20 (127.5)	24.36
	m (30.3)	5.24 (19.0)	3.51	3.73	58.18 (17.2)	41.15 (135.1)	24.85
3b	M (70.9)	5.14 (17.7)	0.41[a]	1.28[a]	58.69 (17.7)	40.44 (125.8)	24.29
	m (29.1)	5.18 (18.9)	1.12[a]	1.29[a]	58.05 (18.9)	40.67 (135.1)	24.92
3c	M (78.1)	5.05 (17.9)	0.51, 0.70[a]	1.20, 1.27[a]	59.19 (17.6)	39.99 (126.0)	23.86
	m (21.9)	5.26 (18.3)	1.14, 1.19[a]	1.25, 1.29[a]	58.75 (18.2)	40.51 (136.0)	24.73
3d	M (89.2)	4.93 (18.0)	0.91[a]	1.51[a]	59.18 (17.6)	39.91 (127.5)	23.92
	m (10.8)	4.95 (20.5)	1.38[a]	1.52[a]	—	—	25.48

[a] The methyl group(s) of the OR moiety.



SCHEME 2

similar to that in $CDCl_3$. Increasing the temperature results in the coalescence of the methoxy resonances ($T_c = 47 \pm 1°C$). At 90°C, a fairly broad singlet was observed, while the CO_2CH_3 protons appear as a sharp single resonance.

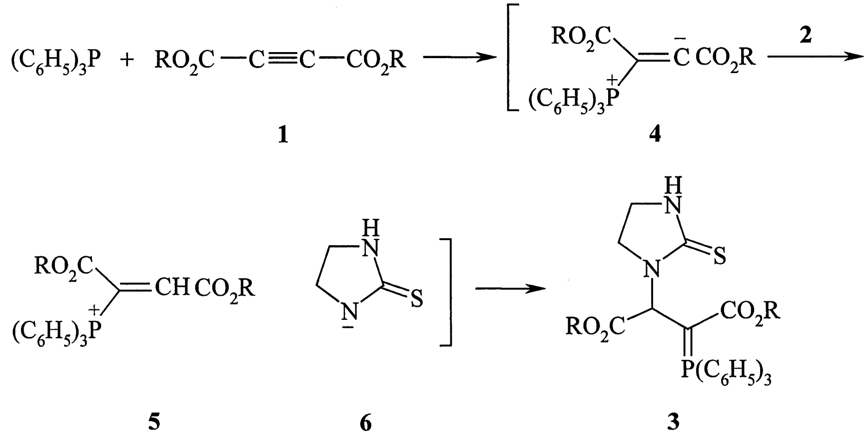
Although an extensive line-shape analysis in relation to the dynamic ^1H NMR effect observed for **3a** was not undertaken, the variable temperature spectra was allowed to calculate the free energy barrier (if not the enthalpy and entropy of activation) for the dynamic NMR process in **3a**. From the coalescence of the methoxy proton resonances and using the expression, $k = \pi \Delta\nu/\sqrt{2}$, we calculate that the first-order rate constant (k) for the dynamic NMR effect in **3a** is 85.8 s^{-1} at 320 K (see Table II). Application of the absolute rate theory with a transmission coefficient of 1 gives a free energy of activation ($\Delta G^{\neq}$) of 66.6 ± 2 $kJmol^{-1}$, where all known sources of errors are estimated and included.[13] The experimental data that are available are not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ are not large.[14]

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[1–12] it is reasonable to assume that the phosphorus ylide **3** results from the initial addition of triphenylphosphine to the acetylenic ester and the subsequent protonation of the 1:1 adduct **4** by the NH-acid **2**. Then the positively charged ion **5** is attacked by the

TABLE II Selected Proton Chemical Shifts (at 89.5 MHz, in ppm, Me_4Si) and Activation Parameters ($kJmol^{-1}$) for 3a in 1,2-Dichlorobenzene

Compound	Temp (°C)	Resonance (OCH_3)		$\Delta\nu$ (Hz)	k (s^{-1})	T_c (K)	ΔG*
3a	5	3.08	3.51	38.6	85.8	320	66.6 ± 2
	90	3.42					

sulfur atom of the conjugate base of the NH-acid **6** to form phosphorane **3** (Scheme 3).



SCHEME 3

The functionalized phosphorus ylides **3a–d** may be considered as potentially useful synthetic intermediates.[1,2] The obtained aminoesters are protected α-aminoacids with β-phosphorus substituents. The procedure discribed here may be an acceptable method for the preparation of phosphoranes with variable functionalities. The one-pot nature of the present procedure makes it an interesting alternative to multistep appoaches.[1–8]

EXPERIMENTAL

Imidazolidine-2-thione, dialkyl acetylenedicarboxylates, and triphenylphosphine were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Diisopropyl acetylenedicarboxylate was prepared by a known method.[15] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1, 125.8, and 202.5 MHz, respectively. Dynamic NMR studies were carried out using a JEOL-EX 90 Fourier transform spectrometer at 89.5 MHz. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

Preparation of Dimethyl 2-(2-thioxoimidazolidin-1-yl)-3-(triphenylphosphoranylidene)butanedioate 3a

General Procedure

To a magnetically stirred solution, triphenylphosphine (0.262 g, 1 mmol) and imidazolidine-2-thione **2** (0.102 g, 1 mmol) in dichloromethane (6 mL) was added dropwise to a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in dichloromethane (2 mL) at −5°C for 10 min. The reaction mixture then was allowed to warm up to room temperature and was stirred for 2 h. The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate. The product **3a** was obtained as colorless crystals, m.p. 139–141°C (dec), yield 1.00 g, 99%. IR (KBr) (υ_{max}/cm^{-1}): 3419 (NH), 1745 and 1631 (C=O), 1433, 1305, 1263, 1184, 1105, 690, 551, 518. MS, *m/z* (%): 506 (M$^+$, 13), 493 (20), 406 (11), 262 (99), 183 (98), 102 (100), 72 (28). Anal. Calcd. for $C_{27}H_{27}N_2O_4PS$ (506.56): C, 64.02; H, 5.37; N, 5.53. Found: C, 63.9; H, 5.4; N, 5.5%.

Diethyl 2-(2-thioxoimidazolidin-1-yl)-3-(riphenylphosphoranylidene)butanedioate ***(3b)****.* Colorless crystals, m.p. 145–147°C (dec), yield 1.05 g, 98%. IR (KBr) (υ_{max}/cm^{-1}): 3425 (NH), 1741 and 1631 (C=O), 1481, 1435, 1365, 1298, 1263, 1186, 1105, 1033, 752, 690, 553, 514. MS, *m/z* (%): 534 (M$^+$, 12), 494 (4), 277 (44), 183 (13), 102 (100). Anal. Calcd. for $C_{29}H_{31}N_2O_4PS$ (534.62): C, 65:15; H, 5.84; N, 5.24. Found: C, 65.2; H, 5.8; N, 5.2%.

Di-iso-propyl 2-(2-thioxoimidazolidin-1-yl)-3-(triphenylphosphoranylidene)butanedioate ***(3c)****.* Colorless crystals, m.p. 156–159°C (dec), yield 1.10 g, 98%. IR (KBr) (υ_{max}/cm^{-1}): 3422 (NH), 1740 and 1634 (C=O), 1434, 1303, 1263, 1186, 1108, 690, 554, 518. MS, *m/z* (%): 562 (M$^+$, 35), 262 (70), 183 (100), 102 (75), 78 (41). Anal. Calcd. for $C_{31}H_{35}N_2O_4PS$ (562.67): C, 66.17; H, 6.27; N, 4.98. Found: C, 66.3; H, 6.3; N, 5.0%.

Di-tert-butyl 2-(2-thioxoimidazolidin-1-yl)-3-(triphenylphosphoranylidene)butanedioate ***(3d)****.* colorless crystals, m.p. 175–177°C, yield 1.13 g, 96%. IR (KBr) (υ_{max}/cm^{-1}): 3420 (NH), 1737 and 1635 (C=O), 1477, 1436, 1315, 1263, 1155, 1109, 752, 690, 555, 518. MS, *m/z* (%): 590 (M$^+$, 49), 262 (76), 183 (100), 102 (86), 78 (8). Anal. Calcd. for $C_{33}H_{39}N_2O_4PS$ (590.72): C, 67.10; H, 6.65; N, 4.74. Found: C, 67.2; H, 6.6; N, 4.7%.

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