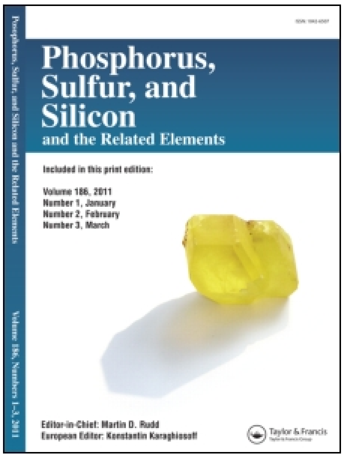

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A Simple Synthesis of Stable Phosphorus Ylides from Indole and Some of Its Derivatives

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To cite this Article Maghsoodlou, Malek Taher , Hazeri, Nourollah , Khorasani, Sayyed Mostafa Habibi , Shahzadeh, Aqil Ghulame and Nassiri, Mahmoud(2006) 'A Simple Synthesis of Stable Phosphorus Ylides from Indole and Some of Its Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 4, 913 — 919

To link to this Article: DOI: 10.1080/10426500500272160

URL: http://dx.doi.org/10.1080/10426500500272160

Phosphorus, Sulfur, and Silicon, 181:913–919, 2006
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500272160

A Simple Synthesis of Stable Phosphorus Ylides from Indole and Some of Its Derivatives

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Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of strong NH acids, such as indole and 2-methyl indole, 3-methyl indole, and 5-boromo indole. These stable ylides exist in a solution as a mixture of two geometrical isomers as a result of the restricted rotation around the carbon–carbon partial double bond resulting from the conjugation of the ylide moiety with the adjacent carbonyl group.

Keywords Acetylenic ester; NH acids; restricted rotation; stable phosphorus ylide; triphenylphosphine

INTRODUCTION

Phosphorus ylides are reactive systems, which take part in many valuable reactions of organic synthesis.[1–11] These ylides are most often prepared by the treatment of a phosphonium salt with a base, and phosphonium salts are usually made from a phosphine and an alkyl halide.[1–5] Phosphonium salts also are obtained by a Michael addition of phosphorus nucleophiles to activated olefins, among other methods.[1,2] We wish to describe here an efficient synthetic route to indole-containing stable phosphorus ylides. The indole moiety and its derivatives are widely used in making perfumes, agrochemicals, and medicines.[12,13] Thus, the reaction of triphenylphosphine with dialkylacetylenedicarboxylates **1**

Received February 1, 2005; accepted April 12, 2005.

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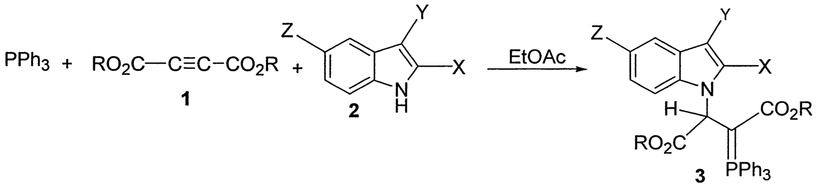
in the presence of strong NH acids **2** leads to the corresponding stable heterocyclic phosphorus ylides **3** in excellent yields (see Scheme 1).



1	**R**
a	Me
b	Et
c	^{t}Bu

2	**X**	**Y**	**Z**
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Br

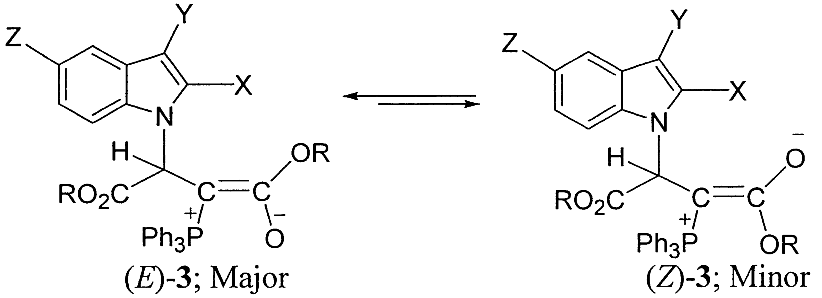
3	**1**	**2**	**% Yield**
a	a	a	97
b	b	a	95
c	c	a	97
d	a	b	98
e	b	b	97
f	c	b	98
g	a	c	95
h	b	c	93
i	c	c	96
j	a	d	96
k	b	d	95
l	c	d	97

SCHEME 1

RESULTS AND DISCUSSION

The reaction of indole, 2-methyl indole, 3-methyl indole, and 5-boromo indole with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine proceeded at r.t. in ethyl acetate and was finished within a few hours. The H and ^{13}C NMR spectra of the crude product clearly indicated the formation of stable phosphorus ylides **3**. Any product other than **3** could not be detected by NMR spectroscopy. The structures of compounds **3a–l** were deducted from their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The mass spectra of these stable ylides displayed molecular ion peaks at appropriate m/z values. Any initial fragmentation involved the loss of the side chains and a scission of the heterocyclic ring system.

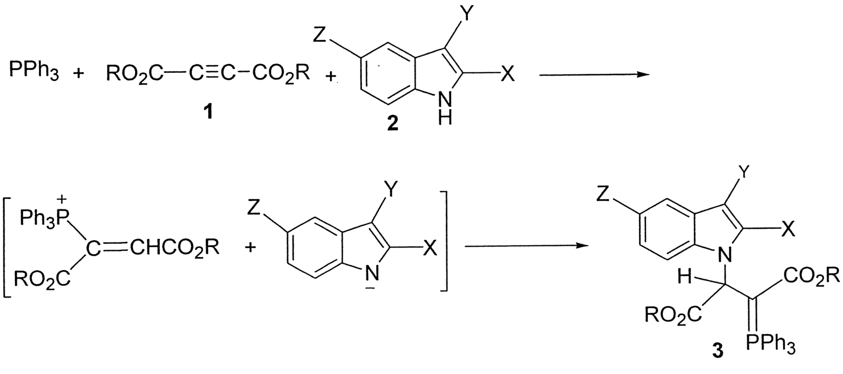
The ^{1}H, ^{13}C, and ^{31}P NMR spectra of ylides **3a–l** are consistent with the presence of two isomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group, and the rotation about the partial double bond in (*E*)-**3** and (*Z*)-**3** geometrical isomers (see Scheme 2) is slow on the NMR timescale at an ambient temperature. Selected ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts and



SCHEME 2

coupling constants in the major (M) and minor (m) geometrical isomers of compounds **3a–l** are shown in Table I. Only one geometrical isomer was observed for the di-*tert*-butyl derivatives of **3** presumably because of the bulky *tert*-butyl groups.

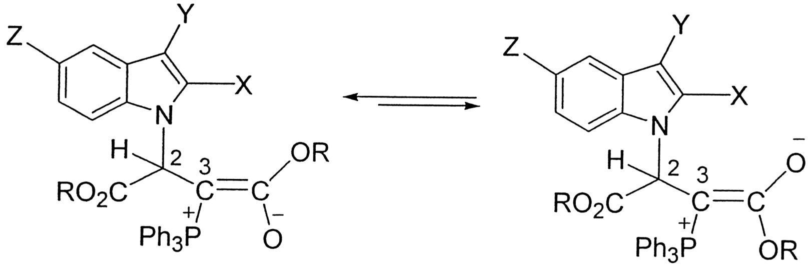
On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[1–5] it is reasonable to assume that the phosphorus ylide **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the N-H acid to form phosphoranes **3** (see Scheme 3).



SCHEME 3

In summary, we have prepared novel indole-containing phosphorus ylides via a one-pot reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of strong NH acids such as indole, 2-methyl indole, 3-methyl indole, and 5-boromo indole. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. Indole-containing phosphorus ylides **3a–l** may be considered potentially useful

TABLE I Selected ^{1}H, ^{13}C, and ^{31}P NMR Chemical Shifts (δ in ppm) and Coupling Constants (J in Hz) for H-2, OR, CO$_2$R, C-2, and C-3 in the Major (M) and Minor (m) Diastereoisomers of Compounds 3a–l



(*E*)-**3**; Major (Z)-**3**; Minor

Compound	Isomer (%)	^{1}H NMR spectroscopic data			^{13}C NMR data		^{31}P NMR
		H-2 ($^3J_{PH}$)	OR	CO$_2$R	C-2 ($^2J_{PC}$)	C-3 ($^1J_{PC}$)	
3a	M(52)	4.98(16.3)	3.29	3.72	53.37(15.5)	38.98(126.6)	24.09
3a	m(48)	5.02(17.7)	3.56	3.72	52.98(14.6)	39.35(135.0)	24.78
3b	M(55)	4.92(16.7)	3.83	4.17	58.11(16.0)	43.46(126.6)	24.06
3b	m(45)	4.97(15.3)	3.82	4.26	57.66(15.8)	43.98(135.6)	24.86
3c	M	4.77(17.4)	1.06	1.56	58.41(16.1)	43.03(127.6)	23.63
3d	M(57)	5.12(19.1)	3.26	3.78	58.66(16.0)	41.76(122.9)	25.27
3d	m(43)	5.18(16.8)	3.73	3.76	58.54(17.7)	42.80(131.7)	24.70
3e	M(60)	5.06(19.8)	3.77	4.22	57.90(12.0)	41.38(125.3)	25.50
3e	m(40)	5.13(16.3)	3.92	4.25	57.40(15.7)	42.43(134.3)	24.62
3f	M	4.80(br)	1.04	1.57	59.19(13.9)	40.50(123.9)	24.04
3g	M(59)	4.91(16.5)	2.38	3.71	57.86(15.8)	43.83(126.5)	24.27
3g	M(41)	4.96(17.7)	3.27	3.71	57.44(15.3)	44.24(135.2)	24.70
3h	M(56)	4.93(17.1)	3.16	3.82	57.90(12.0)	43.51(126.3)	25.50
3h	m(44)	5.08(17.5)	3.87	4.26	57.40(15.7)	44.17(135.8)	24.62
3i	M	4.77(17.4)	1.09	1.58	58.18(16.0)	43.06(127.4)	23.75
3j	M(60)	4.91(16.3)	3.27	3.72	58.45(15.6)	43.55(126.7)	23.96
3j	m(40)	4.93(17.7)	3.69	3.72	58.04(15.7)	43.87(135.2)	24.75
3k	M(70)	4.83(16.4)	3.84	4.17	58.60(12.8)	43.29(126.8)	23.94
3k	m(30)	4.89(16.7)	4.18	4.27	58.40(12.9)	43.77(135.3)	24.83
3l	M	4.66(17.2)	1.01	1.51	58.81(16.3)	42.90(127.9)	23.51

synthetic intermediates. The procedure described here may be an acceptable method for the preparation of phosphoranes with variable functionalities.

EXPERIMENTAL

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively.

^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a Bruker DRX-500 Avence instrument with $CDCl_3$ as solvent at 500.1, 125.8, and 202.4 MHZ, respectively. The mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine, dialkyl acetylenedicarboxylates **1a–c**, and indole **2a–d** were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

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

General Procedure

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol) and indole (0.12 g, 1 mmol) in ethyl acetate (10 mL) a mixture of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) was added dropwise in ethyl acetate (4 mL) at −5°C for 10 min. After 8 h of stirring at r.t., the product was filtered and recrystallized from ethyl acetate. Colorless crystals, m.p. 198–200°C, yield 0.50 g, 97%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1744, 1618 (C=O). MS (m/z %): 521 (M^+, 3), 462 ($M{-}CO_2Me$, 10), 405 (M-heterocyclic, 100), 262 (PPh_3, 55), 183 (PPh_2, 95), 108 (PPh, 43), 77 (Ph, 20), 59 (CO_2Me, 24).

Diethyl 2-(Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3b)

Colorless crystals, m.p. 134–136°C, yield 0.52 g, 95%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1740, 1629 (C=O).

Di-Tert-Buthyl 2-(Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3c)

Colorless crystals, m.p. 158–160°C, yield 0.58 g, 97%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1738, 1634 (C=O)

Dimethyl 2-(2-Methyle Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3d)

Colorless crystals, m.p. 102–104°C, yield 0.52 g, 98%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1740, 1647 (C=O). MS (m/z, %): 535 (M^+, 2), 405 (M-heterocyclic, 30), 348 (M-CO2Me, 15), 262 (PPh_3, 70), 183 (PPh_2, 100), 108 (PPh, 19), 77 (Ph, 35), 59 (CO_2Me, 17).

Diethyl 2-(2-Methyle Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3e)

Colorless crystals, m.p. 114–116°C, yield 0.54 g, 97%. IR (KBr) (ν_{max}, cm^{-1}): 1740, 1638 (C=O).

Di-Tert-Butyl 2-(2-methyle Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3f)

Colorless crystals, m.p. 188–190°C, yield 0.60 g, 98%. IR (KBr) (ν_{max}, cm^{-1}): 1737, 1640 (C=O).

Dimethyl 2-(3-Methyl Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3g)

Colorless crystals, m.p. 146–148°C, yield 0.51 g, 95%. IR (KBr) (ν_{max}, cm^{-1}): 1747, 1636 (C=O). MS (m/z, %): 535 (M^+, 2), 405 (M-heterocyclic, 30), 348 (M-CO_2Me, 1.5), 262 (PPh_3, 70), 183 (PPh_2, 100), 108 (PPh, 19), 77 (Ph, 35), 59(CO_2Me, 17).

Diethyl 2-(3-Methyl Indole-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (3h)

Colorless crystals, m.p. 171–173°C, yield 0.52 g, 93%. IR (KBr) (ν_{max}, cm^{-1}): 1745, 1721, 1623 (C=O).

Di-Tert-Butyl 2-(3-Methyl Indole 1-yl)-3-(triphenylphosphoranylidene)-butandioate (3i)

Colorless crystals, m.p. 202–204°C, yield 0.59 g, 96%. IR (KBr) (ν_{max}, cm^{-1}): 1731, 1631 (C=O).

$^3J_{PC} = 12.5$ HZ, C=O), 170.88 (d, $^2J_{PC} = 13.6$ Hz, P—C=*C*). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 23.75 (Ph_3P^+-C).

Dimethyl 2-(5-Boromo Indole-1-yl)-3-(triphenylphosphoranylidene)-butandioate (3j)

Colorless crystals, m.p. 187–189°C, yield 0.57 g, 96%. IR (KBr) (ν_{max}, cm^{-1}): 1748, 1725, 1634 (C=O). MS (m/z, %): 600 (M^+, 3), 462 (M-CO_2Me, 10), 405 (M-heterocyclic, 90), 262 (PPh_3, 55), 183 (PPh_2, 93), 108 (Ph, 48), 77 (Ph, 35), 59 (CO_2Me, 25).

Diethyl 2-(5-Boromo Indole-1-yl)-3-(triphenylphosphoranylidene)-butandioate (3k)

Colorless crystals, m.p. 91–93°C, yield 0.59 g, 95%. IR (KBr) (ν_{max}, cm^{-1}): 1734, 1624 (C=O).

Di-Tert-Buthyl 2-(5-Boromo Indole 1-yl)-3-(triphenylphosphoranylidene)-butandioate (3l)

Colorless crystals, m.p. 183–185°C, yield 0.66 g, 97%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1733, 1631 (C=O).

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