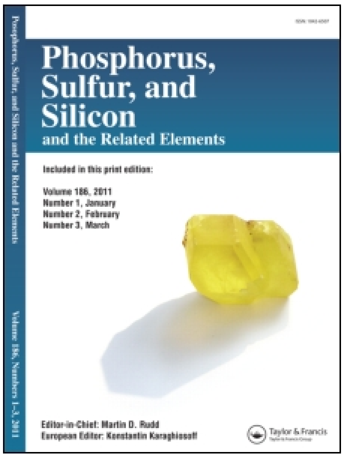

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A Simple Synthesis of Stable Phosphoranes Derived from Imidazole Derivatives

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A Simple Synthesis of Stable Phosphoranes Derived from Imidazole 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 imidazole, 2-methylimidazole, 4-methylimidazole, 2-ethylimidazole, benzimidazole, and 5,6-dimethylbezimidazole. These stable ylides exist in solution as a mixture of two geometrical isomers as a result of 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; stable phosphorus ylides; triphenylphosphine

INTRODUCTION

Phosphorus ylides are reactive systems, which take part in many valuable reactions of organic synthesis.[1–11] These are most often prepared by the treatment of a phosphonium salt with a base. Most of the phosphonium salts are usually made from the phosphine and an alkyl halide,[1–5] and they are also obtained by a Michael addition of phosphorus nucleophiles to activated olefins.[1,2] Here we wish to describe an efficient synthetic route of stable phosphorus ylides using triphenylphosphine, dialkyl acetylenedicarl boxylates, and strong NH acids such as imidazole, 2-methylimidazole, 4-methyl-imidazole, 2-ethylimidazole, benzimidazole, and 5,6-dimethylbezimidazole. As noted earlier, the imidazole moiety and its derivatives are widely used in making medicines,

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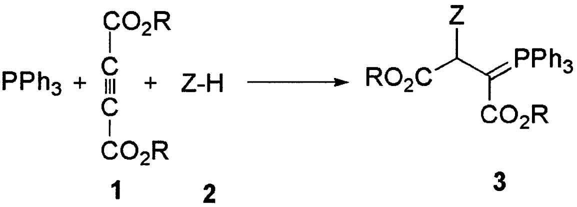
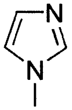
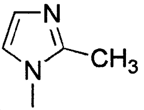
and they also have biological activity.[12] With respect to the importance of the mentioned purpose, the present work was undertaken for the generation of stable phosphoranes and the reaction of triphenylphosphine with dialkyl acetylenedicarboxylates **1** in the presence of a strong NH acid **2** which leads to the corresponding stable heterocyclic phosphorus ylide **3** in excellent yields (see Scheme 1).



3	Z	R	%Yield
a		Me	94
b		Et	91
c		Bu^t	95
d		Me	96
e		Et	94
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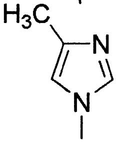
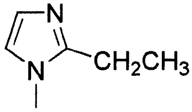
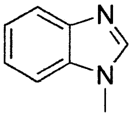
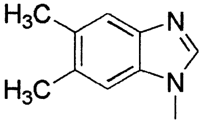
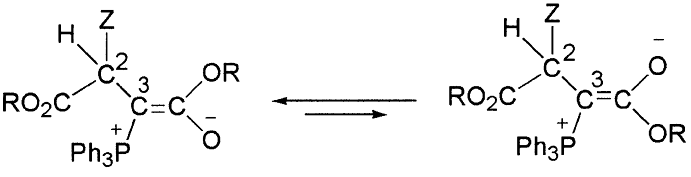
g		Bu^t	96
h		Me	95
i		Et	93
j		Bu^t	96
k		Me	94
l		Et	92
m		Bu^t	95
n		Me	94
o		Bu^t	95

SCHEME 1

RESULTS AND DISCUSSION

The reaction of imidazole and some of its derivatives with dialkyl acetylene-dicarboxylates **1** in the presence of triphenylphosphine proceeded in ethyl acetate as solvent at r.t. and it was finished within a few hours. The ^{1}H and ^{13}C NMR spectrum 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–o** were deduced from their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectrum. The mass spectrum of them displayed molecular ion peaks at appropriate m/z values. Any initial fragmentations involved the missing parts or complete loss of the side chains and a scission of the heterocyclic ring system. The ^{1}H, ^{13}C, and ^{31}P NMR spectrum of ylides **3a–o** were consistent with the presence of two isomers. The ylide moiety of these compounds was strongly conjugated with the adjacent carbonyl group, and the rotation around the partial double bond in (*E*)-**3** and (*Z*)-**3** geometrical isomers was slow on the NMR time scale at ambient temperature (see Scheme 2). Selected ^{1}H, ^{13} C, and ^{31}P NMR chemical shifts and coupling constants in the major (M) and minor (m) geometrical isomers of compounds **3a–o** are shown in Table I.

As can be seen, only one geometrical isomer was observed for the di-tert-butyl derivative of **3**, presumably, because of the bulky tert-butyl groups.


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

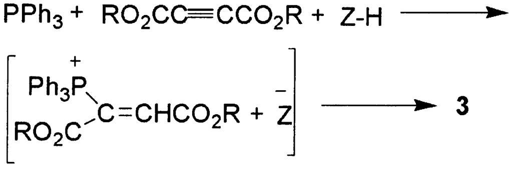
SCHEME 2

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

Briefly, we have prepared novel imidazole-containing phosphorus ylides using a one-pot reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of strong NH-acids such as imidazole, 2-methylimidazole, 4-methylimidazole, 2-ethylimidazole, benzimidazole, and 5,6-dimethylbezimidazole. The present method carries the advantage that not only the reaction is performed under neutral

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_2R, C-2, and C-3, in the Major (M) and Minor (m) Diastereoisomers of Compounds 3a–o

	Isomer	^{1}H NMR spectroscopy data			^{13}C NMR data		
Compound	(%)	H-2 ($^{3}J_{PH}$)	OR	CO_2R	C-2 ($^{2}J_{PC}$)	C-3 ($^{1}J_{PC}$)	^{31}P NMR
3a	M (67)	4.54 (15.7)	3.17	3.75	60.32 (15.7)	43.93 (129.6)	24.12
3a	m (33)	4.60 (17.4)	3.64	3.73	50.66 (14.9)	44.02 (133.8)	24.93
3b	M (58)	4.50 (16.4)	3.72	4.23	64.98 (15.6)	43.70 (124.8)	23.26
3b	m (42)	4.54 (18.4)	4.06	4.15	64.33 (15.8)	43.97 (136.9)	25.02
3c	M	4.32 (16.2)	0.95	1.52	60.55 (15.1)	43.55 (129.1)	23.81
3d	M (66)	4.47 (16.2)	3.19	3.74	58.91 (13.7)	42.47 (127.8)	23.55
3d	m (34)	4.50 (17.7)	3.62	3.73	58.33 (15.1)	43.02 (135.6)	24.37
3e	M (57)	4.44 (16.5)	3.74	4.12	58.97 (15.6)	42.37 (128.1)	23.50
3e	m (43)	4.45 (20.8)	4.04	4.16	58.33 (16.2)	43.03 (136.7)	24.42
3f	M	4.27 (17.1)	0.97	1.52	59.32 (16.9)	42.16 (128.9)	23.06
3g	M	4.24 (16.4)	0.95	1.53	60.61 (15.8)	43.39 (129.1)	22.94
3h	M (68)	4.53 (15.5)	3.16	3.71	58.65 (16.0)	42.93 (128.2)	23.51
3h	m (32)	4.56 (14.5)	3.58	3.77	58.01 (15.9)	43.44 (136.8)	24.27
3i	M (72)	4.48 (16.5)	3.75	4.09	61.58 (12.9)	42.72 (128.2)	23.43
3i	m (28)	4.48 (16.5)	4.05	4.18	61.32 (11.5)	43.32 (136.0)	24.31
3j	M	4.32 (17.0)	0.98	1.51	58.96 (17.0)	42.49 (129.0)	23.05
3k	M (69)	4.89 (16.5)	3.24	3.70	58.09 (16.1)	43.54 (127.4)	23.65
3k	m (31)	4.88 (16.7)	3.66	3.69	57.64 (15.4)	43.66 (136.9)	24.64
3l	M (55)	4.86 (16.1)	4.07	4.22	58.06 (16.1)	43.38 (127.4)	23.60
3l	m(45)	4.84(16.8)	3.75	3.82	57.59(15.6)	43.56(136.3)	24.71
3m	M	4.68(17.0)	0.98	1.51	58.55(17.0)	43.72(132.0)	23.30
3n	M(71)	4.85(16.1)	3.22	3.70	57.75(16.3)	43.95(126.8)	23.66
3n	m(29)	4.86(17.8)	3.66	3.69	57.29(16.2)	44.07(136.1)	24.58
3o	M	4.63(17.0)	0.99	1.53	58.12(15.9)	43.51(128.1)	23.21



SCHEME 3

conditions, but also the substances can be mixed without any activation or modifications. Imidazole-containing phosphorus ylides **3a–o** may be considered as potentially useful synthetic intermediates. It seems that the procedure described here may be employed as an acceptable method for the preparation of phosphoranes with variable functionalities.

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and Shimadzu IR-460 spectrometer, respectively. Also, the ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a BRUKER DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1, 125.8, and 202.4 MHz, respectively. In addition, the mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70eV. Dialkyl acetylenedicarboxylates, triphenlphosphine, imidazole, and its derivatives were purchsed from Fluka (Buchs, Switzerland) and were used without further purification.

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

General Procedure

To a magnetically stirred solution of triphenylphosphine (0.26 g or 1 mmol) and imidazole (0.68 g or 1 mmol) in 10 mL of dry ethyl acetate; a mixture of dimethyl acetylenedicarboxylate (0.12 mL or 1 mmol) was added dropwise in 4 mL of dry ethyl acetate at −5°C for 10 min. after approximately 24 h of stirring at r. t. the product was filtered and recrystallized from ethyl acetate.

Colorless crystals. m.p. 143–145°C, yield 0.44 g, 94%. IR (KBr) (ν_{max}, cm^{-1}): 1754 and 1635 (C=O). MS (*m/z*, *%*): 262 (PPh_3, 84), 183 (PPh_2, 45), 108 (PPh, 35), 77 (Ph, 41), 67 (heterocycle, 10), 59 (CO_2Me, 10), 31 (OCH_3, 14).

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

Colorless crystals. m.p. 185–187°C, yield 0.46 g, 91%. IR (KBr) (ν_{max}, cm^{-1}): 1731 and 1623 (C=O). MS (*m/z*, *%*): 455($M—OCH_2CH_3$,6), 433 (M—Ph, 5), 262 (PPh_3, 80), 183 (PPh_2, 57), 108 (PPh, 41), 77 (Ph, 37), 73 (CO_2Et, 2), 67 (heterocycle, 14).

Di-tert-buthyl 2-(imidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3c)

Colorless crystals. m.p. 150–152°C, yield 0.53 g, 95%. IR (KBr) (ν_{max}, cm^{-1}) 1736 and 1629 (C=O). MS (*m/z*, *%*): 556 (M^+, 17), 489 (M-heterocycle, 10), 455 ($M—CO_2CMe_3$, 38), 262 (PPh_2, 21), 183 (PPh_2, 14), 108 (PPh, 13), 77 (Ph, 6), 67 (heterocyclic, 3), 57 (CMe_3, 47).

Dimethyl 2-(2-methyl imidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3d)

White powder, m.p. 167–169°C, yield 0.47 g, 96%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1741, 1629 (C=O), MS (*m/z*, *%*): 405 (M-heterocycle, 24), 346 (M-heterocycle and CO_2Me), 262 (PPh_3, 87), 183 (PPh_2, 41), 108 (PPh, 23), 81 (heterocycle, 19), 77 (Ph, 39), 59 (CO_2Me, 14).

Diethyl 2-(2-methylimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3e)

White powder, m.p. 143–145°C, yield 0.48 g, 94%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1723, 1623 (C=O). MS (*m/z*, *%*): 441 (M—CO_2Et, 16), 433 (M-heterocycle, 12), 360 (M-heterocycle and CO_2Et,2), 262 (PPh_3, 87), 183 (PPh_2, 25), 108 (PPh, 16), 77 (Ph, 20).

Di-tert-butyl 2-(2-methylimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3f)

White powder, m.p. 174–176°C, yield 0.54 g, 95%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1744, 1630 (C=O), 1643 (N=N). MS (*m/z*, *%*): 489 (M-heterocycle, 62), 469 (M—CO_2CMe_3, 3), 416 (M-heterocycle and $OCMe_3$, 12), 262 (PPh_3, 62), 183 (PPh_2, 31), 108 (Ph, 17), 101 (CO_2CMe_3, 13), 77 (Ph, 10).

Di-tert-butyl 2-(4-methylimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3g)

White powder, m.p. 192–194°C, yield 0.55 g, 96%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1746, 1738 (C=O), 1640 (N=N). MS (*m/z*. *%*): 489 (M-heterocycle, 37), 469 (M—CO_2CMe_3, 18), 387 (M—PPh_2, 21), 262 (PPh_3, 79), 183 (PPh_2, 20), 108 (PPh, 10), 77 (Ph, 24).

Dimethyl 2-(2-ethyl imidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3h)

Colorless crystals. m.p. 147–149°C, yield 0.48 g, yield 95%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}) 1741 and 1629 (C=O). MS (*m/z*, *%*): 500 (M^+, 1), 405 (M-heterocycle, 24), 441 (M—CO_2Me, 7), 262 (PPh_3, 91), 183 (PPh_2, 26), 108 (PPh, 51), 95 (heterocycle, 13).

Diethyl 2-(2-ethylimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3i)

Colorless crystals. m.p. 123–125°C, yield 0.49 g yield 93%. IR (KBr) ($\nu_{\max}$, cm^{-1}): 1723 and 1623 (C=O).

Di-tert-butyl 2-(2-ethylimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3j)

Colorless crystals. m.p. 174–176°C, yield 0.56 g, 92%. IR (KBr) ($\nu_{\max}$, cm^{-1}) 1728 and 1624 (C=O).

Dimethyl 2-(benzimidazole-1-yl)-3-(triphenylphosphanylidene)butanedioate (3k)

Colorless crystals, m.p. 117–119°C, yield 0.49 g, 94%. IR (KBr) ($\upsilon_{\max}$/ cm^{-1}): 1741, 1629 (C=O). MS, m/z (%): 522 (M$^+$, 2), 463 (M-heterocycle and CO$_2$Me, 10), 405 (M-heterocycle, 14), 262 (PPh$_3$, 46), 183 (PPh$_2$, 76), 108 (PPh, 26), 77 (Ph, 50).

Diethyl 2-(benzimidazole-1-yl)-3-(triphenylphosphanylidene) butanedioate (41)

Colorless crystals, m.p. 123–125°C, yield 0.50 g, 92%. IR (KBr) ($\upsilon_{\max}$/ cm^{-1}): 1723, 1623 (C=O). MS (m/z, %): 550 (M$^+$, 2), 477 (M—CO$_2$Et, 9), 367 (M—PPh2, 19), 262 (PPh$_3$, 100), 183 (PPh$_2$, 55), 108 (PPh, 34), 77 (Ph, 42), 73 (CO$_2$Et, 26).

Di-tert-butyl 2-(benzimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3m)

White powder. m.p. 142–144°C, yield 0.57 g, 95%. IR (KBr) ($\nu_{\max}$, cm^{-1}) 1728 and 1624 (C=O). MS (m/z, %): 606 (M$^+$, 3), 505 (M—CO$_2$ CMe$_3$, 23), 423 (M—PPh$_2$, 32), 344 (M—PPh$_3$, 3), 262 (PPh$_3$, 3), 183 (PPh$_2$, 76), 108 (PPh, 3), 101 (CO$_2$CMe$_3$, 3).

Dimethyl 2-(5,6-dimethylbenzimidazole-1-yl)-3-(triphenylphosphanylidene)butanedioate (3n)

Colorless crystals, m.p. 143–145°C, yield 0.51 g, 94%. IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1741, 1629 (C=O).

Di-tert-butyl 2-(benzimidazole-1-yl)-3-(triphenylphosphoranylidene)butanedioate (3o)

White powder. m.p. 165–167°C, yield 0.60 g, 95%. IR (KBr) ($\nu_{\max}$, cm^{-1}) 1728 and 1624 (C=O).

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