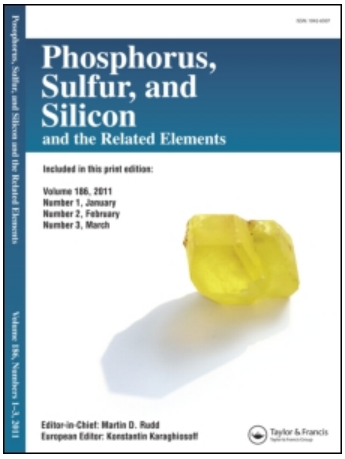

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Synthesis of Highly Functionalized Phosphorus Ylids Containing Heterocyclic Rings and the Related Iminophosphoranes

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Synthesis of Highly Functionalized Phosphorus Ylids Containing Heterocyclic Rings and the Related Iminophosphoranes

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Crystalline phosphorus ylides are obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine, dimethyl acetylenedicarboxylate (DMAD) and NH and SH acids, such as 2-amino-4-phenyl thiazole, 2-amino-5-(3-chloro-benzyl) thiadiazole, 3-amino-2-methyl quinazolin-4-one and 3-amino-2-mercapto quinazolin-4-one. These stabilized phosphoranes undergo a smooth intramolecular reaction in boiling toluene to produce aryliminophosphoranes in excellent yields.

Keywords Dimethyl acetylenedicarboxylate; phosphorus ylide; quinazolin-4-one; thiazole

INTRODUCTION

In the realm of ylide compounds and their value for a variety of industrial, biological and chemical synthetic uses, phosphorus ylides are playing increasingly pivotal roles.[1,2] For a reaction to be synthetically applicable, should have readily available starting materials, high yields and furthermore the product must be free of contaminants so as to avoid the need for extensive purification.[3] The chemistry of ylide compounds has provided chemists with exceptionally fertile ground for the design and development of new bond formation.[4] Since the pioneering work by Staudinger and Meyre in 1919,[5] on the preparation of iminophosphoranes, compounds of general structure $R_3P{=}NR$, the

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synthetic application of phosphorus ylides to the preparation of various organic products has increased enormously during the last three decades.[6] Several methods for the preparation of iminophophoranes have been developed.[7–9]

RESULTS AND DISCUSSION

As part of our continuing interest in this area, we have recently reported synthesis of highly functionalized phosphorus ylides.[10]

Now, in this investigation we wish to report synthesis of stable phosphorus ylides from thiazoles and quinazolinones **1a–d** (Scheme 1).

The ylides **2a**, **b** were converted to iminophosphoranes **3a**, **b**, when the reaction mixture was refluxed in toluene (Scheme 2).

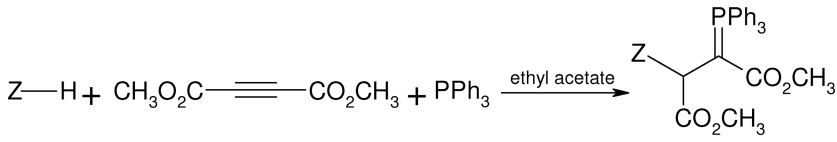
It is reasonable to assume that phosphorus ylide **2** results from the initial addition of triphenylphosphine to DMAD and subsequent protonation of the (1:1) adduct. Then the positively charged ion is attacked by conjugate base of **1** to form stable phosphorus ylide **2** (Scheme 3).

The proposed structures of compounds **2a–d** were supported by their elemental analyses and spectroscopic properties, such as ^{1}H NMR, ^{13}C NMR, IR and mass spectral data.

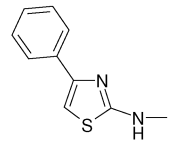
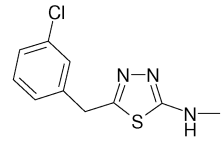
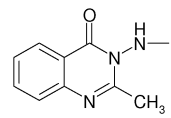
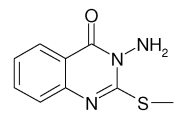
There are two absorptions at the IR spectra in the region of carbonyl groups. One of the carbonyl groups reveals a strong band at 1640 cm^{-1} which is conjugated with ylide moiety and the nonconjugated carbonyl group appears at about 1750 cm.$^{-1}$

Since the rotation about the partial double bond in E and Z isomers is slow on the NMR time scale at ambient temperature (Scheme 4); therefore, the presence of a mixture of two geometrical isomers E and Z for compounds **2a–d** was proven by their ^{13}C NMR & ^{1}H NMR absorption. For example ^{1}H NMR and ^{13}C NMR spectra of these compounds show four singlets for methyl hydrogens and four absorptions for carbonyl groups respectively, which are indicative of the presence of two isomers. Presence of the ^{31}P-nucleus helps in assignment of compounds **2a–d** by long range spin-spin coupling constants of ^{31}P with ^{1}H and ^{13}C nuclei.

The ^{1}H NMR spectrum of **2a** shows four different sharp lines at $\delta =$ 3.15, 3.61, 3.71, and 3.80 ppm, which are due to the methoxy protons, along with signals for methine protons at $\delta = 4.45$ and 4.70 ppm which appear as two multiplets respectively for minor and major isomers. Two fairly broad signals at $\delta = 6.25$ and 6.87 ppm are related to protons of N-H groups. The mass spectra of compounds **2a–d** did not reveal molecular ion peak. Peaks at m/z 262 and 183 which are correspond to Ph_3P^+ and $C_{12}H_8P^+$ were observed. The ^{13}C NMR of compound **2a** is in good agreement with the proposed structure of this compound. The ^{1}H



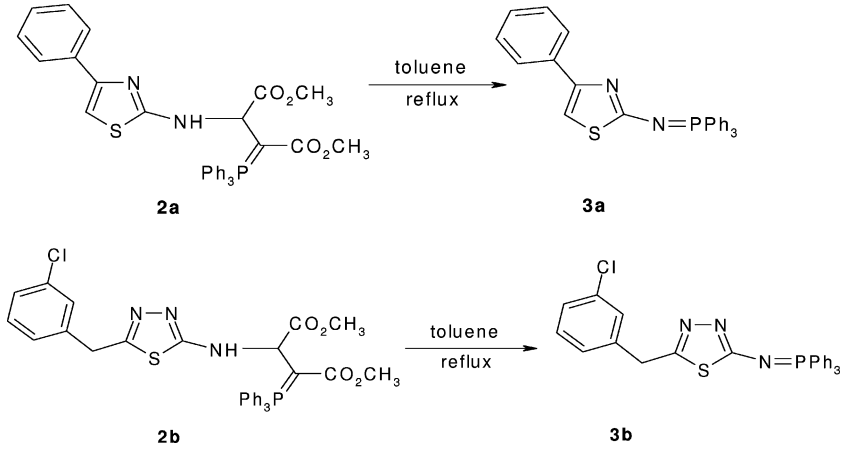
1a-d **DMAD** **2a-d**

1,2	Z	Yield(%) of 2
a		90
b		88
c		85
d		87

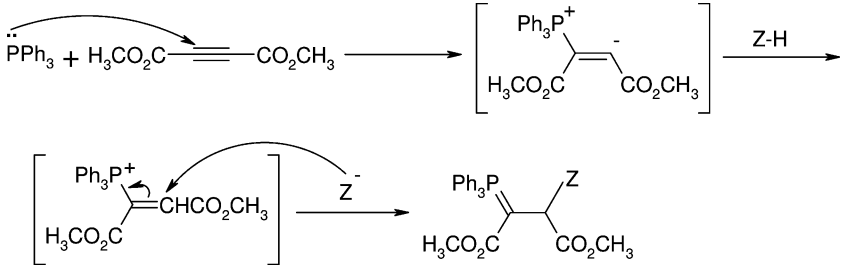
SCHEME 1

NMR and ^{13}C NMR spectra of compounds 2a–d are similar to those of 2a except for the signals from the aromatic rings which appear in the corresponding chemical shifts.

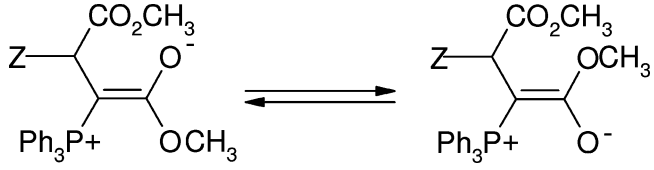
Compounds **2a** and **2b** undergo a smooth and clean reaction in boiling toluene to produce iminophosphoranes **3a** and **3b**. All of the attempts to convert **2c** to its related iminophosophorane were mostly unsuccessful.



SCHEME 2



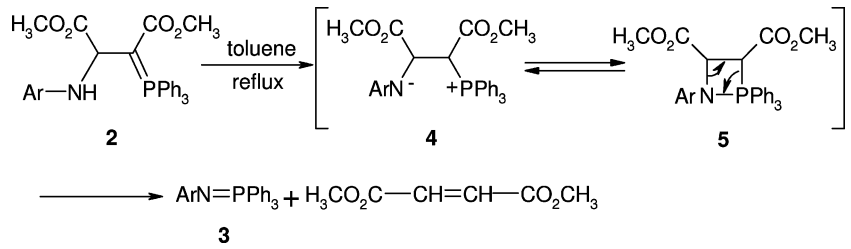
SCHEME 3



SCHEME 4

This transformation was suggested to proceed by an initial N-H proton shift onto the ylide carbon of the **2a** and forms the phosphorus betaine **4** and was followed by intramoleculr ring closure to produce azaphosphetane **5** which can be in equilibrium with betaine **4**. The only product formed under these conditions was iminophosphorane **3** (Scheme 5).

The ^{1}H NMR of **3a** displays proton of thiazole ring at 6.41 and aromatic protons at 7.25–7.89 ppm. The ^{13}C NMR of this compound reveals



2 **4** **5** **3**

SCHEME 5

seven distinct resonances for carbons of phenyl and thiazol rings. Signals of triphenylphosphine group appear at 128.56 (d, $^{3}J_{pc} = 12.3$ Hz, C^{meta}), 128.62 (d, $^{1}J_{pc} = 101.8$ Hz C^{ipso}), 132.21 (d, $^{4}J_{pc} = 2.1$ Hz, C^{para}), 133.22 (d, $^{2}J = 10.1$ Hz, C^{ortho}).

EXPERIMENTAL

General Procedures

Triphenylphosphine, dimethyl acetylenedicarboxylate, toluene, hexane and ethyl acetate were obtained from Merck Chemical Company and were used without further purification. Compounds **1a–d** were prepared according to the reported procedure in the literature.[11–14] Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed by Ferdousi University (Mashhad) using a Heracus CHN-O-Rapid analyzer.

Dimethyl 2-[(4-phenyl-1, 3-thiazol-2-yl) amino]-3-(triphenylphosphoranylidine)-butanedioate (2a)

The procedure for the preparation of the title compound is described as an example. To a magnetically stirred solution of triphenylphosphine (0.52 g, 2.00 mmol) and 2-amino-4-phenyl tiazole (0.35 g, 2.00 mmol) in ethyl acetate (4 mL) was added dropwise a mixture of DMAD (0.28 g, 2.00 mmol) in ethyl acetate (2 mL) at $0^{o}C$ over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 2 h. The resulted precipitate was filtered off and then recrystallized from 1:1 hexane–ethyl acetate.

White powder, m.p. = 140–143°C, yield = 1.04 g (90%); IR (KBr) (ν_{max}, cm^{-1}): 3404 (NH), 1741 (C=O), 1641 (C=O). MS, *m/z*(%): 436 (M^+-$C_6H_8O_4$, 79), 333 (40), 262 (PPh_3, 88), 183 (95), 113 (100). Anal. Calcd. for $C_{33}H_{29}N2O_4PS$: C, 68.26; H, 5.03; N, 4.82%. Found: 68.01; H, 4.95, N, 4.51%.

Major isomer (Z) (63%), ^{1}H NMR: δ 3.15 and 3.71 (6H, s, $2OCH_3$), 4.70 (1H, m, P=C–CH), 6.56 (1H, s, thiazole ring), 6.87 (1H, br s, NH), 7.21–7.77 (40H, m, arom).* ^{13}C NMR: δ 43.29 (d, $^1J_{PC}$ = 128.1 Hz, P=C)*, 49.03 and 52.24 ($2OCH_3$), 57.58 (d, $^2J_{PC}$ = 15.6 Hz, P=C–CH)*, 100.73 (CH)*, 126.13 (2CH)*, 126.73 (d, $^1J_{PC}$ = 97.9 Hz, C^{ipso})*, 128.06 (2CH)*, 128.43 (CH)*, 128.62 (d, $^3J_{PC}$ = 12.4 Hz, C^{meta})*, 131.98 (C^{para})*, 133.78 (d, $^2J_{PC}$ = 9.6 Hz, C^{ortho})*, 150.91 (C)*, 167.94 (C)*, 170.16 (d, $^2J_{PC}$ = 14.6 Hz, C=O)*, 173.99 (C=O)*.

Minor isomer (E) (37%), ^{1}H NMR: δ 3.61 and 3.80 (6H, s, $2OCH_3$), 4.52 (1H, m, P = C-CH), 6.25 (1H, s br, NH), 6.68 (1H, s, thiazole ring). ^{13}C NMR: δ 50.18 and 52.24 ($2OCH_3$).

Dimethyl 2-[5-(3-chloro-benzyl)-[1, 3, 4] thiadiazol-2-yl) amino]-3-(triphenylphosphorany-lidine)-butanedioate (2b)

White powder, m.p. = 120–124°C, yield = 1.05 g (88%); IR (KBr) (ν_{max}, cm^{-1}): 3379 (NH), 1765 (C=O), 1620 (C=O). MS, *m/z* (%): 517 (M^+-$C_6H_8O_4$, 32), 288 (100), 262 (PPh_3, 25), 183 (47).

Major isomer (E) (77%), ^{1}H NMR: δ 3.13 and 3.67 (6H, s, $2OCH_3$), 4.21 (2H, m, CH_2)*, 4.48 (1H, m, P=C–CH)*, 6.88 (1H, br s, NH)*, 7.21–7.68 (38H, m, arom)*. ^{13}C NMR: δ 38.65 (CH_2), 42.89 (d, $^1J_{PC}$ = 126.7 Hz, P=C)*, 49.12 and 52.32 ($2OCH_3$), 57.84 (d, $^2J_{PC}$ = 16.1 Hz, P=C–CH)*, 126.26 (d, $^1J_{PC}$ = 92.6 Hz, C^{ipso})*, 127.27 (CH), 127.77 (CH), 128.67 (d, $^3J_{PC}$ = 12.3 Hz, C^{meta})*, 129.11 (CH), 129.81 (CH), 132.23 (C^{para})*, 133.72 (C)*, 133.75 (d, $^2J_{PC}$ = 9.9 Hz, C^{ortho})*, 134.31 (C), 150.51 (C)*, 165.45 (C)*, 170.29(d, $^2J_{PC}$ = 12.5 Hz, C=O)*, 173.03 (C=O)*.

Minor isomer (Z) (23%), ^{1}H NMR: δ 3.56 and 3.80 (6H, s, $2OCH_3$). ^{13}C NMR: δ 38.34 (CH_2), 50.20 and 52.28 ($2OCH_3$), 128.43 (CH), 128.53 (CH), 132.02 (CH), 132.10 (CH), 132.80 (C), 133.20 (C).

Dimethyl 2-[(2-methyl-4-oxo-3(4H)-quinazolinyl) amino]-3-(triphenylphosphoranylidine)-butanedioate (2c)

White powder, m.p. = 174–177°C, yield = 0.985 g (85%); IR (KBr) (ν_{max}, cm^{-1}): 3305 (NH), 1765 (C=O), 1691 (C=O), 1641(C=N). MS,*m/z*(%): 405 (M^+-$C_9H_8N_3O$, 100), 262 (PPh_3, 18), 183 (25). Anal. Calcd. for $C_{33}H_{30}N_3O_5P$: C, 68.39; H, 5.22; N, 7.25 %. Found: 68.07; H, 5.18, N, 7.25%.

*For two geometrical isomers.

Major isomer (Z) (73%), ^{1}H NMR: δ 2.59 (1H, br s, NH), 3.20 (3H, s, CH_3), 3.66 and 3.76 (6H, s, $2OCH_3$), 3.80 (1H, d, $^3J_{PH}$ = 13.42 Hz, P=C–CH)*, 7.28-8.05 (38H, m, arom)*. ^{13}C NMR: δ 22.01 (CH_3)*, 42.08 (d, $^1J_{PC}$ = 133.9 Hz, P=C), 49.09 and 50.26 ($2OCH_3$), 60.62 (d, $^2J_{PC}$ = 19.5 Hz, P=C–CH), 125.94 (d, $^1J_{PC}$ = 91.8 Hz, C^{ipso}), 128.53 (d, $^3J_{PC}$ = 11.9 Hz, C^{meta}), 131.79 (C^{para})*, 131.95 (CH)*, 132.02 (CH)*, 132.11 (C)*, 132.94 (C)*, 133.29 (CH)*, 133.45 (d, $^2J_{PC}$ = 9.6 Hz, C^{ortho}), 134.13 (CH)*, 147.50 (C)*, 165.25 (C=O)*, 169.60 (d, $^2J_{PC}$ = 14.46 Hz, C=O), 173.03 (C=O).

Minor isomer (E) (27%), ^{1}H NMR: δ 2.47 (1H, br s, NH), 2.70 (3H, s, CH_3), 3.80 and 3.82 (6H, s, $2OCH_3$).^{13}C NMR: δ 39.86 (d, $^1J_{PC}$ = 141.0 Hz, P=C), 50.09 and 52.25 ($2OCH_3$), 61.62 (d, $^2J_{PC}$ = 18.6 Hz, P=C–CH), 126.58 (d, $^1J_{PC}$ = 95.5 Hz, C^{ipso}), 128.39 (d, $^3J_{PC}$ = 11.8 Hz, C^{meta}), 133.38 (d, $^2J_{PC}$ = 9.5 Hz, C^{ortho}), 170.69 (d, $^2J_{PC}$ = 16.5 Hz, C=O).

Dimethyl 2-[(3-amino-4-oxo-3, 4-dihydro-2-quinazolinyl) sulfanyl]-3-(triphenylphosphora-nylidine)-butanedioate (2d)

White powder, m.p. = 157–160°C, yield = 1.04 g (87%); IR (KBr) (ν_{max}, cm^{-1}): 3330 and 3203 (NH_2), 1746 (C=O), 1682 (C=O), 1640 (C=O). MS,*m/z*(%): 320 (M^+-Ph_3P=O, 15), 301 (20), 288 (85), 277 (46), 262 (PPh_3, 67), 183 (100), 108 (39), 77 (44), 51 (40).

Major isomer (Z) (60%), ^{1}H NMR: δ 3.09 and 3.77 (6H, s, $2OCH_3$), 4.39 (2H, s, NH_2), 4.59 (1H, d, $^3J_{PH}$ = 15.6 Hz, P=C–CH)*, 7.05–8.07 (38H, m, arom)*. ^{13}C NMR: δ 40.82 (d, $^1J_{PC}$ = 128.1 Hz, P=C), 49.08 and 52.11 ($2OCH_3$), 62.67 (d, $^2J_{PC}$ = 15.1 Hz, P=C–CH), 122.08 (CH)*, 122.80 (CH)*, 124.93 (CH)*, 126.37 (d, $^1J_{PC}$ = 93.4Hz, C^{ipso}), 126.48 (CH)*, 128.48 (d, $^3J_{PC}$ = 11.6 Hz, C^{meta})*, 131.90 (d, $^4J_{PC}$ = 2.0 Hz, C^{para})*, 133.66 (d, $^2J_{PC}$ = 10.4 Hz, C^{ortho})*, 134.02 (C)*, 134.49 (C)*, 150.25 (C), 161.88 (C=O), 170.10 (d, $^2J_{PC}$ = 14.2 Hz, C=O), 174.96 (d,$^3J_{PC}$ = 7.0 Hz, C=O).

Minor isomer (E) (40%), ^{1}H NMR: δ 3.5 and 3.74 (6H, s, $2OCH_3$), 4.57 (2H, s, NH_2).^{13}C NMR: δ 42.08 (d, $^1J_{PC}$ = 135.2 Hz, P=C), 50.22 and 52.00 ($2OCH_3$), 62.44 (d, $^2J_{PC}$ = 14.1 Hz, P=C–CH), 150.048 (C), 162.019 (C=O), 170.54 (d,$^2J_{PC}$ = 16.3 Hz, C=O), 175.14 (d, ,$^3J_{PC}$ = 6.8 Hz, C=O).

N-(4-Phenyl-1, 3-thiazol-2-yl) triphenyliminophosphorane (3a)

The process for the preparation of **3a** is described as an example. A mixture of **2a** (0.52 g, 1.0 mmol) in toluene (10 mL) was refluxed for 8 h. The solvent was removed under reduced pressure. Dimethyl fumarate sublimated under reduced pressure and the residue recrystallised from 1:1 hexane– ethyl acetate as colorless crystals.

White crystals, m.p. =162–166°C, yield = 0.41 g (95%), IR (KBr) (ν_{max}, cm^{-1}): 1591, 1492, 1443, 1319, 1244. MS, *m/z* (%): 436 (M^+, 100), 262 (PPh_3, 40), 183 (82), 108 (53). Anal. Calcd. for $C_{27}H_{21}N_2PS$: C, 74.29; H, 4.85; N, 6.42 %. Found: 73.97; H, 4.58, N, 6.07%.

^1H NMR: δ 6.41–7.89 (21H, m, arom). ^{13}C NMR: δ 103.29 (C), 125.28 (CH), 125.75 (2CH), 126.77 (C), 128.17 (2CH), 128.56 (d, $^3J_{PC}$ = 12.3 Hz, C^{meta}), 128.62 (d, $^1J_{PC}$ = 101.8 Hz, C^{ipso}), 132.21 (d, $^4J_{PC}$ =2.1 Hz, C^{para}), 133.22 (d, $^2J_{PC}$ =10.1 Hz, C^{ortho}), 137.85 (C), 149.68 (C).

N-(5-(3-Chloro-benzyl)-[1, 3, 4] thiadiazol-2-yl) triphenyliminophosphorane (3b)

White crystals, m.p. = 138–140°C, yield = 0.42 g (93%); IR (KBr) (ν_{max}, cm^{-1}): 1594, 1581, 1481, 1426, 1320, 1230. MS,*m/z*(%): 519 (M+2, 12), 519 (M^+, 30), 282 (100), 183(40). Anal. Calcd. for $C_{27}H_{21}ClN_3PS$: C, 66.73; H, 4.36; N, 8.65 %. Found: 66.42; H, 4.12, N, 8.46%.

^1H NMR: δ 4.28 (2H, s, CH_2), 7.20-7.81 (19H, m, arom). ^{13}C NMR: δ 37.54 (CH_2), 127.26 (d, $^1J_{PC}$ = 91.2Hz, C^{ipso}), 127.32 (CH), 127.62 (CH), 128.82 (d, $^3J_{PC}$ = 12.6 Hz, C^{meta}), 129.14 (CH), 129.74 (CH), 132.65 (C^{para}), 133.12 (d, $^2J_{PC}$ = 10.2 Hz, C^{ortho}), 133.37 (C), 134.21 (C), 138.89 (C), 152.14 (C).

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