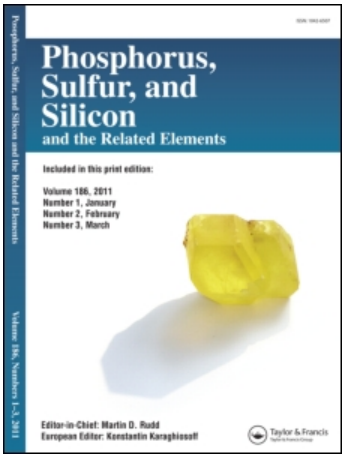

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A NOVEL SYNTHESIS OF PHOSPHORUS HETEROCYCLES. REACTION OF α-HYDRAZIDOYL HALIDES WITH PHOSPHORANES AND LAWESSON'S REAGENT

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*Hydrazidoyl halides **1a** reacted with diethylphosphonoacetonitrile (**2a**) in sodium ethoxide to yield the hydrazine derivative **4a** which readily cyclized to form the corresponding diazaphosphole **5**. The latter was hydrolyzed to form the final product **6**, with the formation of a low yield of a second product **7a**. Similarly **1b,c** reacted with diethylphosphonoacetonitrile and triethylphosphonoacetate **2a,b** to produce the corresponding diazaphospholes **6b–d**. Interaction of hydrazidoyl halides **1b,d–g** with Lawesson's reagent in dry toluene produced 1,3,4-thiadiazaphosphole derivatives **10b,d,e** and **11f,g** respectively.*

Keywords: Hydrazidoyl halides; phospholes; phosphoranes; Lawesson's reagent (LR); diazaphospholes

In view of the diverse biological and physiological activities of phospholes,[1–4] and in connection with our previous efforts directed toward the facile synthesis of heterocyclic phosphole systems,[5–7] we designed a specific simple program aimed at the development of a convenient synthetic approach for the construction of new heterocyclic phospholes with expected potential bioresponses. This article explains the interaction of hydrazidoyl halides with diethylphosphonoacetonitrile, triethylphosphonoacetate, and Lawesson's reagent.

CHEMISTRY AND DISCUSSION

Treatment of hydrazidoyl halide **1a** with diethylphosphonoacetonitrile (**2a**) in sodium ethoxide at room temperature with stirring

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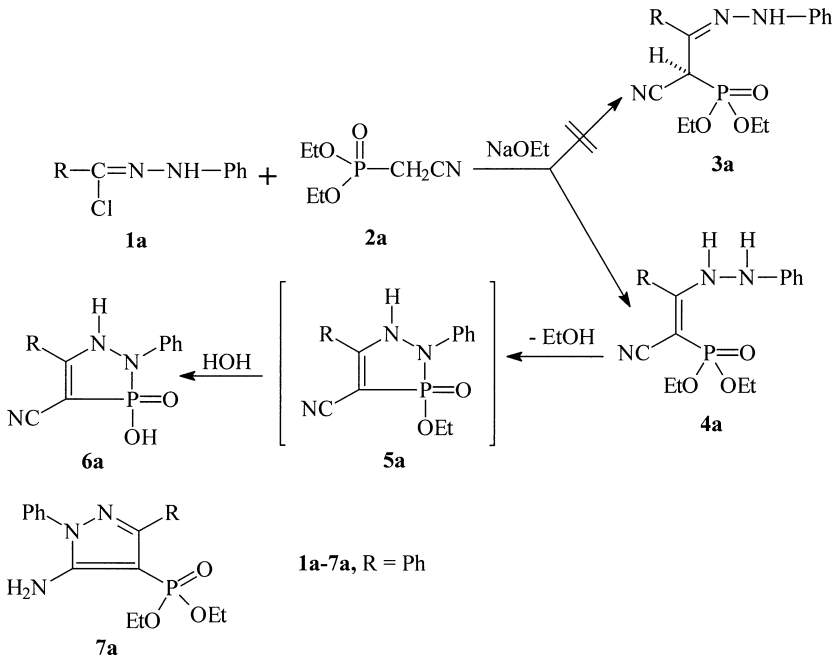
afforded two different products, **6a** and **7a**. It is believed that an additional product formed under the reaction conditions by loss of HCl. This may be formulated as the structure **3a** or the hydrazine structure **4a**.

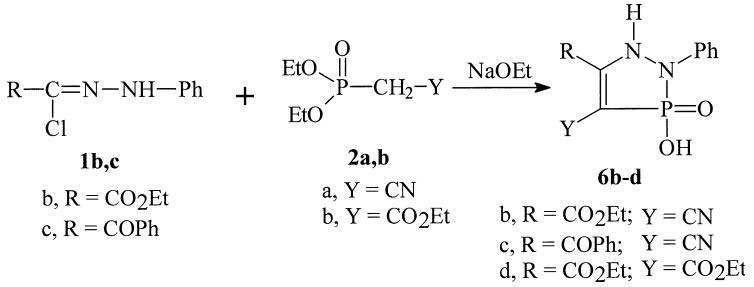
The hydrazine derivative **4a** was preferred based on ^{1}H NMR spectral data which did not reveal any methine proton with expected J_{HP} = 11–13 Hz. Moreover, the reaction product **4a** could be cyclized with stirring overnight to produce the diazaphosphole derivative **6a**. We believe that the final isolable product **6a** was formed by hydrolysis of the phosphole derivative **5a** during the separation via silica gel column chromatography[8] (Scheme 1).



SCHEME 1

It is worth mentioning that the reaction of **1a** with **2a** afforded the aminopyrazole derivative **7a** as a second product (5%). Compound **7a** was obtained via the cyclization of the nitrogen nucleophile with the carbonitrile group in **4a** (Scheme 1).

Similarly the hydrazidoyl halide, **1b**,**c** reacted with the reagents **2a**,**b** to yield the corresponding diazaphosphole derivatives **6b–d** (Scheme 2). The yields of **6b–d** ranged from 45–60%.



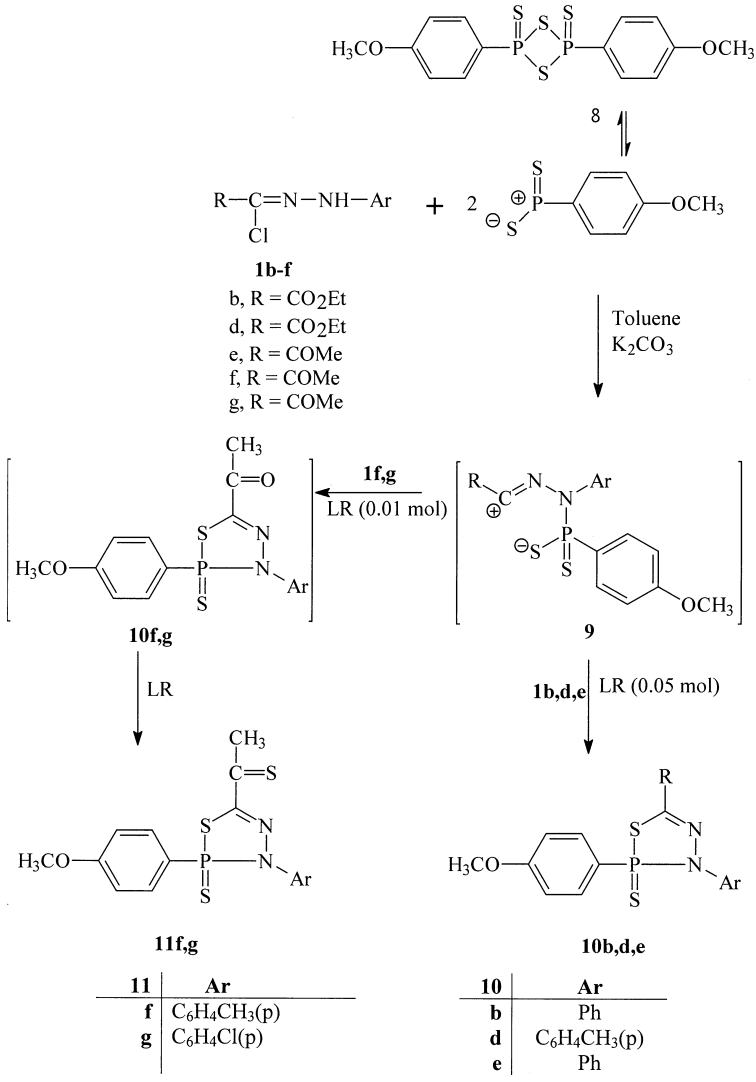
SCHEME 2

At this point, it was of interest to test the reactivity of hydrazidoyl halides with Lawesson's reagent (LR) (**8**).[10–12] Treatment of hydrazidoyl halides **1b**,**d**,**e** with 0.05 mmol equiv. of Lawesson's reagent **8** in dry toluene (containing potassium carbonate) led to formation of the corresponding addition products 1,3,4-thiazaphosphole derivatives **10b**,**d**,**e**. The structures of **10b**,**d**,**e** were confirmed based on their spectral data. The reactions of **1b**,**d**,**e** with LR **8** apparently involved the attack of the nitrogen nucleophile on the polar phosphorus atom and gave the dipolar intermediate **9** which readily cyclized under the reaction conditions to form the isolated phosphole derivatives **10b**,**d**,**e**.

On the other hand, treatment of **1f**,**g** with one mole equivalent of LR **8** generated the corresponding phosphole derivatives **10f**,**g** which were readily thionated with excess LR **8** forming the final products **11f**,**g** respectively. All spectroscopic and the microanalytical data were in accordance with the proposed structure **11f**,**g** (c.f. Experimental section).

EXPERIMENTAL

All melting points were uncorrected. Solvents used were distilled and dried over sodium sulfate. Microanalysis experiments were carried out in the Analytical Lab Unit at the National Research Centre. IR spectra were taken in KBr on a OK 9712 IR spectrometer. ^{1}H NMR were recorded on a Varian EM-360-60 MHz spectrometer with DMSO-D_6 and $CDCl_3$ as solvent and TMS as an internal reference. Chemical shifts are expressed as δ units (ppm). The mass spectra were recorded on Kratos (75 eV) MS equipment.



11	Ar
f	$C_6H_4CH_3$(p)
g	C_6H_4Cl(p)

10	Ar
b	Ph
d	$C_6H_4CH_3$(p)
e	Ph

SCHEME 3

Reaction of Hydrazidoyl Halides 1a–c with Diethylphosphonoacetonitrile (2a)

General Procedure

A solution of 0.01 mmol of sodium metal in absolute ethanol was treated with an equimolar amount of phosphorane **2a** (1.77 g,

0.01 mmol). The solution was stirred for 10 min and then added an equimolar amount of **1a–c**. The reaction mixture was stirred at room temperature overnight. The formed inorganic salt was isolated by filtration. The residual material formed after evaporation of the solvent under vacuum was applied to a silica gel column using (cyclohexane-ethyl acetate, v:v) as an eluent.

*4-Cyano-2-phenyl-5-substituted 1,2,3-diazaphosphole (**6a–c**).* Compound **6a** was isolated from silica gel column chromatography using (cyclohexane-ethyl acetate, 8:2, v:v) as eluent. Colorless crystals, m.p. 110°C (benzene), yield: 1.63 g (55%). IR: ν 3425 (NH), 2222 (CN) and 1590 (C=C) cm^{-1}; ^1H NMR (DMSO-D_6): δ 3.45 (s, 1H, OH), 7.15–7.50 (m, 10H, aromatic protons), 9.60 (s, 1H, NH). ^{13}C NMR (DMSO-D_6): δ ppm 118.33 (CN), 125.27–129.96 (aromatic carbons), 151.88 (C_4), 159.11 (C_5). MS: M/Z = 297 (M^+, 46.34%). Anal. Found C: 60.56; H: 4.08; N: 14.11; P: 10.42 Calcd for $C_{15}H_{12}N_3O_2P$ (297.25), C: 60.61; H: 4.06; N: 14.13; P: 10.42.

Compound **6b** was isolated using (cyclohexane-ethyl acetate, 3:7, v:v) as eluent; yellow crystals, m.p. 137°C (benzene), yield: 1.75 g (60%). IR: ν 3440 (NH), 2932 (CH_3), 2225 (CN) and 1715 (C=O) cm^{-1}; ^1H NMR (DMSO-D_6): δ 1.55 (t, 3H, CH_3), 4.10 (s, 1H, OH), 4.45 (q, 2H, CH_2), 7.25–7.70 (m, 5H, aromatic protons), 9.45 (s, 1H, NH). MS: M/Z = 293 (M^+, 59%). Anal. Found C: 49.10; H: 4.07; N: 14.33; P: 10.55 Calcd for $C_{12}H_{12}N_3O_4P$ (293.22), C: 49.15; H: 4.12; N: 14.33; P: 10.56.

Compound **6c** was isolated using (*n*-hexane-ethyl acetate, 3:7, v:v) as eluent, brown precipitate, m.p. 113–114°C (benzene), yield: 1.88 g (58%). IR: ν 3435 (NH), 2224 (CN), 1665 (C=O) and 1590 (C=C) cm^{-1}; ^1H NMR (DMSO-D_6): δ 4.35 (s, 1H, OH), 7.20–7.35 (m, 5H, aromatic protons), 7.40–7.55 (m, 2H, aromatic protons), 7.65–7.85 (m, 3H, aromatic protons), 9.55 (s, 1H, NH). MS: M/Z = 325 (M^+, 42%). Anal. Found C: 59.02; H: 3.99; N: 12.88; P: 9.50 Calcd for $C_{16}H_{12}N_3O_3P$ (325.26), C: 59.08; H: 3.71; N: 12.91; P: 9.52.

*Diethyl 5-amino-1,3-diphenylpyrazol-4-ylphosphonate (**7**).* Ester **7** was obtained as a second product from the reaction of hydrazidoyl halide **1a** and the phosphorane **2a**. It was isolated from a silica gel column using (cyclohexane-ethyl acetate, 7:3, v:v) as an eluent.

Compound **7** green crystals, m.p. 182°C, yield: 0.185 g (5%). IR: ν 3300–3425 (NH_2), 2923, 2854 (CH_3) and 1604 (C=C) cm^{-1}; ^1H NMR (DMSO-D_6): δ 1.36 (t, 6H, $2CH_3$), 4.31 (m, 4H, $2CH_2$), 7.25–7.30 (m, 2H, aromatic protons), 7.35–7.60 (m, 8H, aromatic protons), 8.25 (br, 2H, NH_2). MS: M/Z = 371 (M^+, 100%). Anal. Found C: 61.40; H: 5.93; N: 11.21; P: 8.30 Calcd. for $C_{19}H_{22}N_3O_3P$ (371.38), C: 61.45; H: 5.97; N: 11.31; P: 8.34.

Reaction of α-Hydrazidoyl Halide 1b with Triethyl Phosphonoacetate

A solution of 0.01 mmol of sodium metal in absolute ethanol was treated with equimolar amount of the diethylphosphorane **2b** (2.24 g, 0.01 mmol). The solution was stirred for 5 min, and then an equimolar amount of the hydrazidoyl halide **1b** was added. The reaction mixture was stirred at room temperature for 6 h and poured onto water and extracted with $CHCl_3$. The residual material produced, after evaporation under vacuum, was separated through silica gel column chromatography using (pet. ether 40–60°C-ethyl acetate-7:3, v:v) as an eluent.

Compound **6d** red crystals, m.p. 141°C, yield: 1.53 g (45%). IR: ν 3433 (NH), 2924, 2855 (CH_3) cm^{-1}; ^1H NMR (DMSO-D_6): δ 1.45 (m, 6H, 2 CH_3), 4.31 (s, 1H, OH), 4.40–4.44 (m, 4H, 2 CH_2), 7.30–7.35 (m, 2H, aromatic protons), 7.35–7.55 (m, 3H, aromatic protons), 8.16 (br, H, NH). ^{13}C NMR (DMSO-D_6): δ ppm 14.02, 14.13 (2 CH_3), 61.11, 61.14 ($2CH_2$), 126.06–129.13 (aromatic carbons), 151.32 (C_4), 159.21 (C_5), MS: M/Z = 340 (M^+, 75%). Anal. Found C: 49.37; H: 5.00; N: 8.20; P: 9.10 Calcd. for $C_{14}H_{17}N_2O_6P$ (340.27), C: 49.41; H: 5.03; N: 8.23; P: 9.10.

Reaction of α-Hydrazidoyl Halides 1b,d,e with Lawesson's Reagent

General Procedure

To a solution of 2.0 g, 0.005 mmol LR **8** in dry toluene (30 ml) were added 0.01 mmol of each of hydrazidoyl halides **1b**,**d**,**e** and potassium carbonate (0.01 mmol). The reaction mixture was heated under reflux for 5 h. The inorganic salt was filtered and the solvent was evaporated under vacuum. The residue was chromatographed on silica gel (ethyl acetate-n-hexane, v:v) to produce the final product of each reaction.

Ethyl 4-Phenyl-1,3,4-thiadiazaphospholine-2-acetate ***10b***. Yellow crystals using eluent (ethyl acetate : *n*-hexane, 2:8, v:v), m.p. 161°C, yield: 2.54 g (65%). IR: ν 2925, 2855 (CH_3), 1735 (C=O) and 1604 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (t, 3H, J = 8.2 Hz, CH_3), 3.82 (s, 3H, OCH_3), 4.13 (q, 2H, CH_2, J = 8.2 Hz), 6.90–7.40 (m, 7H, aromatic protons), 7.75 (m, 2H, ortho-aromatic protons, J_{HP} = 15 Hz, J_{HH} = 9 Hz) ppm. MS: M/Z = 392 (M^+, 38%). Anal. Found C: 51.95; H: 4.32; N: 7.12; S: 16.18; P: 7.78 Calcd. for $C_{17}H_{17}N_2O_3S_2P$ (392.44), C: 52.03; H: 4.36; N: 7.13; S: 16.34; P: 7.89.

Ethyl 4-(p-tolyl)-1,3,4-Thiadiazaphospholine-2-acetate ***10d***. Yellow crystals using eluent (ethyl acetate : *n*-hexane, 3:7, v:v), m.p. 120°C, yield: 2.51 g (62%). IR: ν 2955, 2854 (CH_3) and 1602 (C=C) cm^{-1};

^{1}H NMR ($CDCl_3$): δ 1.21 (t, 3H, J = 8.2 Hz, CH_3), 2.15 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.12 (q, 2H, CH_2, J = 8.2 Hz), 7.35–7.52 (m, 4H, aromatic protons), 7.65–7.85 (m, 4H, aromatic protons) ppm. MS: M/Z = 406.47 (M^+, 45%). Anal. Found C: 53.00; H: 4.62; N: 6.85; S: 15.64; P: 7.61 Calcd. for $C_{18}H_{19}N_2O_3S_2P$ (406.47), C: 53.19; H: 4.71; N: 6.89; S: 15.77; P: 7.62.

2-Acetyl-3-phenyl-1,3,4-thiadiazaphospholines ***10e***. Yellow crystals were isolated from column chromatography using eluent (ethyl acetate : *n*-hexane, 3:7), m.p. 190°C, yield: 2.17 g (60%). IR: ν 2920 (CH_3), 1705 (C=O) and 1602 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.80–7.35 (m, 7H, 5 aromatic protons and 2m-protons), 7.75 (dd, 2H, ortho-aromatic protons-J_{PH} = 15 Hz, J_{HH} = 9 Hz). MS: M/Z = 362 (M^+, 28%). Anal. Found C: 53.00; H: 4.10; N: 7.71; S: 17.62; P: 8.51 Calcd. for $C_{16}H_{15}N_2O_2S_2P$ (362.41), C: 53.03; H: 4.17; N: 7.73; S: 17.69; P: 8.55.

Reaction of α-Hydrazidoyl Halide 1f,g with Lawesson's Reagent

General Procedure

To a solution of 4.04g, 0.01 mmol LR **8** in dry toluene (50 ml) were added 0.01 mmol of each of hydrazidoyl halides **1f,g** and potassium carbonate (0.01 mmol). The reaction mixture was heated under reflux for 3 h. The inorganic salt was filtered and the solvent was evaporated under vacuum. The residue was chromatographed on silica gel (ethyl acetate-n-hexane, v:v) to produce the final product of each reaction.

2-(p-Tolyl)-2-thioacetyl-1,3,4-thiadiazaphospholines ***11f***. Yellow crystals were isolated from column chromatography using eluent (ethyl acetate : *n*-hexane, 4:6, v:v), m.p. 155°C, yield: 2.15 g (55%). IR: ν 2915 (CH_3) and 1604 (C=C) cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 2.21 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.25–7.40 (m, 4H, aromatic protons), 7.55–7.80 (m, 4H, aromatic protons-J_{PH} = 15 Hz, J_{HH} = 9 Hz). MS: M/Z = 392 (M^+, 100%). Anal. Found C: 52.00; H: 4.13; N: 7.00; S: 24.27; P: 7.80 Calcd. for $C_{17}H_{17}N_2OS_3P$ (392.50), C: 52.02; H: 4.37; N: 7.14; S: 24.51; P: 7.89.

2-(p-Chlorophenyl)-2-thioacetyl-1,3,4-thiadiazaphospholines ***11g***. Orange crystals were obtained from column chromatography using eluent (ethyl acetate : *n*-hexane, 2:8, v:v), m.p. 146°C, yield: 2.51 g (61%). IR: ν 2905 (CH_3) and 1600 (C=C) cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 2.60 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.30, 7.45 (2dd, 4H, aromatic protons), 7.61, 7.75 (2dd, 4H, aromatic protons) ppm. MS: M/Z = 413

(M^+, 100%), 381 ((M^+ – S), 85%). Anal. Found C: 46.49; H: 3.31; N: 6.75; S: 23.17; P: 7.50, Cl: 8.50 Calcd. for $C_{16}H_{14}N_2OS_3PCl$ (412.92), C: 46.54; H: 3.42; N: 6.78; S: 23.30; P: 7.50; Cl: 8.59.

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