ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Chemistry of Phosphorus Ylides Part 43. The Reaction of Active Phosphonium Ylides with Aminothioxothiazolidinone, Thiazolamine. Synthesis and Antimicrobial Activity of Phosphanylidenes, Thiazolthione Pyrazoles and Cyclobutanes.

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ABSTRACT

3-Amino-2-thioxo-1,3-thiazolidinone reacted readily with (*N*-phenyliminovinylidene)triphenylphosphorane to give the corresponding addition product phosphanylidene along with thioxo-thiazolidinimidamide, pyrazolothiazolthione and thiazolone. While with (2-oxovinylidene)triphenylphosphorane, only the phosphanylidene derivative was produced. When the aminothioxothiazolidinone was treated with hexaphenylcarbodiphosphorane, the thiazolo-diazaphospholethione was produced. On the other hand, the reactions of thiazol-2-amine with the (*N*-phenyliminovinylidene)- and/or the (2-oxovinylidene)-triphenylphosphorane proceeded with the formation of the phosphanylidene and thia-azabicycloheptadiene-amine and triphenylphosphorane in case of using (*N*-phenyliminovinylidene)triphenylphosphorane or phosphanylidene and thia-azabicycloheptenone when the (2-oxovinylidene)triphenylphosphorane was used. While the thiazolamine gave phosphanylidene-phosphanyl-thiazolamine, when it was allowed to react with diphosphorane. In addition, reactions of (*N*-phenyliminovinylidene)- and (2-oxovinylidene)-triphenylphosphorane with 1-(3-aminophenyl)ethanone resulted in the formation of phosphanylidene cyclobutylidenes and phosphanylidene amides. The difference in the nucleophilic character and reactivity of the phosphorus reagents were discussed. The antimicrobial activity of the new compounds was investigated, too.

Keywords: Aminothioxothiazolidinone, Thiazolamine, Phosphonium Ylides, Phosphanylidenes, Thiazolthione, Pyrazoles Cyclobutanes, Antimicrobial activity.

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ISSN: 0975-8585

INTRODUCTION

There is considerable interest in the chemistry of rhodanine compounds, since they have broad spectrum of significant pharmacological activities [1]. They have emerged as potent antidiabetic [2], antiapoptotic [3], antimicrobial [4,5], antihepatitis C virus (HCV) [6], anti-inflammatory [7,8], anticancer [9,10] and antioxidant agents [11]. Moreover, phosphonium ylides are becoming of increased importance in the synthesis of homo and heterocyclic compounds which have numerous synthetic applications for a wide variety of industrial and biological fields [12-17]. In continuation of our recent work on the reaction of phosphacumulene and phosphallene ylides [18-24], we wish to report our results for the synthesis of phosphanylidenes, thiazolthione pyrazoles, cyclobutanes derived from the reactions of aminothioxothiazolidinone, thiazolamine with these active phosphonium ylides.

MATERIALS AND METHOD

Melting points were determined with an electrothermal digital melting point apparatus (Electro-Thermal Engineering Ltd., Essex, United Kingdom). The IR spectra were recorded in KBr disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC Infrared Spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H and ^{13}C NMR spectra were obtained from a Jeol ECA 500 MHz NMR Spectrometer (Tokyo, Japan) using deuterated dimethylsulphoxide (d_6-DMSO) as a solvent and (TMS) as an internal reference at 500, 125 MHz, respectively and ^{31}P NMR spectra were obtained from a Jeol ECA 500 MHz NMR spectrometer at 200 MHz. Mass spectra (EI-MS) were obtained with ISQ (Single Quadrupole MS, Thermo Scientific). Elemental analyses (C, H, N) results were recorded with Elementar Vario EL Germany, phosphorus was measured by spectrophotometric methods and all of them agreed satisfactory with the calculated values. The using reported yields are of pure isolated materials obtained by column chromatography silica gel 60 (Merck) and thin layer chromatography (TLC) which was performed on Merck Kiesel gel F254 precoated plates (Merck, Darmstadt, Germany). Solvents were dried/purified according to literature procedures. The starting material **1** is commercially bought from Merck Company (Germany), **10** was from Sigma-Aldrich Chemie Company (Steinheim, Germany) and **15** was from Sisco Research Laboratories pvt. LTD Company, (Mumbai, India).

Reaction of (*N*-phenyliminovinylidene)triphenylphosphorane (2a) with 3-amino-2-thioxo-1,3-thiazolidin-4-one (1)

A solution of (*N*-phenyliminovinylidene)triphenylphosphorane **(2a)** [25] (377 mg, 1 mmol) in 20 mL of dry *THF*, was added drop by drop with stirring at room temperature, to a solution of 3-amino-2-thioxo-1,3-thiazolidin-4-one **(1)** (148 mg, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was stirred for 6 hrs during which the color was changed from yellow to dark brown with the progress of the reaction, which was monitored by (TLC). *THF* was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 ^{0}C)/ ethyl acetate as eluent (85:15, *v/v*), gave two products: **3a** and **4** with triphenylphosphane (m.p. and mixed m.p. 78^{0}C).

N-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N'*-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethanimidamide (3a)

Colorless crystals, yield 55 %, mp:140-142^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1}*) 3432 (NH), 1684 (C=O), 1586 (C=N), 1187 (C=S). ^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.31 (s, 2H, CH_2), 7.45-7.66 (m, 22 H, arom.-H+NH); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 188.25 (C=S), 163.56 (C=O), 162.52 (C=N), 153.23 (C=P),128.57 - 132.89 (arom-C), 49.88 (CH_2). ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): δ = 21.26. MS *m/z* (%) 525 [(M)$^{+}$, 3]. Anal. Calcd. for $C_{29}H_{24}N_3OPS_2$(525.62): C, 66.27; H, 4.60; N, 7.99; P, 5.89; S, 12.20 %; Found: C, 65.94; H, 4.25; N, 7.52; S, 11.95 %.

N-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N'*-phenylethanimidamide (4)

Yellow crystals, yield 25 %, mp: 134-136 ^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1}*) 3228 (NH), 1652 (C=O), 1579 (C=N), 1229 (C=S). ^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 2.17 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.15-7.43 (m, 5 H, arom.-H), 11.21 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 182.43 (C=S), 162.73 (C=O),

162.66 (C=N), 125.04 - 129.73 (arom-C), 51.12 (CH_2), 19.00 (CH_3). MS *m/z* (%) 265 [$(M)^+$, 100]. Anal. Calcd. for $C_{11}H_{11}N_3OS_2$(265.35) C, 49.79; H, 4.18; N, 15.84; S, 24.17%; Found: C, 48.34; H, 3.95; N, 15.12; S, 23.77 %.

When the reaction was repeated using one mol-equivalent of **1** and two mol-equivalents of **2a** under the same experimental conditions, two different products only were isolated, **5** and **6** along with triphenylphosphane oxide and triphenylphosphane sulphide (m.p. and mixed m.p. 151^{0}C and 156 ^{0}C respectively).

1,2-Dihydro-2-(phenylimino)pyrazolo[1,5-c]thiazole-6*(4H)*-thione (5)

Buff crystals, yield 42 %, mp:340-342 ^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1})* : 3405 (NH), 1593 (C=N), 1238 (C=S).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.20 (s, 2H, CH_2), 5.80 (s, 1H, CH), 7.28-7.57 (m, 6 H, arom.-H +NH); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 187.50 (C=S), 160.16 (C=N), 115.20 (CH), 124.89 -133.60 (arom.-C), 55.80 (CH_2). MS *m/z* (%) 247 [$(M)^+$, 5]. Anal. Calcd. for $C_{11}H_9N_3S_2$ (247.34) : C, 53.42; H, 3.67; N, 16.99; S, 25.23 %; Found: C, 52.64; H, 3.65; N, 16.55; S, 24.99 %.

5,6-Dihydro-6-(phenylimino)pyrazolo[5,1-b]thiazol-3(*2H*)-one (6)

Red crystals, yield 23 %, mp: 184-186 ^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1})* : 3373 (NH), 1693 (C=O), 1611 (C=N).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.20 (s, 2H, CH_2), 5.80 (s, 1H, CH), 7.28-7.57 (m, 6 H, arom.-H +NH). MS *m/z* (%) 230 [$(M-H)^+$, 20]. Anal. Calcd. for $C_{11}H_9N_3OS$ (231.27): C, 57.13; H, 3.92; N, 18.17; S, 13.86 %; Found: C, 57.04; H, 3.85; N, 18.05; S, 13.79 %.

***Reaction of (2-oxovinylidene)triphenylphosphorane (2b) with* 3-amino-2-thioxo-1,3-thiazolidin-4-one (1)**

A solution of (2-oxovinylidene)triphenylphosphorane **(2b)** [26] (302 mg, 1 mmol) in 20 mL of dry toluene was added to a solution of **1** (148 mg, 1 mmol) in 20 mL of dry toluene and refluxed for 10 hrs, during which the color was changed from yellow to brown and precipitate was formed. The reaction mixture was filtered off, the product crystallized from cyclohexane to form **3b**.

***N*-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)-2-(triphenyl-λ^5-phosphanylidene)acetamide (3b)**

Yellow crystals, yield 90 %, mp: 120-122^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1}*): 3404 (NH), 1634 (C=O), 1620 (C=O), 1532 (C=P), 1434, 1406 (P-aryl), 1186 (C=S).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.25(s, 2H, CH_2), 5.65 (d, 1H, CH=P), 7.30-7.75 (m, 15 H, arom.-H), 8.01 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 186.29 (C=S), 172.10 (C=O), 159.90 (C=O), 154.44 (C=P), 124.80 -133.60 (arom.-C), 51.05 (CH_2); ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 35.04. MS *m/z* (%) [173 $(M-277)^+$,5]. Anal. Calcd. for $C_{23}H_{19}N_2O_2PS_2$ (450.51) : C, 61.32; H, 4.25; N, 6.22; P, 6.88; S, 14.23 %; Found: C, 60.94; H, 4.15; N, 6.09; P, 6.69; S, 13.70 %.

Interaction of hexaphenylcarbodiphosphorane (7) with 3-amino-2-thioxo-1,3-thiazolidin-4-one (1)

To a solution of **1** (148 mg, 1 mmol) in 20 mL of dry *THF,* was added a solution of hexaphenylcarbodiphosphorane **(7)** [27] (536 mg, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was refluxed for 12 hrs during which the color changed from red to dark red. *THF* was distilled off under reduced pressure and the remained residue was chromatographed on silica gel using pet. ether (60-80 ^{0}C): ethyl acetate as eluent (90:10, *v/v*), to give compound **9** and triphenylphosphane oxide (m.p. and mixed m.p. 151^{0}C).

2,2,2-Triphenyl-2,4-dihydro-1H-2λ^5-[1,3]thiazolo[4,3-e][1,2,3]diazaphosphole-6-thione (9)

Yellowish brown crystals, yield 77 %, mp: 190-192 ^{o}C, IR (KBr, $\tilde{\nu}$, *cm^{-1})* : 3397 (NH), 1238 (C=S).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.11 (s, 2H, CH_2), 5.00 (d, 1H, CH=P), 7.11-7.79 (m, 15 H, arom.-H), 8.60 (s, 1H, NH, exchangeable with D_2O; ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 21.20. MS *m/z* (%) 408 [$(M+2H)^+$, 8]. Anal. Calcd. for $C_{22}H_{19}N_2PS_2$ (406.5): C, 65.00; H, 4.71; N, 6.89; P, 7.62; S, 15.78 %; Found: C, 64.94; H, 4.65; N, 6.76; P, 7.51; S, 15.65 %.

Interaction of (*N*-phenyliminovinylidene)triphenylphosphorane (2a) with thiazol-2-amine (10)

A mixture of (*N*-phenyliminovinylidene)triphenylphosphorane **(2a)** (754 mg, 2 mmol) in 20 mL of dry *THF*, was added drop by drop with stirring at room temperature, to thiazol-2-amine **(10)** (100 mg, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was stirred for 4 hrs during which the color was changed from brown to black with the progress of the reaction, which was monitored by (TLC). *THF* was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 ^{0}C)/ ethyl acetate as eluent (70:30, *v/v*), two products **11a** and **13** were isolated along with triphenylphosphane (m.p. and mixed m.p. 78^{0}C).

***N'*-Phenyl-*N*-(1,3-thiazol-2-yl)-2-(triphenyl-λ^5-phosphan- ylidene)ethanimidamide (11a)**

Colorless crystals, yield 55 %, mp: 158-160^{o}C. ^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 6.93-7.77 (m, 23H, arom.-H), 12.60 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 169.21 (C=N), 167.87 (S-C=N), 152.5 (C=P), 139.38 (-N-CH=), 129.71 -134.20 (arom.-C), 106.35 (S-CH=). MS *m/z* (%) 479 [(M+2H))$^+$, 10]. Anal. Calcd. for $C_{29}H_{24}N_3PS$ (477.56): C, 72.94; H, 5.07; N, 8.80; P, 6.49; S, 6.71 %; Found: C, 72.85; H, 5.00; N, 8.69; P, 6.39; S, 6.59 %.

6-(Phenylimino)-4-thia-2-aza-bicyclo[3.2.0]hepta-1(7),2-dien-3-amine (13)

Colorless crystals, yield 25 %, mp: 194-196^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}) : 3289, 3227 (NH_2), 1614 (H_2N-C=N), 1543 (C=N).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 3.04 (s, 1H, S-CH), 5.35 (s, 1H, =CH), 7.25-7.55 (m, 7 H, arom.-H+NH_2); ^{13}C NMR (125 MHz, d6-DMSO, δ, ppm): 183.55 (H_2N-C=N), 168.26 (C=N), 129.71-134.20 (arom.-C), 113.38 (=CH), 37.22 (S-CH). MS m/z (%) [215 (M)$^+$, 100]. Anal. Calcd. for $C_{11}H_9N_3S$(215.27): C, 61.37; H, 4.21; N, 19.52; S, 14.89 % ; Found: C, 61.19; H, 4.25; N, 19.29; S, 14.75 %.

Reaction of (2-oxovinylidene)triphenylphosphorane (2b) with thiazol-2-amine (10)

A solution of (2-oxovinylidene)triphenylphosphorane **(2b)** (604 mg, 2 mmol) in 20 mL of dry toluene was added to a solution of **10** (100 mg, 1 mmol) in 20 mL of dry toluene and refluxed for 10 hrs, during which the color was changed from brown to black with the progress of the reaction, which was monitored by (TLC). Toluene was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 ^{0}C)/ ethyl acetate as eluent (85:15, *v/v*), two products, **11b** and **12b** were isolated.

***N*-(1,3-Thiazol-2-yl)-2-(triphenyl-λ^5-phosphanylidene)acetamide (11b)**

Colorless crystals, yield 45 %, mp: 293-295^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3492 (NH), 1759 (C=O), 1525 (C=P), 1462, 1406 (P-aryl) .^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 6.25 (d, 1H, CH=P), 6.90-7.77 (m, 18 H, arom.-H+NH); ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 31.97. MS *m/z* (%) [401(M-1H)$^+$, 3], [140 (M-Ph_3P)$^+$, 8]. Anal. Calcd. for $C_{23}H_{19}N_2OPS$ (402.45) :C, 68.64; H, 4.76; N, 6.96; P, 7.70; S, 7.97. %; Found: C, 68.55; H, 4.62; N, 6.89; P, 7.58; S, 7.91 %.

3-Amino-6-(triphenyl-λ^5-phosphanylidene)-2-thia-4-azabicyclo[3.2.0]hept-3-en-7-one (12b)

Colorless crystals, yield 32 %, mp: 219-221^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3464, 3366 (NH_2), 1666 (C=O), 1593 (H_2N-C=N), 1520 (C=P), 1488, 1454 (P-aryl). ^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 3.04 (d, 1H, S-CH), 3.23 (m, 1H, N-CH), 7.18-7.74 (m, 15 H, arom.-H), 9.60 (s, 2H, NH_2, exchangeable with D_2O); ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 185.84 (C=O), 158.64 (H_2N-C=N), 154.50 (C=P), 122.68-139.59 (arom.-C), 64.32 (N-CH-), 56.74 (S-CH); ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): -23.20. MS *m/z* (%) [404 (M+2H)$^+$, 10]. Anal. Calcd. for $C_{23}H_{19}N_2OPS$(402.45) : C, 68.64; H, 4.76; N, 6.96; P, 7.70; S, 7.97 %; Found: C, 68.54; H, 4.70; N, 6.89; P, 7.65; S, 7.89 %.

Interaction of hexaphenylcarbodiphosphorane (7) with thiazol-2-amine (10)

To a solution of **10** (100 mg, 1 mmol) in 20 mL of dry *THF,* was added a solution of hexaphenylcarbodiphosphorane **(7)** (536 mg, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was refluxed

for 12 hrs during which the color changed from colorless to yellowish brown and the precipitate is formed and filtered. Crystalization from diethylether to form compound **14**.

***N*-{Triphenyl[(triphenyl-λ^5-phosphanylidene)methyl]-λ^5-phosphanyl}-1,3-thiazol-2-amine (14)**

Yellowish brown crystals, yield 90 %, mp: 181-183^{o}C, IR (KBr, $\tilde{\nu}$,cm^{-1}) : 3397 (NH), 1522 (C=P).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 4.00 (dd, 1H, CH=P), 6.94-7.81 (m, 32 H, arom.-H), 9.26 (s, 1H, NH, exchangeable with D_2O); ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 30.84 (C=P), 43.98 (NH-P). MS *m/z* (%) [636 $(M)^+$, 2]. Anal. Calcd. for $C_{40}H_{34}N_2P_2S$(636.72) : C, 75.45; H, 5.38; N, 4.40; P, 9.73; S, 5.04%; Found: C, 75.34; H, 5.25; N, 4.29; P, 9.59; S, 5.03 %.

Interaction of (*N*-phenyliminovinylidene)- (2a) and (2-oxovinylidene)-triphenylphosphorane (2b) with 1-(3-aminophenyl)ethanone (15)

A mixture of (N-phenyliminovinylidene)- **(2a)** (754 mg, 2 mmol) or (2-oxovinylidene)triphenyl-phosphorane (604 mg, 2 mmol) **(2b)** in 20 mL of dry *THF*, was added drop by drop with stirring at room temperature, to 1-(3-aminophenyl)ethanone **(15)** (135 mg, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was stirred for 6 hrs in case of **2a** and 12 hrs in case of **2b** during which the color was changed from yellow to brown then black with the progress of the reaction, which was monitored by (TLC). *THF* was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 ^{0}C)/ ethyl acetate as eluent (25:75, *v/v*) in case of **2a** and (60:40, *v/v*) for **2b**, two products were isolated in each case, **18a** and **19a** in case of **2a** and **18b** and **19b** in case of **2b** along with triphenylphosphane oxide (m.p. and mixed m.p. 151^{0}C).

3-{1-[2,4-Bis(phenylimino)-3-(triphenyl-λ^5-phosphanylidene)cyclobutylidene]ethyl}aniline (18a)

Yellow crystals, yield 32 %, mp: 123-125^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}) : 3310, 3295 (NH_2), 1620, 1615 (2 C=N), 1545 (C=P).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 1.99 (s, 3H, CH_3), 3.66 (s, 2H, NH_2, exchangeable with D_2O), 7.46-7.68 (m, 29 H, arom.-H). MS *m/z* (%) [509 $((M\text{-}C{=}N\text{-}Ph))^+$, 10]. Anal. Calcd. for $C_{42}H_{34}N_3P$ (611.71): C, 82.47; H, 5.60; N, 6.87; P, 5.06 %; Found: C, 82.34; H, 5.55; N, 6.79; P, 5.99 %.

***N*-(3-Acetylphenyl)-*N'*-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethanimidamide (19a)**

Colorless crystals, yield 45 %, mp: 144-146^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3353 (NH), 1610 (C=N), 1525 (C=P), 1477, 1454 (P-aryl).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 2.26 (s, 3H, $COCH_3$), 5.6 (d, 1H, CH=P), 7.07-7.52 (m, 25 H, arom.-H+NH). MS *m/z* (%) [513 $(M+1H)^+$ 15], [262, Ph_3P, 70]. Anal. Calcd. for $C_{34}H_{29}N_2OP$ (512.58) : C, 79.67; H, 5.70; N, 5.47; P, 6.04 %; Found: C, 79.44; H, 5.65; N, 4.39; P, 5.99 %.

2-[1-(3-Aminophenyl)ethylidene]-4-(triphenyl-λ^5-phosphanylidene)cyclobutane-1,3-dione (18b)

Yellow crystals, yield 37 %, mp: 112-114^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3110, 3058 (NH_2), 1700, 1696 (2 C=O), 1540 (C=P), 1477, 1455 (P-aryl).^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 1.96 (s, 3H, CH_3), 2.58 (s, 2H, NH_2, exchangeable with D_2O), 7.45-7.58 (m, 19 H, arom.-H). MS *m/z* (%) [461 $(M)^+$, 5]. Anal. Calcd. for $C_{30}H_{24}NO_2P$(461.49): C, 78.08; H, 5.24; N, 3.04; P, 6.71%; Found: C, 77.97; H, 5.15; N, 3.00; P, 6.60 %.

***N*-(3-Acetylphenyl)-2-(triphenyl-λ^5-phosphanylidene)acetamide (19b)**

Yellow crystals, yield 37 %, mp: 210-212^{o}C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3335 (NH), 1645 (C=O), 1512 (C=P), 1455, 1437 (P-aryl). ^{1}H NMR (500 MHz, d_6-DMSO, δ, ppm): 2.57 (s, 3H, $COCH_3$), 7.34-8.08 (m, 20 H, arom.–H), 8.8 (s, 1H, NH, exchangeable with D_2O). MS *m/z* (%) [437 $(M)^+$, 20]. Anal. Calcd. for $C_{30}H_{24}NO_2P$(437.47) : C, 76.87; H, 5.53; N, 3.20; P, 7.08 %; Found: C, 76.74; H, 5.45; N, 3.12; P, 7.00%.

ISSN: 0975-8585

Biological Evaluation of the Tested Compounds

Biological Screening

The antibacterial and antifungal activities were carried out in the Microbial Chemistry Department, National Research Centre, using the diffusion plate method [28-31].

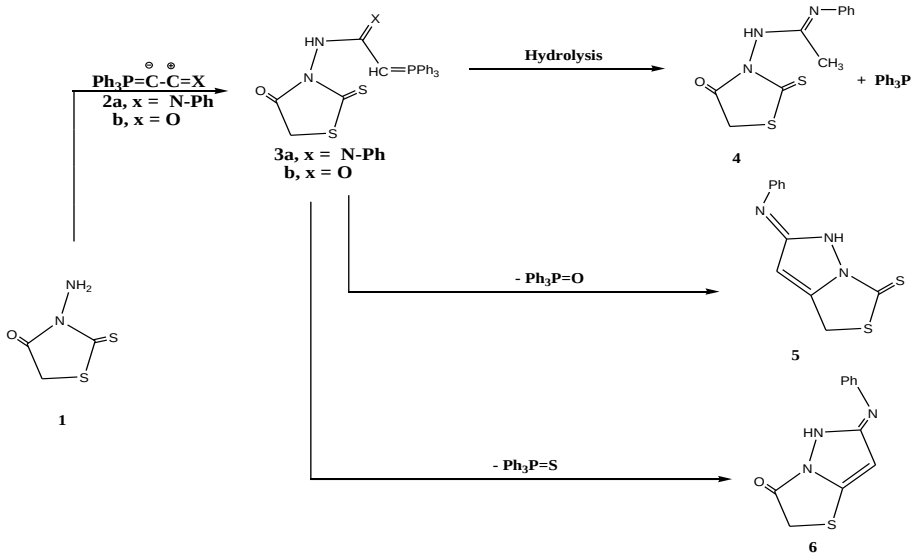
Procedure

A disc of sterilized filter paper saturated with measured quantity (25 µL) of the tested sample (1 mg/mL final concentration) was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37 °C for 24 h for bacteria (in case of fungi, at 25 °C for 72 h), the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in chloroform as a solvent.

RESULTS AND DISCUSSION

The reaction of 3-amino-2-thioxo-1,3-thiazolidinone (**1**) with (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**) in *THF* (1:1 molar ratio) gave *N*-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N'*-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethanimidamide **(3a)**. The key step in this transformation involves protonation of the nucleophilic phosphorane **2a** to form the phosphanylidene **3a**. Hydrolysis of compound **3a**, resulted in the formation of *N*-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N'*-phenylethanimidamide (**4**) and triphenylphosphane. Moreover, when the reaction was performed using (1:2 molar ratio) intramolecular *Wittig* reaction of compound **3a** afforded 1,2-dihydro-2-(phenylimino)pyrazolo[1,5-c]thiazole-6(4*H*)-thione **(5)** together with triphenylphosphane oxide or gave 5,6-dihydro-6-(phenylimino)pyrazolo[5,1-b]thiazol-3(2*H*)-one (**6**) along with triphenylphosphane sulphide. The proposed structures of the new compounds **3a**, **4**, **5** and **6** were supported by their analytical and spectroscopic data such as IR, ^{1}H- ^{13}C-, ^{31}P NMR and MS spectra. For example, IR spectrum of **3a** showed the NH, C=O and C=S at 3432, 1684 and 1187 cm^{-1} respectively. Moreover, signals at δ 188.25 (C=S), 163.56 (C=O), 162.52 (C=N) and 153.23 ppm (C=P) were recorded in ^{13}C NMR spectrum of **3a**. In its ^{31}P NMR spectrum a signal at δ 21.26 ppm was found which fits with phosphorane structure [32-34]. The mass spectrum indicated the presence of an ion peak at m/z (%) 525 [(M)$^+$, 3]. Next, when the amino-thioxothiazolidinone **1** was treated with (2-oxovinylidene)triphenylphosphorane (**2b**) in boiling toluene, only the addition product *N*-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-2-(triphenyl-λ^5-phosphanylidene)acetamide (**3b**) was isolated (Scheme 1).

Scheme 1



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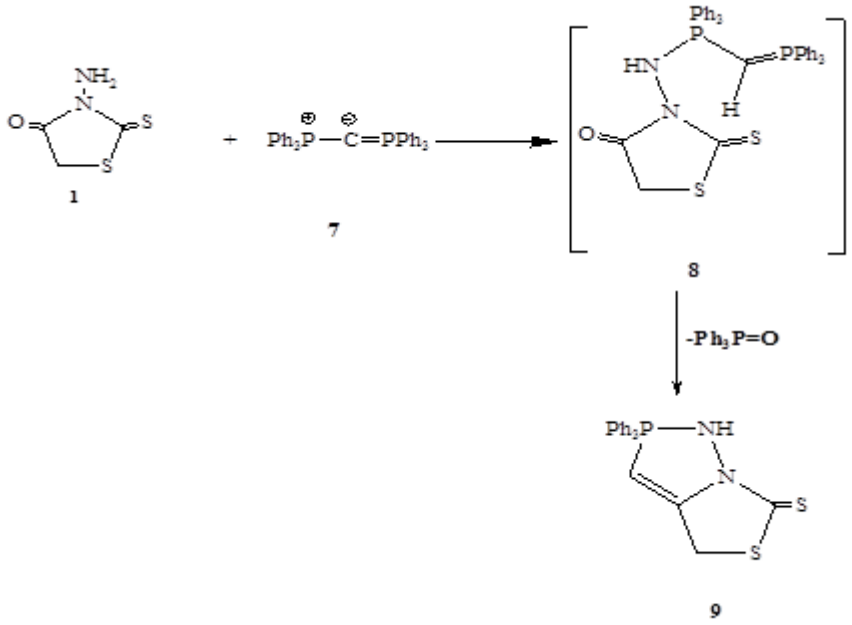
In addition, the behavior of the amino-thioxothiazolidinone **1** towards the bisphosphorane, hexaphenylcarbodiphosphorane (**7**) was studied. When **1** was treated with **7** in boiling *THF*, 2,2,2-triphenyl-2,4-dihydro-1*H*-2λ^5-[1,3]thiazolo[4,3-e][1,2,3]diazaphosphole-6-thione (**9**) along with triphenylphosphane oxide were obtained. It could be demonstrated that formation of **9** from the reaction of **1** with **7** can be explained by addition of **1** to **7** followed by intramolecular *Wittig* reaction to give the final product **9** and triphenylphosphane oxide. The IR spectrum of **9** showed strong absorption bands at 3397 (NH) and 1238 cm^{-1} (C=S). Its ^{1}H NMR spectrum showed bands at δ 4.11 ppm (s, CH_2), 5.00 (d, CH=P), 7.11 – 7.79 (m, arom-H) and 8.60 (s, NH) exchangeable with D_2O. Moreover, a signal at δ 21.20 ppm was observed in the ^{31}P NMR spectrum of **9** and in its mass spectrum, m/z (%) 408 [$(M+2H)^+$, 8] (Scheme 2).

Scheme 2



When thiazol-2-amine **(10)** was treated with two mol equivalents of (*N*-phenyliminovinylidene) triphenylphosphorane **(2a)** in *THF*, at room temperature, two products **11a** and **13** were obtained along with triphenylphosphane. Addition of the thiazolamine **10** to the phosphacumulene **2a** gives *N'*-phenyl-*N*-(1,3-thiazol-2-yl)-2-(triphenyl-λ^5-phosphanylidene)ethanimidamide (**11a**). This reaction proceeds *via* [2+2] cycloaddition to furnish **12a**, which directly under the condition of *Hoffmann degradation* results in the formation of 6-(phenylimino)-4-thia-2-aza-bicyclo[3,2.0]hepta-1(7)2-dien-3-amine **(13)** and triphenylphosphane. The mass spectrum of **11a** indicated the presence of an ion peak at m/z (%)[479 (M^+), 10], and the mass spectrum of **13** showed the presence of an ion peak at m/z (%) [215 (M^+), 100].

When thiazolamine **10** was allowed to react with (2-oxovinylidene)triphenylphosphorane (**2b**) in boiling toluene two products were isolated. Addition of compound **10** to the phosphacumulene **2b,** afforded *N*-(1,3-thiazol-2-yl)-2-(triphenyl-λ^5-phosphanylidene)acetamide **(11b)**. In addition the reaction of **10** with **2b** proceeds also by [2+2] cycloaddition to give the stable 3-amino-6-(triphenyl-λ^5-phosphanylidene)-2-thia-4-azabicyclo[3.2.0]hept-3-en-7-one **(12b)**. The ^{31}P NMR spectrum of **11b** showed signal at δ 31.97 ppm and in its mass spectrum m/z = 401 [$(M-H)^+$, 3%]. Moreover, a signal at δ (-23.20) ppm was observed in the ^{31}P NMR spectrum of **12b** and the mass spectrum indicated the presence of an ion peak at m/z (%); 404 [$(M+2H)^+$, 10]. On the other hand, when the thiazolamine **10** was treated with equimolar amounts of the diphosphorane **7** in *THF*, the corresponding *N*-{triphenyl[(triphenyl-λ^5-phosphanylidene)methyl-λ^5-phosphanyl}-1,3-thiazol-2-amine **(14)** was obtained. Two signals were observed in its ^{31}P NMR spectrum at δ 30.84 (C=P) and δ 43.98 ppm (N-P-C), and the mass spectrum indicated the presence of an ion peak at m/z (%) [636 $(M)^+$, 2] (Scheme 3).

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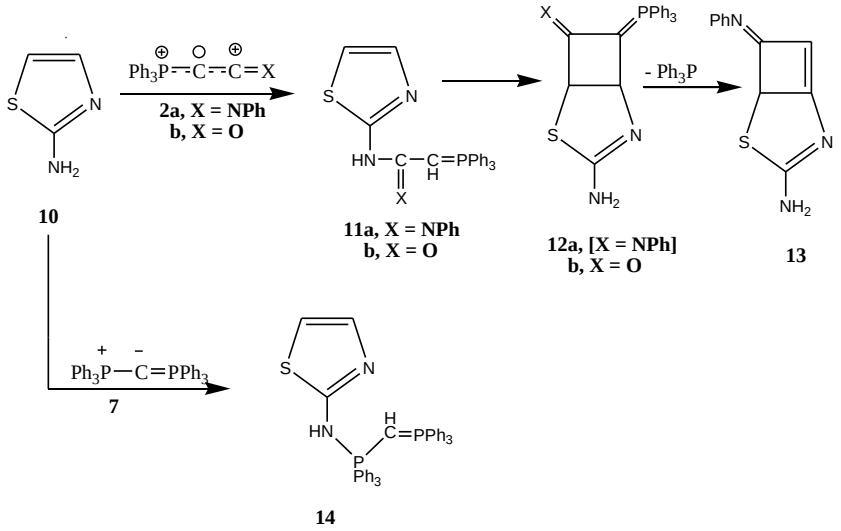
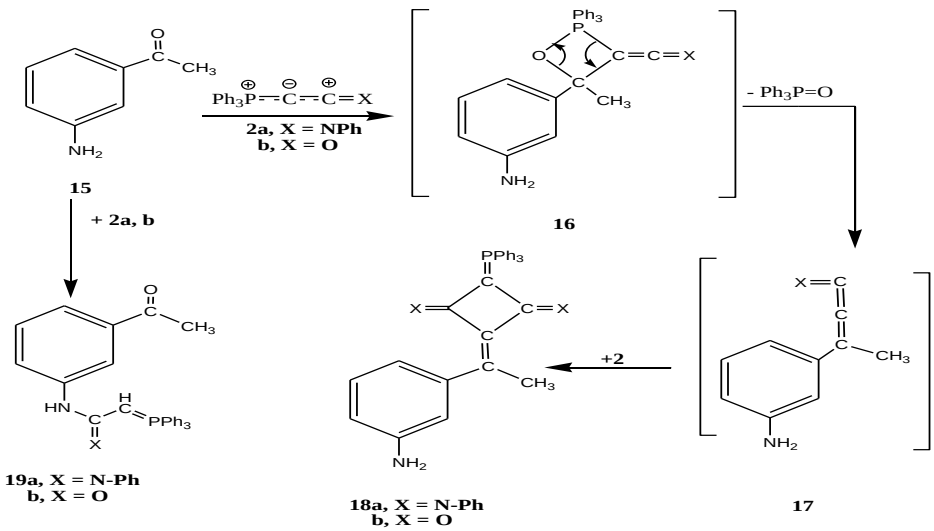
Scheme 3



The study was extended to investigate the behavior of 1-(3-aminophenyl)ethanone **(15)** towards the phosphacumulenes **2a,b**. Treatment of compound **15** with the reagents **2a,b** in *THF* for 6 hrs in case of using **2a** and for 12 hrs with **2b**, afforded two reaction products in each case along with triphenylphosphane oxide. In the first pathway, compound **15** reacts with the reagent **2a** by [2+2] cycloaddition of C-carbonyl group [35,36], to the ylidic C-P bond to give the unstable oxaphosphetane **16**, through a dipolar intermediate [37-39]. The oxaphosphetane decomposed to the unstable ketene **17 [**40] and triphenylphosphane oxide, which is a good leaving group. [2+2] Cyclization of a second molecule of **2a** to the ketene **17**, afforded the four-membered ring 3-{1-[2,4-bis(phenylimino)-3-(triphenyl-λ^5-phosphanylidene)cyclobutylidene]ethyl}aniline **(18a)**. In the second pathway the aminoethanone **15** adds to the reagent **2a** to give *N*-(3-acetylphenyl)-*N'*-phenyl-2-(triphenyl- λ^5-phosphanylidene)ethanimidamide **(19a)**. The mass spectrum of **18a** indicated the presence of an ion peak at m/z (%) [509 ((M-C=N-Ph))$^+$, 10]. On the other hand, the mass spectrum of **19a** showed the presence of an ion peak at m/z (%) [513 (M+H)$^+$, 15]. Furthermore, the reaction of the aminoethanone **15** with (2-oxovinylidene)triphenylphosphorane (**2b)** afforded, 2-[1-(3-aminophenyl)ethylidene]-4-(triphenyl-λ^5-anyli dene)cyclobutane-1,3-dione **(18b)** and *N*-(3-acetylphenyl)-2-(triphenyl-λ^5-phosphanylidene)acetamide **(19b)** (Scheme 4).

Scheme 4



ISSN: 0975-8585

Antimicrobial Evaluation

The antimicrobial activity of the tested compounds was examined against Gram-positive bacteria *Bacillus cereus* and *Staphylococcus aureus*, Gram-negative bacteria *Escherichia coli, Salmonella,* and *Pseudomonas aeruginosa*, and fungus *Candida albicans*. The obtained results are compared with the reference antibiotics [28-31] that were purchased from Egyptian markets. Antibiotic were used as positive control, while chloroform used as negative control.

Table (1) summarize the results of the bioassays. Among antibacterial and antifungal bioassays, an antibacterial test was found comparatively more successful than antifungal test. The antifungal assay indicated that none of the tested compounds showed significant activity towards the fungus except compound **18a** showed 50% inhibition against the pathogen *Candida albicans*. It is observed that compound **5** exhibited higher activity than the reference antibiotic against *Salmonella*, with inhibition zone reached 20 mm compared to 15 mm of the tested reference antibiotic. Excellent antibacterial activity was achieved by compounds **9** and **18b** against Gram negative bacteria Salmonella, compound **13** against *E. coli*, and compounds **13** and **19b** against *P. aeruginosa* with inhibition activity equal to the inhibitory effect of the standard antibiotic used. In addition compound **12b** has high antibacterial effect against Gram positive bacteria *B. cereus* with inhibition zone reaching 33 mm compared to 35 mm of the tested reference. Moreover, compounds **9, 11b, 12b** and **18b** showed moderate activity against *P. aeruginosa,* while compounds **3b, 4, 11a, 11b** and **13** showed also moderate effect against *Salmonella*. The remaining compounds displayed weak or none activity against all microbes under investigation. The obtained results are highly valuable and of biological sound to application in discovering novel antimicrobial material.

Table 1: The antibacterial and Antifungal Activities of the Synthesized Compounds

	Inhibition zone diameter *mm/mg* sample Compound No.																
Microorganism	Gram Strain	**3a**	**3b**	**4**	**5**	**6**	**9**	**11a**	**11b**	**12b**	**13**	**14**	**18a**	**18b**	**19a**	**19b**	**Ref. antib. ***
Bacillus cereus	+ve	15	12	15	18	16	12	10	12	**33**	18	0.0	15	12	8	0.0	35
Staphylococcus aureus	+ve	10	0.0	.0.0	12	10	0.0	12	15	0.0	13	8	20	15	8	16	30
Escherichia coli	-ve	0.0	0.0	0.0	0.0	8	0.0	0.0	0.0	0.0	**15**	0.0	12	10	0.0	0.0	15
Pseudomonas aeruginosa	-ve	0.0	0.0	0.0	12	11	16	12	15	15	**20**	11	2	15	0.0	**20**	20
Salmonella typhimurium	-ve	0.0	13	12	**20**	0.0	**15**	13	12	0.0	12	0.0	0.0	**15**	0.0	0.0	15
Candida albicans	fungus	0.0	0.0	0.0	0.0	14	0.0	11	10	0.0	12	0.0	20	0.0	0.0	0.0	40

** Reference antibiotics are Nizo-arm (antifungal) and Penicillin (antibacterial)*

CONCLUSION

The reaction of nucleophilic active phosphacumulene and phosphallene ylides with aminothioxothiazolidinone, thiazolamine and aminophenylethanone represent an interesting approach to the synthesis of new carbocyclic and heterocyclic bioactive compounds. Cycloaddition, intramolecular *Wittig* and *Hoffmann degradation* reactions took place and the reaction products depend on the nature of the substrate, reagents and reaction condition used. Moreover, the difference in the nucleophilic character and reactivity of the phosphorus reagents were noticed, (*N*-phenyliminovinylidene)- > (2-oxovinylidene)-triphenylphosphorane > hexaphenylcarbodiphosphorane. While the (*N*-phenyliminovinylidene)triphenylphosphorane reacts smoothly with the reactants, the (2-oxovinylidene)triphenylphosphorane and the hexaphenylcarbodiphosphorane react less rapidly [41]. These processes can be considered as simple and efficient route for the formation of phosphanylidenes, thiazolthione, pyrazoles, diazaphospholes, cyclobutanes. The antimicrobial activity of the tested compounds was examined against Gram positive bacteria, Gram negative bacteria and fungus. Compound **5** exhibited higher activity than the reference antibiotic against *Salmonella*. Excellent antibacterial activity was achieved by compounds **9**, **18b, 13** and **19b** against bacteria with inhibition activity equal to the inhibitory effect of the standard antibiotic.

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