Chemistry of Phosphorus Ylides: Part 46—Efficient Synthesis and Biological Evaluation of New Phosphorus, Sulfur, and Selenium Pyrazole Derivatives

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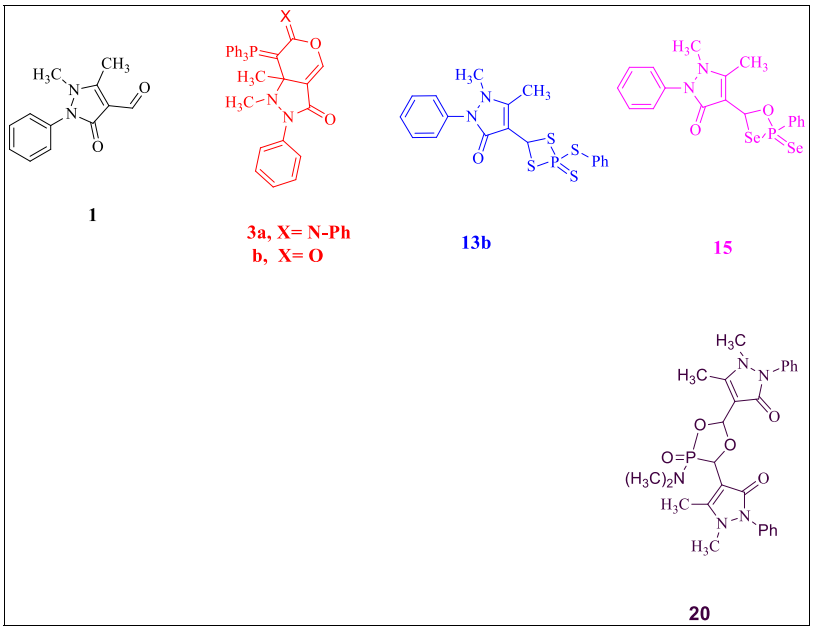


1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde was allowed to react with different phosphorus, sulfur, and selenium reagents. The reaction products depend on the nature of the reagent and the condition of the reaction used. Treatment of the carbaldehyde with the active phosphacumulene ylides afforded the phosphoranylidene pyranopyrazoles. On the other hand, its reaction with the stable phosphonium ylides gave the oxaphosphetanes. Sulfidodithiaphosphetane pyrazole was generated from the reaction of Japanese reagent with the carbaldehyde. Selenido-oxaselenaphosphetane and dioxaphospholane pyrazoles were obtained from the reaction of the carbaldehyde with *Woolin*'s reagent and phosphorus triamide, respectively. The antimicrobial screening of the synthesized compounds was also evaluated.

INTRODUCTION

Pyrazole and its derivatives constitute an important compound covering a broad range of synthetic as well as natural products that display innumerable chemical, biological, agrochemical, and pharmacological properties [1–7]. Moreover, considerable amount of work has been carried out in the synthetic development of envisaging the pyrazole fusion with the pyran heterocyclic unit with potential applications in medicinal chemistry. Pyranopyrazole derivatives have been particularly found to exhibit anticancer [8], antimicrobial [9], insecticidal [10], anti-inflammatory [11], and molluscicidal activities [12]. Moreover, some of these analogues have shown promising human Ch K1 kinase growth inhibition [13].

RESULTS AND DISCUSSION

Chemistry. In our continuing studies, we have described the development of new biomolecules of therapeutic interest from the reaction of active and stabilized phosphonium ylides with bioactive natural and unnatural products with potential applications in medicinal chemistry [14–21].

By reacting 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (**1**) with (*N*-phenyliminovinylidene)-triphenylphosphorane (**2a**) in tetrahydrofuran (THF), compound 1,7a-dimethyl-2-phenyl-6-(phenylimino)-7-(triphenylphosphoranylidene)-1,6,7,7a-tetrahydropyrano[4,3-*c*]pyrazol-3(2*H*)-one (**3a**) was obtained. The phosphacumulene ylides can be represented by the resonance structures **2A** and **2B**. They react with some unsaturated compounds with the resonance structure **2A** and with carbonyl compounds the resonance structure **2B** (*Wittig reaction*). Thus, the reaction of the carbaldehyde **1** with the cumulated phosphonium ylide **2a** run by [4 + 2]-cycloaddition and gave the pyran **3a**. No triphenylphosphane oxide was isolated from the reaction, which means that no [2 + 2]-cycloaddition of **2a** to the aldehyde group of **1** occurred. The structure of product **3a** was confirmed on the basis of the respective spectral data. In the ^{1}H NMR spectrum of **3a** signals appeared at δ 1.62 (s, 3 H, CH_3), 3.10 (s, 1 H, *N*–CH_3), 6.16 (s, 1 H, CH═C), 6.79–7.77 (m, 25 H, Ar–H). The ^{13}C NMR spectrum of **3a** showed signals at δ 162.46 (C═O, pyrazolone), 154.15 (C═N), 148.86 (C═P), 111.17–143.84 (arom.-C), 39.96 (N–CH_3), and 27.50 ppm (CH_3). Moreover, a signal at δ 28.79 ppm was observed in its ^{31}P NMR spectrum [22].

When the reaction of the carbaldehyde **1** with (2-oxovinylidene) triphenylphosphorane (**2b**) was carried out in boiling toluene, 1,7a-dimethyl-2-phenyl-7-(triphenylphosphoranylidene)-1,2,7,7a-tetrahydropyrano[4,3-*c*]pyrazole-3,6-dione (**3b**) was obtained (Scheme 1).

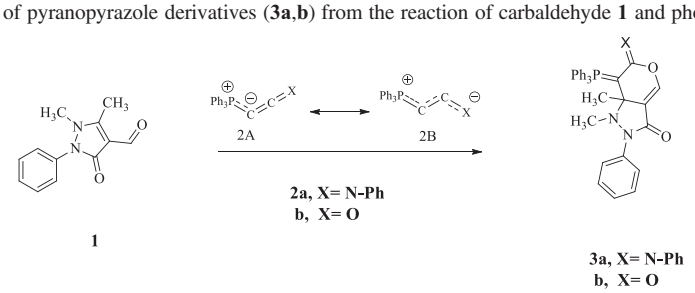
The behavior of the stabilized phosphonium ylides **4a**–**4f** toward the carbaldehyde **1** was studied, too, to determine the site of attack. It was found that methoxycarbonyl-(**4a**), ethoxycarbonyl-(**4b**), acetyl-(**4c**), benzoyl-(**4d**), formyl-(**4e**), and nitrile-(**4f**) methylene triphenylphosphorane react with the carbaldehyde **1** to give the intermediates betains **5a**–**5f**, by addition of the ylide carbon atom to the carbonyl group of the carbaldehyde **1**. In the second step, a four-membered ring **6** is formed. Compounds **6a** and **6b** are stable, but the intermediates **6c**–**6f** decompose into the olefins **7c**–**7f** and triphenylphosphane oxide. The structure of the oxaphosphetane **6a** was established on the basis of IR, ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data. The mass spectrum of **6a** showed the molecular ion peak at *m*/*z* 550 $(M)^+$ and a signal in the ^{31}P NMR spectrum at δ 31.79 ppm, which supports the oxaphosphetane structure [23,24]. On the other hand, in the mass spectrum of the oxobutene **7c**, the molecular ion peak was found at *m*/*z* (%) = 256 (M^+, 100) (Scheme 2).

The reaction of phosphinimine **8** was studied with the carbaldehyde **1**, too. In their reactivity, the iminophosphoranes are inferior to phosphinalkylenes [25–27]. We have found that the carbaldehyde **1** reacted with *N*-(triphenylphosphoranylidene) aniline (**8**) in boiling toluene for 20 h, to give 1,5-dimethyl-2-phenyl-4-((phenylimino)methyl)-1*H*-pyrazol-3(2*H*)-one (**9**), together with triphenylphosphane oxide. The mass spectrum of **9** showed an molecular ion peak at *m*/*z* = (291, $[M]^+$) (Scheme 3).

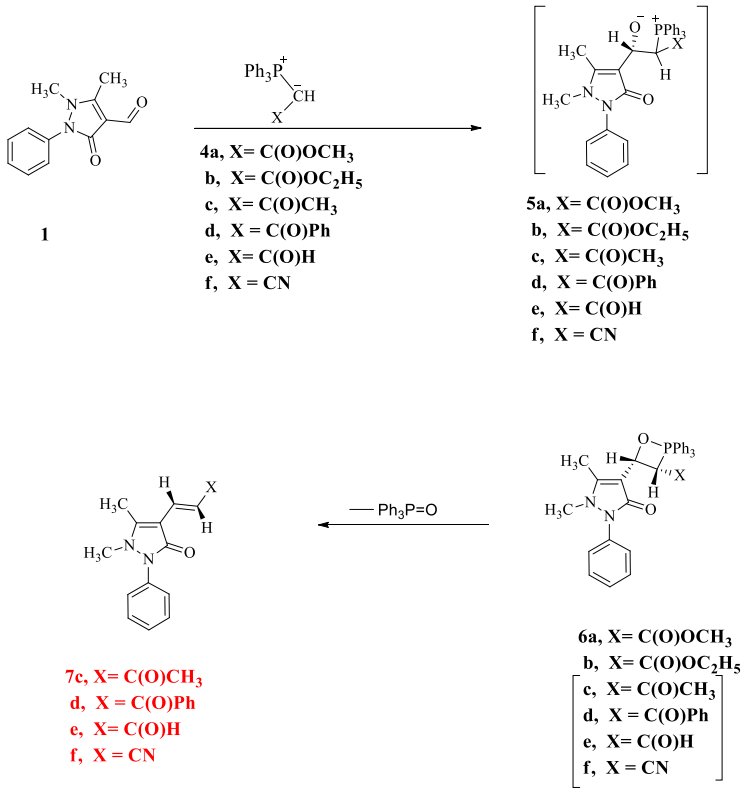
P-S heterocycles have been well established, and they are widely used [28–31]. In the present study, we investigated the reactions of some thionating agents on the carbaldehyde **1**. When phosphorus pentasulfide was allowed to react with carbaldehyde **1** in THF at room temperature, 1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1*H*-pyrazole-4-carbothialdehyde (**10**) was obtained. The IR spectrum of **10** showed the characteristic band due to the C═S at 1185 and 1120 cm^{-1}, and in its MS, an ion peak was observed at *m*/*z* 247 $[M–H]^+$.

Chemistry of Japanese reagent (JR) (2,4-bis(phenylthio)-1,2,3,4-dithiaphosphetane-2,4-disulfide) (**11a**) has been studied for many years. This reagent **11a** exists in equilibrium with the monomeric form **11b**, which can be incorporated with the substrate [32–35]. When the carbaldehyde **1** reacted with JR **11b** in THF at room temperature, 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbothialdehyde (**12**) was isolated. The mass spectrum of **12** showed an ion peak *m*/z (%) at 232 (M^+, 15), and its IR spectrum showed the (C═O, pyrazole) and the C═S at 1649 and 1159 cm^{-1}, respectively. On the other hand, when the carbaldehyde **1** reacted with JR in dry boiling toluene for 10 h, 1,5-dimethyl-2-phenyl-4-(2-(phenylthio)-2-sulfido-1,3,2-dithiaphosphetan-4-yl)-1*H*-pyrazol-3(2*H*)-one (**13b**) was formed. It could be concluded that formation of the dithiaphosphetane **13b**

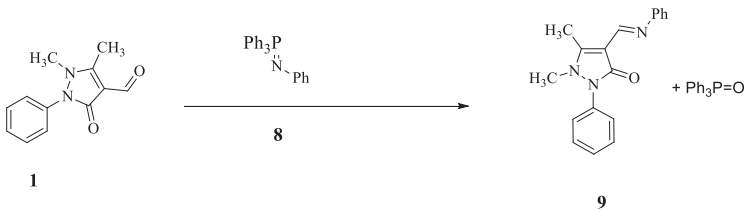
Scheme 1. Synthesis of pyranopyrazole derivatives (**3a**,**b**) from the reaction of carbaldehyde **1** and phosphacumulene (**2a**,**b**).



Scheme 2. Synthesis of oxaphosphetane (**6a**, **6b**) and olfin derivatives **7c**–**7f** from the reaction of carbaldehyde **1** and stabilized phosphonium ylides **4a**–**4b**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Synthesis of iminopyrazole derivative **9**.

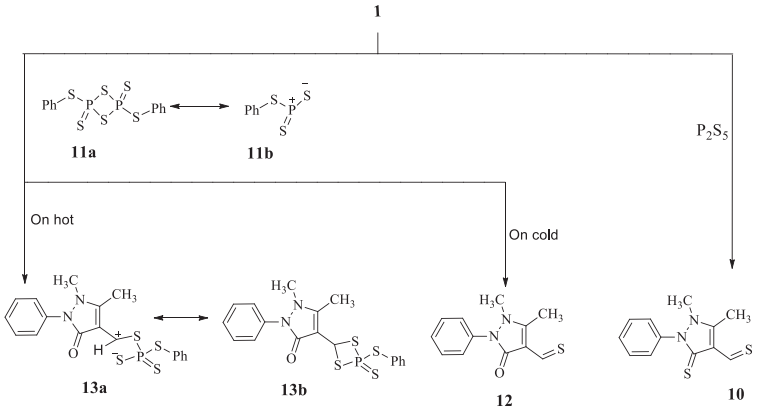


from the reaction of JR **11b** and carbaldehyde **1**, firstly, thionation reaction occurred to the oxygen atom of carbaldehyde **1** followed by the nucleophilic attack of the sulfur center of compound **1** on the electron-deficient center of the monomeric species of JR **11b** to give the zwitterionic adduct **13a**, which cyclizes to give the dithiaphosphetane **13b**. Upon treatment of the carbaldehyde **1** with phosphorus pentasulfide or JR on cold temperature, thionation reactions occur, and we isolate only compound **10** or **12**, respectively. But when the reaction of **1** with JR was performed on hot temperature, the new heterocyclic sulfur compound **13b** was obtained (Scheme 4). The most important feature in the spectroscopic data of compound **13b** is that an ion peak at *m*/*z* (20%) 436 $(M)^+$ was found in the MS.

Selenium is an essential element for life; selenocysteine is viewed as the 21st amino acid in the natural repertoire, and the importance of selenium-containing enzymes in redox processes has been increasingly recognized [36–38]. Moreover, organoselenium compounds have been studied as biological models that are capable of simulating catalytic functions demonstrated by natural enzymes [39–41].

Woolin's reagent (**14a** ⇌ **14b**), just like JR, dissociates, and as a result in the solution, there is diselenophosphine ylide, which is the appropriate nucleophilic reagent (**14b**) [42]. So the present study was extended also to the reaction of the carbaldehyde **1** with Woolin's reagent in boiling toluene. 1,5-Dimethyl-2-phenyl-4-(2-phenyl-2-selenido-1,3,2-oxaselenaphosphetan-4-yl)-1*H*-pyrazol-3

Scheme 4. Synthesis of organophosphorus and sulfur pyrazole derivatives **10**, **12**, and **13b** from the reaction of carbon disulfide and Japanese reagent **11a** with pyrazolone carbaldehyde **1**.



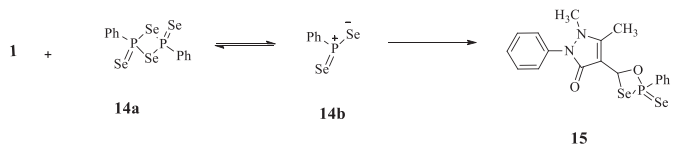
(2*H*)-one (**15**) was obtained (Scheme 5). The structure of compound **15** was confirmed through its MS; it showed the *m*/*z* (%) at 482 (M^+, 8).

Hexamethylphosphorus triamide (**16**) is a strong nucleophile used to synthesize epoxides and arene oxides from aldehydes [43–45]. Thus, the reagent also replaces triphenylphosphane in the Wittig reaction [46].

Now, the reaction of the aldehyde **1** with the phosphorus triamide reagent **16** was performed in boiling toluene. The product of the reaction depends upon the electronegativity of the aldehyde and the mode of carrying out the reaction. Compound 4,4′-(dimethylamino)-2-oxido-1,4,2-dioxaphospholane-3,5-diyl)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(*H*)-one (**20**) was only isolated. The mechanism of this reaction can be explained by initial nucleophilic attack of the aldehyde **1** by the phosphorus triamide **16** to form the phosphonium 1:1 adduct **17**. This adduct **17** reacted with a second aldehyde molecule to form the 2:1 adduct **18**, which cyclizes to the dioxaphospholane **19**. The intermediate **19** adds molecule of water in the presence of unavoidable moisture to give the final stable oxaphospholane pyrazole **20** along with dimethylamine (Scheme 6). The ^{1}H NMR of **20** shows signals at δ 1.74 (s, 6 H, C–CH_3), 2.01 (d, 6 H, P–N–CH_3), 2.51 (s, 6H, N–CH_3), 5.45 (d, 1H, $^2J_{HP}$ = 6 Hz, O–CH–P), 6.49 (d, 1H, $^3J_{HP}$ = 3 Hz, O–CH–O), and 7.31–7.81 ppm (m, 10 H, aromatics).

Antimicrobial evaluation. The newly prepared compounds **3a**, **3b**, **6a**, **6b**, **7c**, **7d**, **7e**, **10**, **12**, **13b**, **15**, and **20** were screened for their antimicrobial activity against Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Pseudomonas aeruginosa* by using acetyltetracyclene as reference standard. The solvent control used was dimethyl sulfoxide (DMSO). The yeast and antifungal activities were screened against *Candida albicans* and *Aspergillus niger*. The inhibition zone for each compound was measured and compared with the reference. The results of antimicrobial screening are illustrated in Table 1 and show that most of the tested compounds have excellent to good antimicrobial interest. Compounds **3a**, **3b**, **6a**, **7c**, **10**, **13b**, and **15** are the most active compounds against the yeast *C. albicans*, exceeding the inhibitory effect of the reference drug; the clear inhibition zone reached from 6 to 11 mm, while the inhibition zone for the reference was zero, and it is considered an excellent result. Moreover, compounds **3a** and **7c** showed good inhibition zone that reached 7 mm for both compounds and 6 mm for compound **13b** equal to that of the reference antibiotic against the fungus *A. niger*. On the other hand, excellent antimicrobial activity was also achieved by compounds **6b** and **7c** against the Gram-negative strain pathogen *P. aeruginosa* with clear zone higher than that of the reference drug. It is well known that pyrazole derivatives have a big diversity in antimicrobial activity [47], especially pyranopyrazoles. Therefore, compound **3a** showed a good result; the clear inhibition zone reached 21 mm, and it is a good result, near to the inhibitory effect of the reference against Gram-positive bacteria *S. aureus* because it contains phosphopyranpyrazole, which is

Scheme 5. Synthesis of selenido-oxaselenaphosphetane derivative **15**.



Scheme 6. Synthesis of dioxaphospholane derivative **20** from the reaction of pyrazolone carbaldehyde **1** and hexamethylphosphorus triamide **16**.

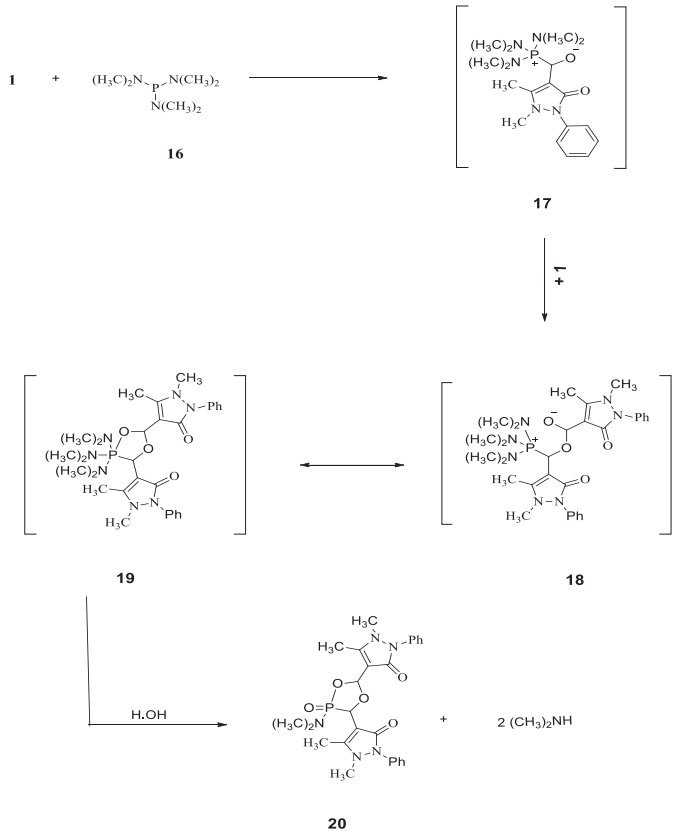


Table 1

Antimicrobial activities of the new compounds.

Microorganism	Gram stain reaction	Inhibition clear zone (mm)											
		Compound no.											Reference antibiotic (acetyltetracyclene)
		3a	**3b**	**6a**	**6b**	**7c**	**7d**	**7e**	**10**	**12**	**13b**	**15**	**20**	
Staphylococcus aureus	Positive	**21**	11	6	6	NA	NA	NA	6	9	15	NA	NA	**25**
Pseudomonas aeruginosa	Negative	**9**	6	8	**15**	**11**	NA	NA	6	6	7	8	NA	**10**
Candida albicans	Yeast	**8**	**9**	**7**	NA	**11**	NA	NA	**6**	NA	**11**	**6**	NA	**0**
Aspergillus niger	Fungus	**7**	NA	NA	NA	**7**	NA	NA	NA	NA	**6**	NA	NA	**7**

NA, no activity.

bioactive against these pathogens [48]. Moreover, the skeleton of **6a** includes the oxaphosphetane group, which increases the physiological properties. In addition, a few of the tested compounds appeared to have moderate inhibitory effect; some of them had no inhibitory effect as well.

CONCLUSION

The synthesis of pyrazole derivatives containing phosphorus, sulfur, and selenium reagents represent an interesting approach to the preparation of new bioactive heterocyclic compounds. The reaction of pyrazole

carbaldehyde **1** with the active phosphacumulenes **2a**,**b** took place smoothly with the formation of the phosphoranylidene pyranopyrazoles **3a**,**b**, while the reaction of the stable phosphonium ylides **4a**–**b** with the aldehyde **1** afforded the oxaphosphetanes **6a**,**b**, and the phosphonium ylides **4c**–**f** gave the olefins **7c**–**f**. On the other hand, the phosphinimine **8**, which is less reactive than are the phosphinalkylenes **4a**–**f**, afforded the iminomethylpyrazole **9**, on reaction with the carbaldehyde **1**. Moreover, the reaction of the sulfur reagents phosphorus pentasulfide and JR **11** with the carbaldehyde **1** resulted in the formation of the thioxopyrazole **10**, pyrazole carbothialdehyde **12**, and sulfidodithiaphosphetane pyrazole **13**. The present investigation afforded also the selenido-oxaselenaphosphetane pyrazole **15** from the reaction of Woolin's reagent **14** with the carbaldehyde **1**. Finally, the oxaphospholane pyrazole **20** was isolated from the reaction of hexamethylphosphorus triamide **16** and the carbaldehyde **1**. These reactions supply direct route for the synthesis of phosphorus, sulfur, and selenium derivatives. Moreover, the antimicrobial activity of the synthesized compounds showed that compounds **3a**, **3b**, **6a**, **7c**, **10**, **13b**, and **15** recorded a marked high activity against the yeast *C. albicans*, while compounds **3a**, **7c**, and **13b** were the most active with the fungus than was the reference drug, and compounds **6b** and **7c** have the highest activity against the Gram-negative bacteria *P. aeruginosa*. In addition, compound **3a** recorded moderate activity with *S. aureus*, the Gram-positive bacteria.

EXPERIMENTAL

Chemistry. Melting points were determined with an electrothermal digital melting point apparatus (Electrothermal Engineering Ltd., Essex, UK). The IR spectra were recorded in KBr discs on a Pye Unicam SP 3300 and Shimadzu FTIR 8101 PC Infrared Spectrophotometers (Pye Unicam Ltd., Cambridge, UK, and Shimadzu, Tokyo, Japan, respectively). ^{1}H and ^{13}C NMR spectra were obtained from a JEOL ECA 500 MHz (Tokyo, Japan), Bruker Avance 300 MHz, and a Varian Mercury VXR-300 MHz NMR spectrometers using hexadeuterated DMSO (DMSO-d_6) as a solvent and tetramethylsilane as an internal reference at 500 and 300 MHz (^{1}H NMR) and at 125 and 75.46 MHz (^{13}C NMR), respectively. ^{31}P NMR spectra were obtained from Bruker Avance 300 MHz and a JEOL ECA 500 MHz NMR spectrometer at 121 and 202 MHz using DMSO-d_6 as a solvent and tetramethylsilane as an internal reference. Chemical shifts were related to those of the solvent. Mass spectra (electron-impact mass spectrometry) were obtained with ISQ (single quadrupole MS, Thermo Scientific) and Shimadzu GCMS-QP EX mass spectrometer at 70 eV. Elemental analysis (C, H, N) results were recorded with Elementar Vario EL Germany, and all of these agreed satisfactory with the calculated values. The 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). The starting material, no. 1, was purchased from Aldrich Company under CAS no. 950-81-2; compound **8** was from Aldrich Company CAS no. 2325-27-1; compound **14** was from Aldrich Company CAS no. 122039-27-4; and compound **16** was from Merck Company CAS no. 680-31-9. Solvents were dried/purified according to literature procedures [49].

Interaction of (*N*-phenyliminovinylidene) triphenylphosphorane (2a) with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). A solution of (*N*-phenyliminovinylidene) triphenylphosphorane (**2a**) [50] (0.377 g, 1 mmol) in 20 mL of THF was added dropwise with stirring at room temperature to a solution of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (**1**) (0.216 g, 1 mmol) in 20 mL of THF. The reaction mixture was stirred for 10 h, during which the color changed from buff to red (the progress of the reaction was monitored by TLC). THF was distilled under reduced pressure, and the residue was chromatographed on silica gel column using petroleum ether (60–80°C)/ethyl acetate (60:40, v/v) as an eluent; product **3a** was isolated.

1,7a-Dimethyl-2-phenyl-6-(phenylimino)-7-(triphenylphosphoranylidene)-1,6,7,7a-tetrahydropyrano[4,3-c]pyrazol-3(2H)-one (3a). Yield 55%, yellow crystals, m.p. 238–240°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1727 (C═O, pyrazolone), 1653 (C═N), 1589 (C═P), 1495, 1449 (P-aryl). ^{1}H NMR (300 MHz, DMSO, δ, ppm): 1.62 (s, 3 H, CH_3), 3.10 (s, 1 H, *N*–CH_3), 6.16 (s, 1 H, CH═C), 6.79–7.77 (m, 25 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 162.46 (C═O, pyrazolone), 154.15 (C═N), 148.86 (C═P), 111.17–143.84 (arom.-C), 39.96 (N–CH_3), 27.5 (CH_3). ^{31}P NMR (202.4 MHz, DMSO-d_6, δ, ppm): 28.79. MS (*m*/*z*, %): 315 [M–(Ph_3P═O) 100]$^+$, 300 [M–(Ph_3P═O + CH_3), 65]$^+$, 285 [M–(Ph_3P═O + 2 CH_3), 5]$^+$. *Anal*. Calcd for $C_{38}H_{32}N_3O_2P$ (593.65). Calcd: C, 76.88; H, 5.43; N, 7.08; P, 5.22. Found: C, 76.79; H, 5.33; N, 6.55; P, 5.10.

Reaction of (2-oxovinylidene) triphenylphosphorane (2b) with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). A solution of (2-oxovinylidene) triphenylphosphorane (**2b**) [51] (0.302 g, 1 mmol) in 20 mL of dry toluene was added to a solution of **1** (0.216 g, 1 mmol) in 20 mL of dry toluene and refluxed for 12 h, during which the color was changed from colorless to brown and precipitate formed (the progress of the reaction was monitored by TLC). Filter and recrystallize by ethyl acetate to give compound **3b**.

1,7a-Dimethyl-2-phenyl-7-(triphenylphosphoranylidene)-1,2,7,7a-tetrahydropyrano[4,3-c]pyrazole-3,6-dione (3b). Yield 70%, colorless crystals, m.p. 106–108°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1624 (br, 2 C=O), 1483 (C=P), 1431, 1381 (P-aryl). ^1H NMR (300 MHz, DMSO, δ, ppm): 2.51 (s, 3 H, CH_3), 3.13 (s, 3 H, N–CH_3), 7.37–8.34 (m, 21 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 172.80 (C=O, pyrazol), 158.58 (C=O, pyranone), 151.79 (C=P), 119.79–135.29 (arom.-C), 79.67 (CH–O), 39.10 (N–CH_3), 8.01 (CH_3). ^{31}P NMR (202.4 MHz, DMSO-d_6, δ, ppm): 29.64. MS (*m/z*, %): 433 [M–(2 CO + 2 CH_3)$^+$ 15], 417 [(M–CO_2+ CO+ 2 CH_3)$^+$, 80], 263 [(PPh_3) 7], 215 [pyrazole carbaldehyde, 100]. *Anal*. Calcd for $C_{32}H_{27}N_2O_3P$ (518.54). Calcd: C, 74.12; H, 5.25; N, 5.40; P, 5.97. Found: C, 73.99; H, 5.18; N, 5.33; P, 5.85.

The reaction of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1) with stabilized phosphonium ylide (4a, 4b). ***General procedure.*** A mixture of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (**1**) (0.216 g, 0.001 mol) and stabilized phosphonium ylides (**4a**,**b**) [52] (0.001 mol) in 30 mL of dry toluene was boiled for 10 h. The colors changed to yellow, and the precipitates are formed in both reactions. The precipitate was filtered and crystallized from benzene to give **6a** and **6b**, respectively.

Methyl-4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2,2,2-triphenyl-1,2λ^5-oxaphosphetane-3-carboxylate (6a). It was isolated from the reaction of the carbaldehyde **1** and methoxycarbonyl-methylenetriphenylphosphorane (**4a**). Yield 55%, colorless crystals, m.p. 133–135°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1665 (C=O, pyrazole), 1615 (C=O), 1485, 1433 (P-phenyl). ^1H NMR (300 MHz, DMSO, δ, ppm): 2.39 (s, 3 H, CH_3), 3.24 (s, 3 H, N–CH_3), 3.77 (s, 3 H, O–CH_3), 7.03–7.72 (m, 22 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 169.11 (2 C=O), 125.14–133.24 (arom.-C), 115.52 (CH), 51.38 (OCH3), 34.5 (*N*–CH_3), 10.84 (CH_3). ^{31}P NMR (121 MHz, DMSO-d_6, δ, ppm): 31.79. MS (*m/z*, %): 550 [M]$^+$, 272 [M–(Ph_3P=O), 60]$^+$, 277 (Ph_3P=O, 9). *Anal*. Calcd for $C_{33}H_{31}N_2O_4P$ (550.58). Calcd: C, 71.99; H, 5.68; N, 5.09; P, 5.63. Found: C, 71.79; H, 5.63; N, 5.01; P, 5.57.

Ethyl-4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2,2,2-triphenyl-1,2 λ^5-oxaphosphetane-3-carboxylate (6b). It was obtained from the reaction of **1** and ethoxycarbonylmethylenetriphenylphosphorane (**6b**). Yield 45%, colorless crystals, m.p. 158–160°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1700 (C=O, pyrazole), 1661 (C=O), 1485 (br, p-Phenyl). ^1H NMR (300 MHz, DMSO, δ, ppm): 1.28 (t, 3 H, *CH_3*–CH_2), 2.35 (s, 3 H, CH_3), 3.21 (s, 3 H, N–CH_3), 4.17–7.25 (m, 4 H, CH_3*CH_2* + *CH*O–P + *CH*–COO), 6.98–7.71 (m, 20 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 168.60 (C=O, ester), 163.44, (C=O, pyrazole), 125.16–134.27 (arom.-C), 115.84 (CH), 59.98 (CH_2), 34.92 (N–CH_3), 14.37 (CH_3), 10.84 (CH_3, pyrazole). ^{31}P NMR (121 MHz, DMSO-d_6, δ, ppm): 33.34. MS (*m/z*, %): 565 [M + H]$^+$, 550 [M–CH_3]$^+$, 286 [M–Ph_3P=O]$^+$, 277 (Ph_3P=O). *Anal*. Calcd for $C_{34}H_{33}N_2O_4P$ (564.61). Calcd: C, 72.33; H, 5.89; N, 4.96; P, 5.49. Found: C, 72.19; H, 5.82; N, 4.88; P, 5.37.

The reaction of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1) with stabilized phosphonium ylides (4c–f). ***General procedure.*** A mixture of **1** (0.216 g, 0.001 mol) and stabilized phosphonium ylides (**4c**–**f**) (0.001 mol) [53] was refluxed in dry toluene (50 mL) for 10 h. The solvent was distilled under reduced pressure, and the remaining residue was purified on silica gel column chromatography to give compounds (**7c**–**f**) and triphenylphosphane oxide (m.p. and mixed m. p. 151°C).

1,5-Dimethyl-4-(3-oxobut-1-en-1-yl)-2-phenyl-1*H*-pyrazol-3(2*H*)-one (7c). It was isolated by using petroleum ether (60–80°C)/ethyl acetate as an eluent (80:20, v/v), from the reaction of **1** with acetylmethylenetriphenylphosphorane (**4c**). Yield 35%, colorless crystals, m.p. 165–167°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1648 (C=O, pyrazole), 1608 (C=O). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.27 (s, 3 H, $COCH_3$), 2.38 (s, 3 H, CH_3), 3.25 (s, 3 H, N–CH_3), 7.31–7.48 (m, 7 H, Ar–H). MS (*m/z*, %): 256 [[M]$^+$ 100], 241 [(M–CH_3)$^+$ 40], 213 [(M–$COCH_3$)$^+$ 65], 198 [M–(2CH_3 + CO)$^+$ 7]. *Anal*. Calcd for $C_{15}H_{16}N_2O_2$ (256.30). Calcd: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.89; H, 6.21; N, 10.80.

1,5-Dimethyl-4-(3-oxo-3-phenylprop-1-en-1-yl)-2-phenyl-1H-pyrazol-3(2H)-one (7d). It was obtained by using petroleum ether (60–80°C)/ethyl acetate as an eluent (65:35, v/v), from the reaction of **1** and benzoylmethylenetriphenylphosphorane (**4d**). Yield 40%, colorless crystals, m.p. 273–275°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1663 (C=O, pyrazole), 1598 (C=O). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.44 (s, 3 H, CH_3), 3.28 (s, 3 H, N–CH_3), 7.37–7.68 (m, 12 H, Ar–H). MS (*m/z*, %): 318 [[M]$^+$ 100], 213 [[M–(COPh)]$^+$ 40], 105 [COPh, 70]. *Anal*. Calcd for $C_{20}H_{18}N_2O_2$ (318.37). Calcd: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.33; H, 5.58; N, 8.77.

(3-(1,5-Dimethyl-3-oxo-2-phenyl 2,3-dihydro-1H-pyrazol-4-yl) acrylaldehyde (7e). It was isolated by using petroleum ether (60–80°C)/ethyl acetate as an eluent (35:65, v/v), from the reaction of 2-(triphenylphosphoranylidene) acetaldehyde (**4e**). Yield 35%, yellow crystals, m.p. 241–243°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 3425 (OH), 1657 (C=O, pyrazole), 1598 (C=O). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.42 (s, 3 H, CH_3), 3.15 (s, 3 H, N–CH_3), 7.21–7.66 (m, 7 H, Ar–H), 9.86 (s, 1 H, CHO). MS (*m/z*, %): 242 [[M]$^+$ 5], 188 [[M–CHCHCHO]$^+$ 55]. *Anal*. Calcd for $C_{14}H_{14}N_2O_2$ (242.27). Calcd: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.32; H, 5.75; N, 11.49.

3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) acrylonitrile (7f). It was obtained by using petroleum ether (60–80°C)/ethyl acetate as an eluent (90:10, v/v)

from the reaction of **1** and 2-(triphenylphosphoranylidene) acetonitrile (**4f**). Yield 43%, colorless crystals, m.p. 175–177°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 2196 (C ≡ N), 1658 (C═O, pyrazole). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.16 (s, 3 H, CH_3), 3.25 (s, 3 H, N–CH_3), 6.58 (d, 1H, CH, $J_{H–H}$ = 15 Hz), 7.45 (d, 1H, CH, $J_{H–H}$ = 15 Hz), 7.46–7.63 (m, 5 H, Ar–H). MS (*m*/*z*, %): 238 $[M–H]^+$. *Anal*. Calcd for $C_{14}H_{13}N_3O$ (239.27). Calcd: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.13; H, 5.45; N, 17.49.

Interaction of *N*-(triphenylphosphoranylidene) aniline (8) with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). This is a mixture of *N*-(triphenylphosphoranylidene) aniline (**8**) (0.353 g, 0.001 mol) and pyrazole carbaldehyde (**1**) (0.216 g, 0.001 mol) in 20 mL of dry toluene. The reaction mixture was refluxed for 20 h. The color changed to yellow until no more starting materials could be detected (TLC). The solvent was distilled under reduced pressure, and the remaining residue was purified on silica gel column chromatography using petroleum ether (60–80°C)/ethyl acetate as an eluent (35:65, v/v) to give triphenylphosphane oxide (m.p. and mixed m.p. 151°C) and 1,5-dimethyl-2-phenyl-4-((phenylimino)methyl)-1*H*-pyrazol-3(2*H*)-one (**9**). Yield 43%, brown crystals, m.p. 172–174°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1698 (C═O, pyrazole), 1608 (C═N). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.62 (s, 3 H, CH_3), 3.31 (s, 3 H, N–CH_3), 7.21–7.75 (m, 10 H, Ar–H), 9.90 (s, 1H, CH═N). MS (*m*/*z*, %): 291 $([M]^+$, 4), 290 $([M–H]^+$, 20), 261 $(M^+–2CH_3)$, 35). *Anal*. Calcd for $C_{18}H_{17}N_3O$ (291.35). Calcd: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.08; H, 5.85; N, 14.39.

Reaction of phosphorus pentasulfide with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). A solution of phosphorus pentasulfide (0.22 g, 1 mmol) was added dropwise with stirring at room temperature to a solution of **1** (0.216 g, 1 mmol) in 20 mL of THF. The reaction mixture was stirred for 10 h during which the color changed to black and the precipitate formed and then crystallized from benzene to give 1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1*H*-pyrazole-4-carbothialdehyde (**10**). Yield 65%, colorless crystals, m.p. > 300°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1185, 1120 (2 C═S). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.39 (s, 3 H, CH_3), 3.07 (s, 3 H, N–CH_3), 5.56 (s, 1H, CH), 7.29–7.67 (m, 5 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 201.48 (HC═S), 190.74 (C═S), 125.97–133.45 (arom.-C), 24.25 (N–CH_3), 14.15 (CH_3). MS (*m*/*z*, %): 247 $[(M–H)^+$, 5]. *Anal*. Calcd for $C_{12}H_{12}N_2S_2$ (248.37). Calcd: C, 58.03; H, 4.87; N, 11.28; S, 25.82. Found: C, 57.93; H, 4.83; N, 11.21; S, 25.75.

Interaction of (2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) Japanese reagent (11) with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). A solution of JR **11** [54] (0.404 g, 1 mmol) was added dropwise with stirring at room temperature to a solution of **1** (0.216 g, 1 mmol) in 20 mL of THF. The reaction mixture was stirred for 12 h during which the color changed from brown to black (the progress of the reaction was monitored by TLC). THF was distilled under reduced pressure, and the residue was chromatographed on silica gel column using petroleum ether (60–80°C)/ethyl acetate (20: 80, v/v) as an eluent; 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbothialdehyde (**12**) was isolated. Yield 55%, colorless crystals, m.p. 208–210°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1649 (C═O, pyrazole), 1159 (C═S). ^1H NMR (500 MHz, DMSO, δ, ppm): 2.50 (s, 3 H, CH_3), 3.24 (s, 3 H, N–CH_3), 5.76 (s, 1 H, CH), 7.25–7.60 (m, 5 H, Ar–H). MS (*m*/*z*, %): 232 $[[M]^+$ 15], 202 $[[(M)^+–2CH_3]$ 5]. *Anal*. Calcd for $C_{12}H_{12}N_2OS$ (232.30). Calcd: C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 61.90; H, 5.19; N, 11.95; S, 13.69.

Interaction of Japanese and Woolin's reagents with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (1). A mixture of **1** (0.216 g, 0.001 mol) and JR **11** or Woolin's reagents **14** (0.001 mol) was refluxed in dry toluene (50 mL) for 10 h in the case of **11** and 20 h in the case **14** until no more starting materials could be detected (TLC). The solvent was distilled under reduced pressure, and the remaining residue was purified on silica gel column chromatography to give compounds **13** and **15**, respectively.

1,5-Dimethyl-2-phenyl-4-(2-(phenylthio)-2-sulfido-1,3,2-dithiaphosphetan-4-yl)-1H-pyrazol-3(2H)-one (13b). Petroleum ether (60–80°C)/acetone (45: 55, v/v) was used as an eluent. Yield 72%, buff crystals, m.p. 122–125°C. ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3 H, CH_3), 3.65 (s, 3 H, *N*–CH_3), 5.74 (s, 1 H, CH), 7.15–7.73 (m, 10 H, Ar–H). MS (*m*/*z*, %): 436 $[[M]^+$ 20], 434 $[[M–(2H)]$ 100$]^+$, 264 $[[M–PhPS_2]^+$ 50], 188 $[[M–PhPCS_4]^+$ 10]. *Anal*. Calcd for $C_{18}H_{17}N_2OPS_4$ (436.57). Calcd: C, 49.52; H, 3.92; N, 6.42; P, 7.09; S, 29.38. Found: C, 49.44; H, 3.89; N, 6.38; P, 7.00; S, 29.32.

1,5-Dimethyl-2-phenyl-4-(2-phenyl-2-selenido-1,3,2-oxaselenaphosphetan-4-yl)-1H-pyrazol-3(2H)-one (15). Petroleum ether (60–80°C)/acetone (20: 80, v/v) was used as an eluent. Yield 85%, gray crystals, m.p. 228–230°C, IR (KBr, $\tilde{\nu}$, cm^{-1}): 1633 (C═O, pyrazole), 608 (P═Se). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.46 (s, 3 H, CH_3), 2.07 (s, 3 H, N–CH_3), 5.20 (s, 1 H, CH), 7.46–7.70 (m, 10 H, Ar–H). MS (*m*/*z*, %): 482 $[[M]^+$ 8], 467 $[[M–CH_3]^+$ 4]. *Anal*. Calcd for $C_{18}H_{17}N_2O_2PSe_2$ (482.23). Calcd: C, 44.83; H, 3.55; N, 5.81; P, 6.42. Found: C, 44.75; H, 3.51; N, 5.73; P, 6.33.

Interaction of hexamethylphosphorus triamide (16) with 4-hydroxy-3-methoxybenzaldehyde (1). A mixture of hexamethylphosphorus triamide (**16**) (0.163 g, 1 mmol) in 20 mL of dry boiling toluene was added to a solution of compound **1** (0.216 g, 1 mmol) in 20 mL of dry toluene and refluxed for 3 h. Toluene is distilled, and the residue was crystallized from ethanol to form adduct **20**.

4,4′-(2-(Dimethylamino)-2-oxido-1,4,2-dioxaphospholane-3,5-diyl)bis(1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) (20). Yield 77%, yellowish brown crystals, m.p. 105–107°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.74 (s, 6H, C–CH_3), 2.01 (d, 6H, P–N–CH_3), 2.51 (s, 6H, N–CH_3), 5.45 (d, 1H, $^2J_{HP}$ = 6 Hz, O–CH–P), 6.49 (d, 1H, $^3J_{HP}$ = 3 Hz, O–CH–O), and 7.31–7.81 (m, 10 H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.71 (2 C═O), 120.16–133.45 (arom.-C), 106.50 (O–CH–O), 89.41 (O–CH–P), 38.76 (P–N–CH_3), 21.32 (N–CH_3), 14.15 (CH_3, pyrazole). ^{31}P NMR (121 MHz, DMSO-d_6, δ, ppm): 21.59. MS (*m*/*z*, %): 445 [M–(Ph) 3]$^+$, 417 [M–(Ph + CO)]$^+$, 216 [pyrazolone carbaldehyde]. *Anal*. Calcd for $C_{26}H_{30}N_5O_5P$ (523.52). Calcd: C, 59.65; H, 5.78; N, 13.38; P, 5.92. Found: C, 59.55; H, 5.73; N, 13.27; P, 5.87.

Determination of antimicrobial activity. The obtained extract was dissolved in DMSO at a concentration of 500 μg/mL. Aliquots of 50 μL were soaked on filter paper discs (5 mm, Whatman no. 1 filter paper) [55,56] and dried at room temperature under sterilized conditions. The paper discs were placed on agar plates seeded with test microbes and incubated for 24 h at the appropriate temperature of each test organism. Both bacterial and yeast microbes were grown on nutrient agar medium. The fungal strain was on the other hand grown on PDA medium (DSMZ 130). The culture of each microorganism was diluted by sterile distilled water to 10^7 to 10^8 CFU/mL. The inoculated agar plates were incubated in the upright position for 24 h (yeast and bacteria) at 37°C (bacteria) and 48 h (fungi) at 30°C (fungi and yeast). After incubation, the diameter of inhibition zones was measured against a wide range of test microorganisms comprising Gram-positive bacteria (*S. aureus* ATCC6538-P), Gram-negative bacteria (*P. aeruginosa* ATCC 27853), yeasts (*C. albicans* ATCC10231), and fungus (*A. niger* NRRLA-326).

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