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Comparative Study on the Reaction of Organophosphorus Reagents with *Moringa Oleifera* Vanillin. Synthesis of Phosphoranylidenepyranone, Dioxaphospholane and Butenethione Derivatives as Antitumor Agents

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VANILLIN from *Moringa oleifera* plant was allowed to react with different nucleophilic organophosphorus reagents. Treatment of 4-hydroxy-3-methoxybenzaldehyde (vanillin) with the active phosphacumuleneylides (*N*-phenyliminovinylidene)- and (2-oxovinylidene)-triphenylphosphorane afforded the homocyclic phosphoranylidene-cyclobutylidenes. On the other hand, its reaction with the satabilized phosphoniumylide, acetylmethylenetriphenylphos phorane gave the corresponding butenone, which reacted with the active phosphacumulene to give finally the pyran derivative. Next, the phenyliminophenol derivative was obtained from the reaction of vanillin with the iminophosphorane. Moreover, dioxaphospholane oxide was isolated from the reaction of vanillin with phosphorus triamide. Finally, the butenethione was generated from the reaction of Japanese reagent with vanillin.

Keywords: *Moringa oleifera*, Vanillin, Phosphoranylidene, Heterocycles, Antitumors.

Introduction

Vanillin **1** is a naturally occurring substance. It is extracted from *Moringa oleifera* which is a multipurpose plant, utilized for medicinal applications such as cardiac and circulatory stimulants, antitumor, antiulcer, anti-inflammatory, antimicrobial, antihypertensive, antioxidant and antidiabetic agents [1-3]. Vanillin can be considered as one of the most important constituents of *Moringa* plant [4-6] and isolated also from tropical *Vanilla orchid*. It is also widely used in the food and beverage industry and is responsible for the characteristic vanilla flavor. This substance is also relevant to the synthesis of different agrochemicals, antifoaming and pharmaceutical products [7], such as antioxidants [8], antimicrobials [9-11], anti-mutagenic [12,13] and anti-carcinogenic agents [14]. Conversely, vanillin may also induce oxidative stress in yeast cells [15].

Experimental

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 PyeUnicam SP 3300 and Shimadzu FT IR 8101 PC Infrared Spectrophotometers (PyeUnicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H 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 MHz. Mass spectra (EI-MS) were obtained with ISQ (Single Quadrupole MS, Thermo Scientific). Elemental analyses agreed satisfactory with the calculated values. The using reported yields are of pure isolated materials obtained by column chromatography on 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.

Interaction of (N-phenyliminovinylidene) triphenylphosphorane (2a) and 4-hydroxy-3-methoxybenzaldehyde (1)

A solution of (N-phenyliminovinylidene) triphenylphosphorane (2a) [16] (0.377 g, 1 mmol)

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in 20 mL of tetrahydrofuran, was added drop by drop with stirring at room temp, to a solution 4-hydroxy-3-methoxybenzaldehyde (1) (152g, 1 mmol) in 20 mL of tetrahydrofuran. The reaction mixture was stirred for 10 h during which the colour changed from yellow to dark brown (the progress of the reaction was monitored by TLC). *THF* was distilled off under reduced pressure and the residue was chromatographed on silica gel column using petroleum ether (60–80°C): ethyl acetate (30:70, *v/v*) as eluent. Product 5a was isolated along with triphenylphosphane oxide (m.p. and mixed m.p. 151°C).

2,4-Bis(phenylimino)-3-(triphenylphosphoranylidene) cyclobutylidene)methyl)-2-methoxyphenol (5a)

Yield 55%, yellow crystals, m.p. 270-272°C, IR (KBr, *cm*$^{-1}$): 3461 (OH), 1627 (2 C=N), 1557 (C=P), 1487, 1451 (P-Aryl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 3.02 (s, 3 H , OCH_3), 6.28 (s, 1 H, OH, exchangeable with D_2O), 6.36- 6.38 (d, 1 H, $^{5}J_{PH}$ = 10 Hz, CH=P), 6.68-7.60 (m, 28H, Ar-H).^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm):163.12, 163.03 (C=N), 153.48 (C=P), 118.37-138.72 (arom.-C). ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 29.79. MS(*m/z, %)*: 628 [M]$^{+}$, 6]. $C_{42}H_{33}N_2O_2P$ (628.70).

Reaction of (2-oxovinylidene)triphenylphosphorane (2b) with 4-hydroxy-3-methoxybenzaldehyde (1)

A solution of (2-oxovinylidene) triphenylphosphorane (2b) [17] (302 g, 1 mmol) in 20 mL of dry toluene was added to a solution of 1 (0.152 g, 1 mmol) in 20 mL of dry toluene and refluxed for 10 h, during which the color was changed from colorless to yellow and precipitate is formed (the progress of the reaction was monitored by TLC). It was filtered and crystallized from ethyl acetate to give 5b and triphenylphosphane oxide.

2-(4-Hydroxy-3-methoxybenzylidene)-4-(triphenylphosphoranylidene)cyclob-utane-1,3-dione (5b)

Yield 66%, colorless crystals, m.p. 309-310°C, IR (KBr, *cm*$^{-1}$): 3414 (OH), 1661 (br, 2 C=O), 1608 (C=C), 1504 (C=P), 1465, 1435 (P-aryl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 3.02 (s, 3 H , OCH_3), 5.89 (s, 1 H, OH, exchangeable with D_2O), 6.79 - 7.92 (m, 19 H, Ar-H). ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 186. 28 (2 C=O), 153.48 (C=P), 115.72-148.16 (arom.-C). ^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 30.65.MS(*m/z, %)*: 478 [M^{+}], 6]. $C_{30}H_{23}O_4P$(478.47).

Preparation of 4-hydroxy-3-methoxyphenyl)but-3-en-2-one (7)

A solution of 1-(triphenylphosphoranylidene) propan-2-one (6) (0.318 g) in 20 mL of dry toluene was added to a solution of 1 (0.152 g,1 mmol) in 20 mL of dry toluene and refluxed for 15h, during which the colour was changed from colorless to yellow to dark brown, toluene was distilled off under reduced pressure and the residue was chromatographed on silica gel column using petroleum ether (60–80°C) and ethyl acetate. Product 7 was isolated along with triphenylphosphane oxide [18].

Interaction of (N-phenyliminovinylidene) triphenylphosphorane (2a) and 4-hydroxy-3-methoxyphenyl)but-3-en-2-one (7)

A mixture of (N-phenyliminovinylidene) triphenylphosphorane (2a) (0.377 g, 1 mmol) in 20 mL of dry THF, was added drop wise with stirring at room temperature, to a solution of 4-hydroxy-3-methoxyphenyl)but-3-en-2-one (7) (0.192 g, 1 mmol) in 20 mL of dry THF. The reaction mixture was stirred for 4 h during which the color was changed from yellow to red (the progress of the reaction was monitored by TLC). THF was distilled off and the residue was subjected to silica gel column chromatography using petroleum ether (60–80°C)/ethyl acetate as eluent (40: 60, v/v), to give compound 9. along with triphenylphosphane (m.p. and mixed m.p. 78°C).

2-Methoxy-4-(6-methyl-2-(phenylimino)-2H-pyran-4-yl)phenol (9)

Yield 45%, yellowish brown crystals, m.p. 120-122°C, IR (KBr, *cm*$^{-1}$): 3420 (OH). ^{1}HNMR (500 MHz, DMSO, δ, ppm): 2.20 (s, 3 H, CH_3), 3.70 (s, 3 H , OCH_3), 5.07 (s, 1 H, =CH), 7.05 - 7.89 (m, 9 H, Ar-H), 12.52 (s, 1 H, OH, exchangeable with D_2O). MS (*m/z, %)*:307 [M^{+},2], 230 [(M^{+}-C_6H_5) 10]. $C_{19}H_{17}NO_3$(307.34).

Reactionof(2-oxovinylidene)triphenylphosphorane (2b) with 4-hydroxy-3-methoxyphenyl)but-3-en-2-one (7)

A solution of (2-oxovinylidene) triphenylphosphorane (2b) (0.302 g,1 mmol) in 20 mL of dry toluene was added to a solution of (0.192 mg,1 mmol) in 20 mL of dry toluene and refluxed for 8h, during which the color was changed from yellow to brown (the progress of the reaction was monitored by TLC). Toluene was distilled off under reduced pressure and

the residue was subjected to silica gel column chromatography using petroleum ether (60–80°C)/ethyl acetate as an eluent (80: 20, *v/v*) to form compound **8b**.

4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3-(triphenylphosphoran- ylidene)-3,6-dihydro-2H-pyran-2-one (8b)

Yield 67%, colorless crystals, m.p. 163-165°C, IR (KBr, *cm*$^{-1}$): 3425 (OH), 1680 (C=O), 1580 1480, 1437 (P-aryl). ^{1}HNMR (500 MHz, DMSO, δ , ppm):2.00 (s, 3 H, CH_3), 3.40 (s, 3 H, OCH_3), 5.82 (s, 1 H, OH, exchangeable with D_2O), 7.01-7.71 (m, 20 H , Ar.-H).^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 26.18.MS(*m/z, %)*:494 [M^+], 6]. $C_{31}H_{27}O_4P$(494.52).

Interaction of (triphenylphosphoranylidene)aniline (12) and 4-hydroxy-3-methoxybenzaldehyde (1)

A solution of (triphenylphosphoranylidene) aniline **(12)** (0.353 g, 1 mmol) in 20 mL of dry toluene was added to a solution of **1** (0.152 g, 1 mmol) in 20 mL of dry toluene and refluxed for 15 h, during which the colour was changed from colorless to yellow and then dark brown(the progress of the reaction was monitored by TLC. Toluene was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography using petroleum ether (60–80°C)/ethyl acetate as eluent (55 : 45, *v/v*) to form compound **13** and triphenylphosphane oxide.

2-Methoxy-4-((phenylimino)methyl)phenol (13)

Yield 45%, pale red crystals, m.p. 183-185°C, IR (KBr, *cm*$^{-1}$): 3417 (OH), 1590 (C=N). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 3.93 (s, 3 H , OCH_3), 5.94 (s, 1 H, OH, exchangeable with D_2O), 6.56 - 7.42 (m, 8 H, Ar-H), 7.46 (s, 1 H, CH=N). MS(*m/z, %)*: 227 [M^+], 6]. $C_{14}H_{13}NO_2$(227.26).

Interaction of hexamethyl phosphorus triamide (14) with 4-hydroxy-3-methoxybenzaldehyde (1)

A mixture of hexamethyl phosphorus triamide **(14)** (0.163 g, 1mmol) in 20 mL of boiling toluene was added to a solution of **1** (0.152 g, 1 mmol) in 20 mL of dry toluene and refluxed for 3 h. Toluene is distilled off and the residue was crystallized from ethanol to form compound 18.

12-(dimethylamino)-3,5-bis(4-hydroxy-3-methoxyphenyl)-1,4,2-dioxaphospholane 2-oxide (18)

Yield 53%, colorless crystals, m.p. 111-113°C .^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.63 (d, 6 H , 2 N-CH_3), 3.38 (s, 1 H, CH), 3. 73 (s, 6 H, 2 OCH_3), 3.94 (s, 1 H, CH), 6.86- 7.38(m, 6 H, Ar-H), 9.8 (s, 2 H, OH, exchangeable with D_2O).^{31}P NMR (202.4 MHz, d_6-DMSO, δ, ppm): 25.57. MS(*m/z, %)*: 395 [M^+], 10], 347 [M^+-OCH_3+OH], 6], 299 [M^+-2OCH_3+OH], 2]. $C_{18}H_{22}NO_7P$(395.34).

Reaction of (2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) Japanese reagent (19) with 4-hydroxy-3-methoxyphenyl) but-3-en-2-one (7)

A mixture of JR **19** (0. 408 g,1 mmol) in 20 mL of dry *THF*, was added drop wise with stirring at room temperature, to a solution of 4-hydroxy-3-methoxyphenyl)but-3-en-2-one **(7)** (0.192 g, 1 mmol) in 20 mL of dry *THF*. The reaction mixture was stirred for 10 h (the progress of the reaction was monitored by TLC). *THF* was distilled off and the residue was subjected to silica gel column chromatography using petroleum ether (60–80°C)/ethyl acetate as eluent (75: 25, *v/v*) to form **20**.

(Z)4-(4-Hydroxy-3-methoxyphenyl)but-3-ene-2-thione (20)

Yield 75%, colorless crystals, m.p. 235-237°C, IR (KBr, *cm*$^{-1}$): 3432 (OH), 1187 (C=S). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.45 (s, 3 H, CH_3), 3.4 (s, 3 H, OCH_3), 6.21 (s, 1 H, OH, exchangeable with D_2O), 6.89 (d, 1 H, J_{HH} = 5 Hz, CH), 7.28 (d, 1 H, J_{HH} = 5 Hz, CH), 7.46 -7.78 (m, 3 H , Ar-H). ^{13}C NMR (125 MHz, d_6-DMSO, δ, ppm): 24.23 (CH_3), 44.44 (OCH_3), 112 (CH), 120.56 -123.13 (arom.-C), 200.38 (C=S). $C_{11}H_{12}O_2S$(208.28).

Results and Discussion

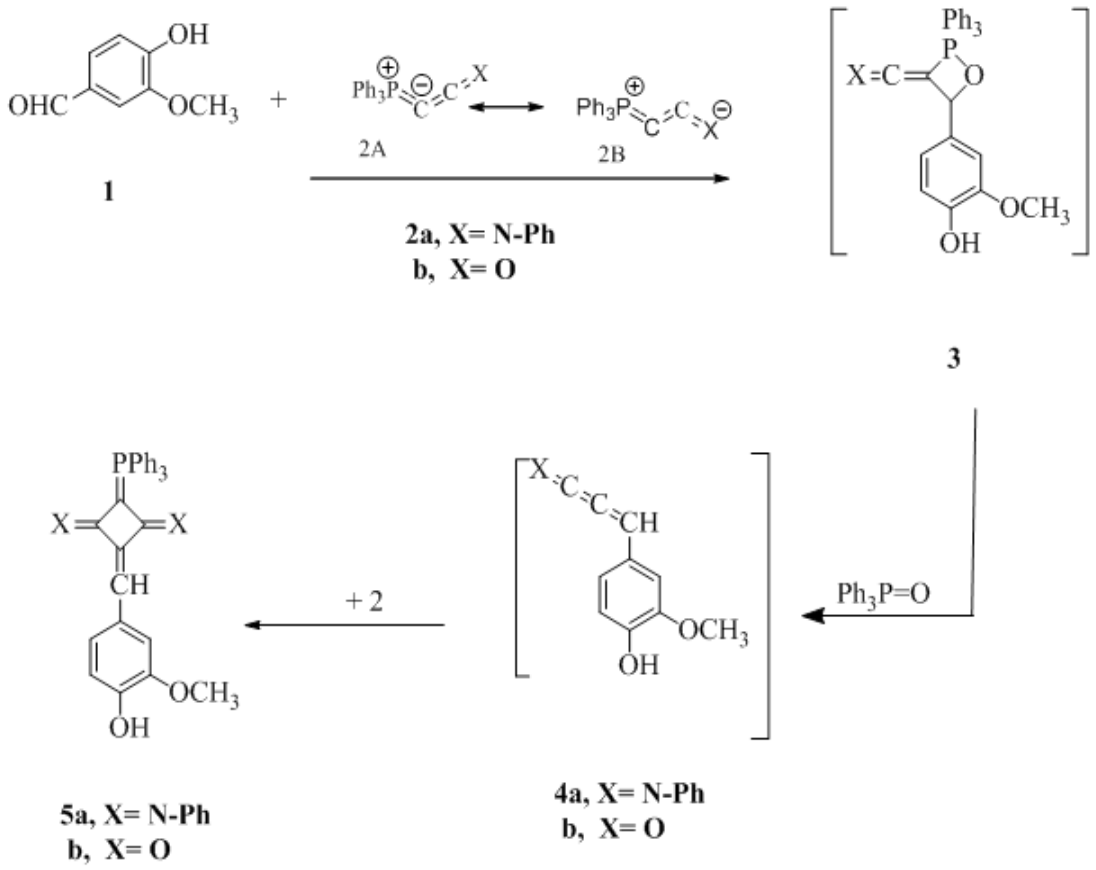
Our interest in studying the reactions of organophosphorus reagents to synthesize pharmacologically interesting carbocyclic and heterocyclic systems containing phosphorus moieties [19-28] led us to examine the reactions of vanillin **(1)** with active phosphacumulenes, stabilized phosphonium ylides, phosphinimine, hexamethyl phosphorus triamide and Japanese reagent.

When vanillin (4-hydroxy-3-methoxybenzaldehyde) (1) was treated with two mole equivalent of active phosphacumulene ylide, namely, (*N*-phenyliminoivinylidene)-triphenylphosphorane (2a) in *THF* at room temperature, the corresponding 2,4-bis(phenylimino)-3-(triphenylphosphoranylidene) cyclobutylidene)methyl)-2-methoxyphenol(5a)

was obtained. Carrying out the reaction of vanillin 1 with (2-oxovinylidene) triphenylphosphorane (2b) in hot dry toluene afforded 2-(4-hydroxy-3-methoxybenzylidene)-4-(triphenylphosphoranylidene)cyclobutane-1,3-dione (5b).The phosphacumuleneylides can be described by the resonance structures 2A and 2B. So, initial nucleophilic attack by the carbanion center in the active phosphacumulene ylides (2a, b) furnishes the oxaphosphetane 3, as an intermediate [29-31]. Expulsion of triphenylphosphane oxide from 3 affords the unstable ketene 4 [32], which is followed immediately by [2+2]-cycloaddition to a second molecule of the active phosphacumulenes 2a,b giving the four-membered ring compounds 5a and b. Structural support for 5a was based upon correct elemental analysis and spectroscopic data. The IR spectrum of 5a (KBr, cm^{-1}) showed strong bands at 3461 (OH), 1627 (2 C=N), 1557 (C=P) [33], 1487, 1451 (P-Aryl) [34].Moreover,^{1}HNMR (500 MHz, DMSO, δ, ppm)spectrum of 5a showed signals at : 3.02 (s, 3 H , OCH_3), 6.28 (s, 1 H, OH, exchangeable with D_2O), 6.36 - 6.38 (d, 1 H, CH=P), 6.68-7.60 (m, 28 H, Ar-H).There are signals at 163.12, 163.03 (C=N), 153.48 (C=P), 118.37-138.72 (arom.-C) in the ^{13}C NMR(125 MHz, d_6-DMSO, δ, ppm) spectrum of 5a. A signal at δ 29.79 ppm was recorded in the ^{31}P NMR spectrum which fits with phosphorane in a four-membered ring [35-37] (Scheme 1).

The behavior of the stabilized phosphoniumylides, acetylmethylenetriphenyl-phosphorane 6 towards vanillin 1, afforded 4-hydroxy-3-methoxyphenyl)but-3-en-2-one (7) together with triphenylphosphane oxide [38]. When the butenone 7 was treated with (N-phenyliminivinylidene)triphenylphosphorane (2a), the corresponding,

2-methoxy-4-(6-methyl-2-(phenylimino)-*2H*-pyran-4-yl)phenol (9) was produced. Formation of compound 9 is proposed to occur by [2+4]-cycloaddition of the ylide to compound 7 to give the phosphoranylidenepyran 8a. Since triphenylphosphane is a good leaving group, so



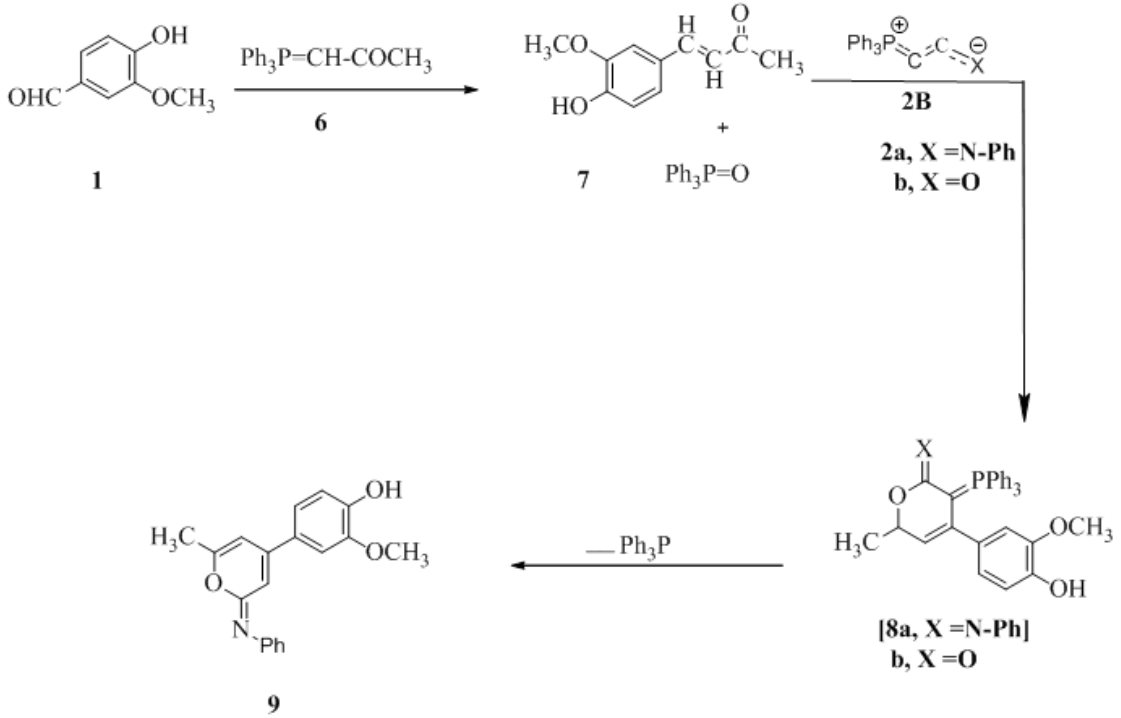
Scheme 1

Hoffmann degradation reaction occurs directly on compound 8a with the formation of the final product 9 and triphenylphosphane. On the other hand, reaction of (2-oxovinylidene) triphenylphosphorane (2b) with the butenone 7 afforded the stable 4-(4-Hydroxy-3-methoxyphenyl)-6-methyl-3-(triphenylphosphoranylidene)-3,6-dihydro-*2H*-pyran-2-one (8b). The most important features in the spectroscopic data of 8b is the appearance of a signal at δ 26.18 ppm and the mass spectrum showed an ion peak at m/z 494 [M^+,6] (Scheme 2)

The reaction of phosphinimines are often analogous to those of phosphonium ylides But in their activity iminophosphoranes are inferior to phosphinalkylenes [39-40]. We have found that 4-hydroxy-3-methoxybenzaldehyde (1) reacts with (triphenylphosphranylidene)aniline (12) in boiling toluene to give 2-methoxy-4-((phenylimino)methyl)phenol (13), along with triphenyphosphane oxide. The mass spectrum of 13 showed a peak at m/z 227 [$(M)^+$,6] (Scheme 3).

The reaction of hexamethyl phosphorustriamide (14) and the aldehyde 1 was investigated, too. When the phosphorus reagent 14 was boiled with the aldehyde 1 in toluene, compound 2-(dimethylamino)-3,5-bis(4-hydroxy-3-methoxyphenyl)-1,4,2-dioxaphospholane 2-oxide (18) was obtained. As shown in scheme 4, formation of compound 18 is proposed to proceed by initial nucleophilic attack on the aldehyde 1 by hexamethylphosphorustriamide 14 to form the phosphonium species 15. Subsequent attack on another molecule of aldehyde 1 by the ylide 15 generates the intermediate 16 which can undergo ring closure to form 17. The last intermediate adds elements of water in the presence of unavoidable moisture to give the final stable product 18 together with dimethyl amine. The most important features in the spectroscopic data of the dioxaphospholane 18 is that it shows a signal at 25.57 ppm in P^{31} NMR spectrum which supports the dioxaphospholane structure [41]. The *m/z* was found at 395 $[M]^+$ in the mass spectrum of 18 (Scheme 4).

Chemistry of Japanese reagent (2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) has been studied for many years [42]. This reagent 19a exists in equilibrium with the monomeric forms 19b, 19c, which can be incorporated with the substrate [43-45]. When the

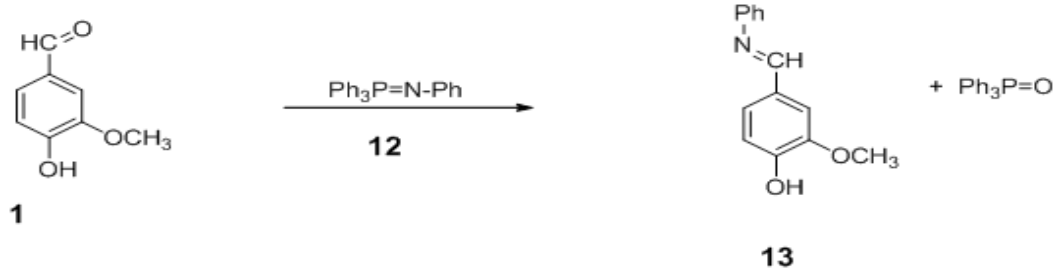


Scheme 2

butene 7 was reacted with JR 19a, in dry *THF*, (4-hydroxy-3-methoxyphenyl)but-3-ene-2-thione (20) was formed. Only thionation reaction was happened and no addition reaction was observed between compound 7 and the monomer 19c (Scheme 5).

Conclusion

Vanillin 1 which can be extracted from the multipurpose plant *Moringa oleifera* was allowed to react with different organophosphorus reagents to prepare carbocyclic and heterocyclic compounds containing phosphorus which



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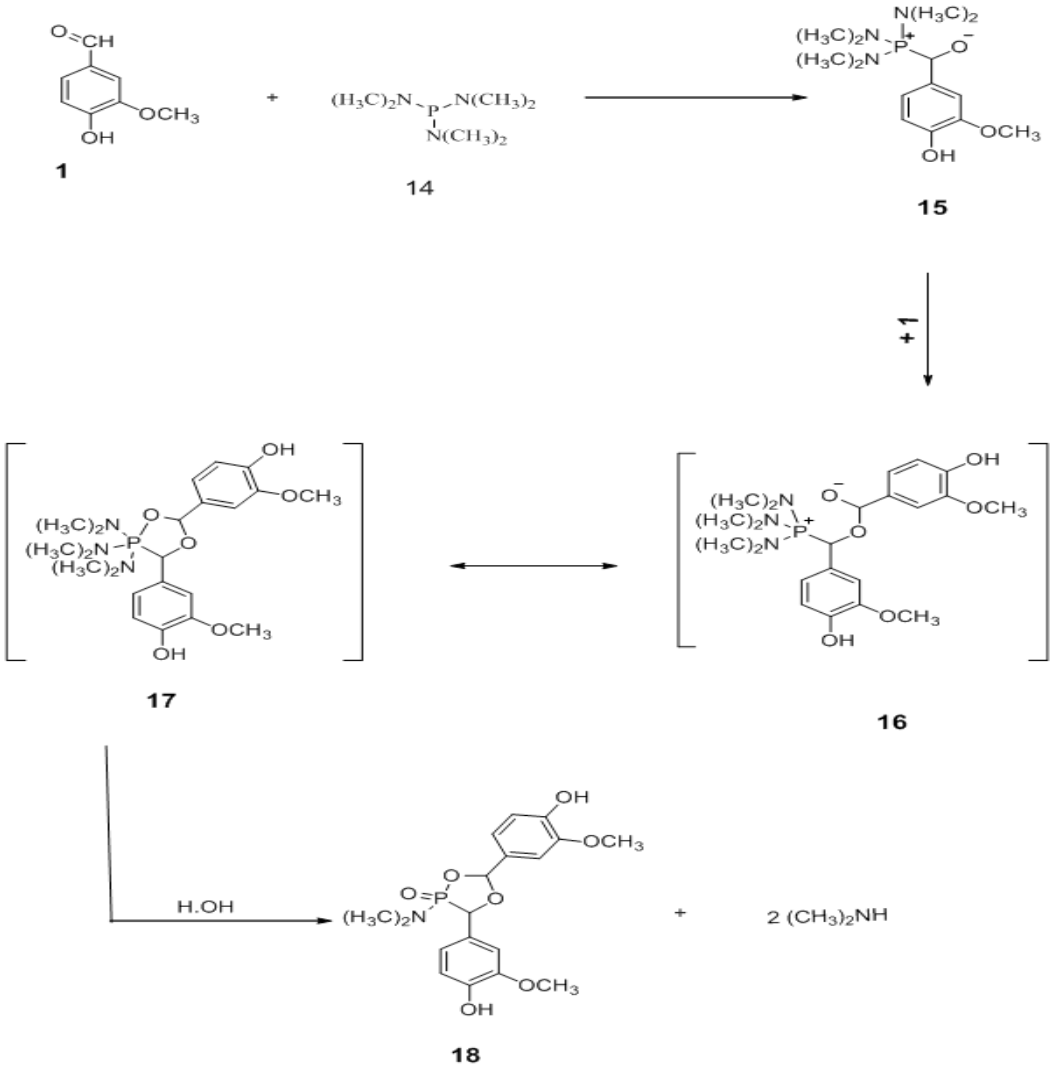
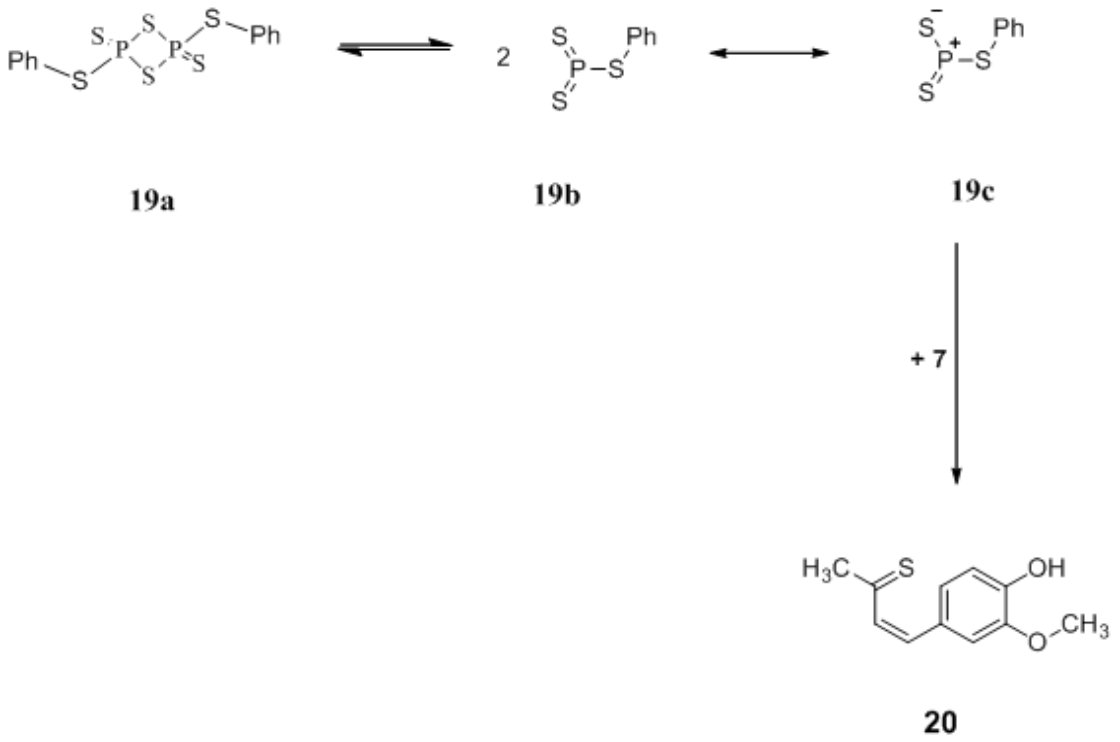
Scheme 3



Scheme 4



Scheme 5

may be pharmacologically active. While vanillin reacts smoothly with the active (*N*-phenyliminivinylidene)-(2a) and (2-oxovinylidene)-triphenylphosphorane (2b), to give the four-membered ring phosphoranylidenecyclobutylidenes 5a,b, the stabilized phosphonium ylides (6) afforded the butenone (7), which reacted with the phosphacumulene (2a) to give the corresponding pyran derivatives (9). Moreover the difference in the nucleophilic character of 2a> 2b> 6 can be noticed in these reactions. These investigations afforded also the phenyliminophenol derivative (13) from the reaction of vanillin 1 with the iminophosphorane (12). Moreover the dioxaphospholane oxide derivative (18) was obtained from the reaction of phosphorus triamide 14 and the aldehyde vanillin 1. Finally, the butenethione 20 was produced from the reaction of the butenone 7 and Japanese reagent 19a. Only thionation reaction was observed in this investigation and no addition reaction between the butene 7 and the monomer of JR 19c occurred.

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دراسة مقارنة عن تفاعل كواشف الفوسفور العضوية مع الفانيلين المستخرج من نبات المورينجا أوليفيرا
تشييد مشتقات الفوسفورانيليدين بيرانون، و الداى أوكسافوسفولان و البيوتين ثيون ذات نشاط متوقع كمضادات للأورام

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نظرا للأهمية الفارماكولوجية لنبات المورينجا أوليفيرا لاستخداماته المتعددة فى المجالات الطبية و حيث أن مركب الفانيلين يعتبر من أهم مكونات هذا النبات. لذا فلقد تم مفاعلة مركب الفانيلين (٤-هيدروكسى-٣-ميثوكسى بنزالدهايد) مع كواشف الفوسفور النيكليوفيلية المتراكمة النشطة و هى (ن-فينيل امينوفينيليدين)،(٢-أوكسوفينيليدين) ثلاثى فينيل الفوسفوران و التى أعطت مركبات متجانسة الحلقة و هى الفوسفورانيليدين سيكلوبيوتايليدين. وعلى صعيد آخر وعند تفاعل الأيليدات الفوسفوية الثابتة مثل مشتق اسيتيل ميثيلين ثلاثى فينيل الفوسفوران مع مركب الفانيلين نتج عن هذا التفاعل مركب البيوتينون. و عند مفاعلة هذا البيوتينون مع الإيليدات الفوسفورية المتراكمة تم فصل مشتقات البيران. و علاوة على ذلك تم الحصول على مركب أوكسيد الداى أوكسافوسفولون و ذلك من تفاعل الفانيلين مع كاشف ثلاثى اميد الفوسفور . و أخيرا تم فصل مركب البيوتين ثيون و ذلك من تفاعل كاشف جبانيز مع البيوتينون.