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European Journal of Medicinal Chemistry 44 (2009) 526–532
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Application of phosphonyl carbanions to highly regioselective synthesis of some diazaphospholes and pyrazolinyl phosphonates

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Received 3 February 2008; received in revised form 25 March 2008; accepted 27 March 2008
Available online 4 April 2008

Abstract

A series of substituted spiro[3′]pyrazolinylphosphonates and spiro[3]diazaphospholes were synthesized *via* 1:3-dipolar cycloaddition reaction of 2-diazonio-1,3-dioxo-2,3-dihydro-1*H*-inden-2-ide with phosphonyl carbanions: diethyl-cyanomethylphosphonate, -phosphono-acetates, and -vinylphosphonate. On the other hand, treatment of the diazo substrate with diethyl (thiomethyl)methylphosphonate led to the formation of condensed oxadiazine and spiro[3]diazaphosphole. Some compounds were found to possess antibacterial and antifungal activities.

Keywords: Diazo chemistry; Wittig–Horner carbanions; Phosphole-and phosphonate derivatives; Antimicrobial and antifungal activities; Structure–activity relationship (SAR)

1. Introduction

Recent work [1] on the chemistry of 2-diazonio-1,3-dioxo-2,3-dihydro-1*H*-inden-2-ide (**1**) has shown that they react with alkylidenephosphoranes and their relevant phosphonium salts *via* a variety of routes, and that the preferred reaction path depends strongly on the nature of the substituents attached to the ylidic carbon. Resonance stabilized ylide, cyanomethylene-triphenylphosphorane reacted with **1** either by initial Wittig reaction, followed by Michael addition of a second ylide species and cyclization to give pyridazine **A**, or *via* cycloaddition reaction accompanied with triphenylphosphine extrusion leading to the conjugated oxadiazine **B** (Scheme 1 – i). On the other hand, 1,3-dipolar cycloaddition reaction occurred between diazoketone **1** and unsaturated phosphonium salt, vinyltriphenylphosphonium bromide, leading to the corresponding phosphonium salt **C** in an excellent yield. The latter salt **C** was much longer-lived and readily alkali-hydrolyzed, as well as reacted with alkyl halides and aldehydes/in the presence of alkali to give a series of pyrazoline derivatives (Scheme 1 – ii).

It is pertinent to mention that pyridazine- and pyrazole derivatives find extensive applications in various fields like agriculture and pharmaceutical industry [2–9]. A literature survey, however, revealed scanty information on recent application of phosphonate carbanions on diazo compounds [10–12]. In effect, no systematic study or review is available, in particular on α-diazoketones. In view of the above interesting facets of diazo chemistry and the utility of phosphorus compounds in biological activities [13–16], it was considered of interest to extend the investigations on pyrazoline derivatives, particularly having a species of phosphor ester moiety in the molecule. Thus, we report herein the synthesis of new substituted pyrazole phosphor esters and diazaphospholes in order to study their chemical reactivity, spectroscopical properties, and their biological activity. The methodology depended on the interaction of α-diazoketone **1** with different types of Wittig–Horner (WH) reagents **2**, **7a**,**b**, **11** and **14**. Similarities and differences in the reactivity of α-phosphonate carbanions and

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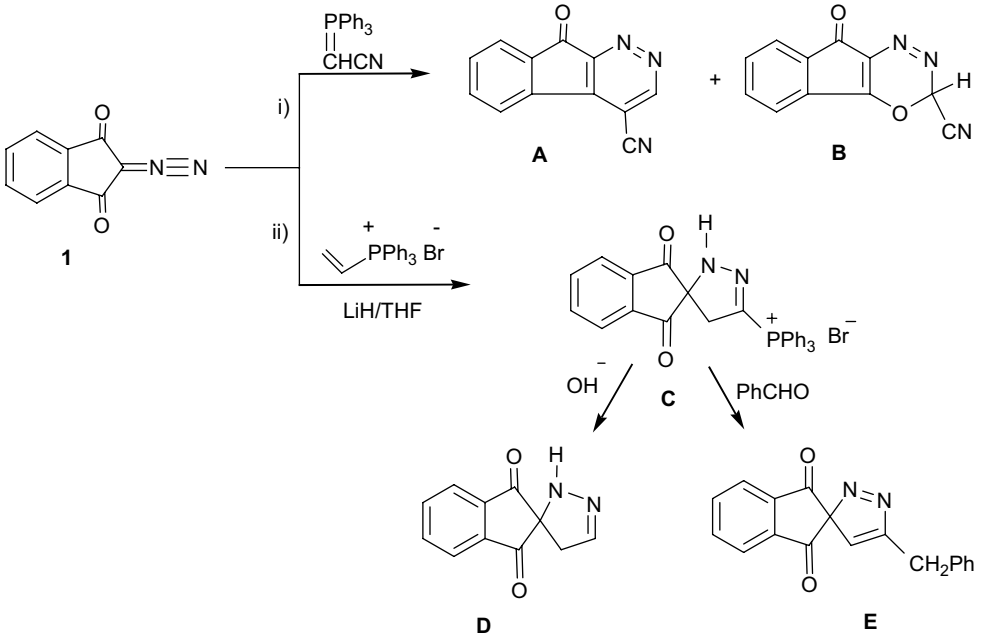
doi:10.1016/j.ejmech.2008.03.032



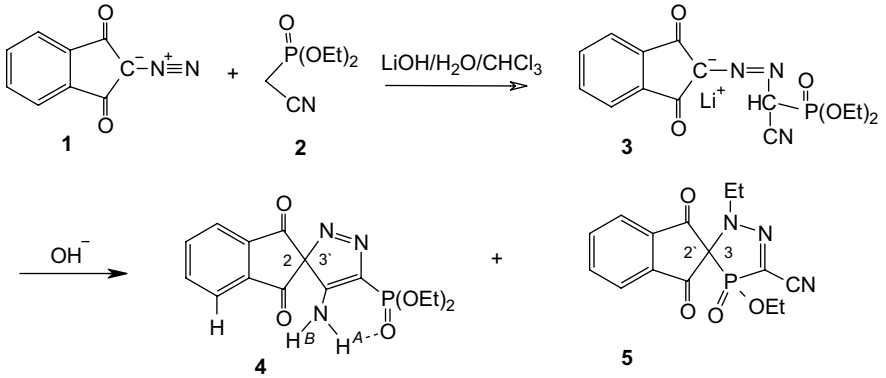
Scheme 1.

phosphorane counterparts toward compound **1** are also discussed.

2. Results and discussion

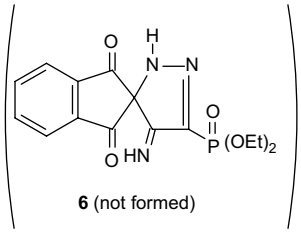
In the present study, 2-diazo-1,3-indandione (**1**) was treated with a little excess of molar amount of diethyl cyanomethylphosphonate (**2**) in a mixture of $LiOH/H_2O/CHCl_3$ at room temperature. The mixture was further heated for ≈30 h (TLC) at the reflux temperature to give diethyl (4′-amino-1,3-dioxo-1,3-dihydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate (**4**, 38% yield) and 4-ethoxy-2-ethyl-1′,3′-dioxo-1′,2,3′,4-tetrahydrospiro[1,2,4-diazaphosphole-3,2′-indene]-5-carbonitrile-4-oxide (**5**, 33% yield) (Scheme 2).

The structure of phosphonate **4** ($\delta_p = 29.7$ ppm) was investigated by NMR spectroscopy (nOe measurements) [17,18]. The ^1H NMR spectrum of **4** showed two types of the NH_2-protons [$\delta(H^A) = 6.35$ (br s, 1H) and $\delta(H^B) = 9.71$ ppm (br s, 1H)]. The different chemical shifts of the NH_2 protons are the spectroscopic evidence for the presence of intramolecular hydrogen bond between one of the hydrogens of the NH_2-protons and the oxygen atom of the P═O bonding in the phosphonate group. Furthermore, the nOe experiments showed us the lack of nOe between H-4, (or *C*(3)═O, $\delta_C = 183.1$ ppm) and NH_2 in **4**. This can be explained by a preferred conformation of intramolecular hydrogen bonding between one of the NH_2-proton and the phosphonate-oxygen atom. Therefore, H-4 is too far from NH_2 to give an observable nOe. The nOe-experiments also showed us that the NH_2-protons are localized at the nitrogen of the NH_2-group, and there is no imino-tautomerism **6** observed in solution. However, one would expect little Overhauser effects between NH_2 protons and 4-H or the carbonyl carbon atoms in **4**. This is because the carbonyl-C signal, in general, has a rather low intensity and also because the two ring systems in **4** in a spiro-fused system are perpendicular to each other; and



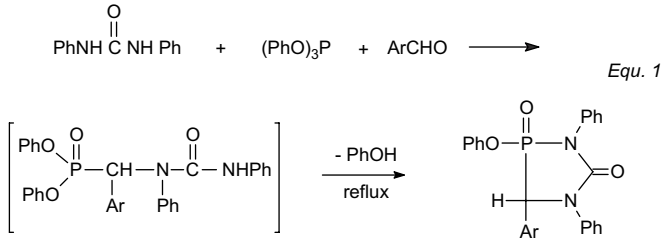
Scheme 2.

due to this geometry, the nOe will be very low. Nevertheless, the complete lacking of nOe in the studied NMR, even with the difference spectroscopy technique confirms the suggested structure.



6 (not formed)

Diazaphosphole **5** is distinguished by its ^{31}P and ^{13}C NMR signals. The ^{31}P NMR spectrum of compound **5** showed a sharp singlet at δ_p ($CDCl_3$) = 11.2 ppm, *vs.* H_3PO_4, which is within the range expected for diazaphospholes [19]. The main features of ^{13}C NMR spectrum of **5** was the presence of signals at 120.1 (CN), 38.6 (d, $^1J_{P-C} = 96.5$ Hz, 3-*C*) and at 109.8 (d, $^1J_{P-C} = 68.6$ Hz, 5-*C*) ppm. The magnitude of the phosphorus coupling with *C*-3, and *C*-5 are in accord with the assigned structure. The reaction mechanism outlined in Scheme 2 can be described with an initial electrophilic attack on the carbanion-carbon by the diazo-group of **1**. Subsequent cyclization and transformation of the cyano-group led directly to the observed pyrazolinyl phosphonate **4** in one stage process. On the other hand, the collapse of the phosphonate moiety and extrusion of an ethyl alcohol molecule gave rise to the formation of the diazaphosphole **5**. An analogous mechanism was previously reported by He et al. [19] for the formation of diazaphospholidinones *via* Mannich-type reaction, involving urea, aldehyde and triphenyl phosphite according to Eq. (1).



Considering the *N*-alkylation of compound **5** by WH-reagents, it is well established that these reagents are also good alkylating agents for the acidic NH- or OH-proton [20]. Similar process has been observed in their reactions with pyrimidines, quinonimines, pyrroles and thiazolidinones [20–25].

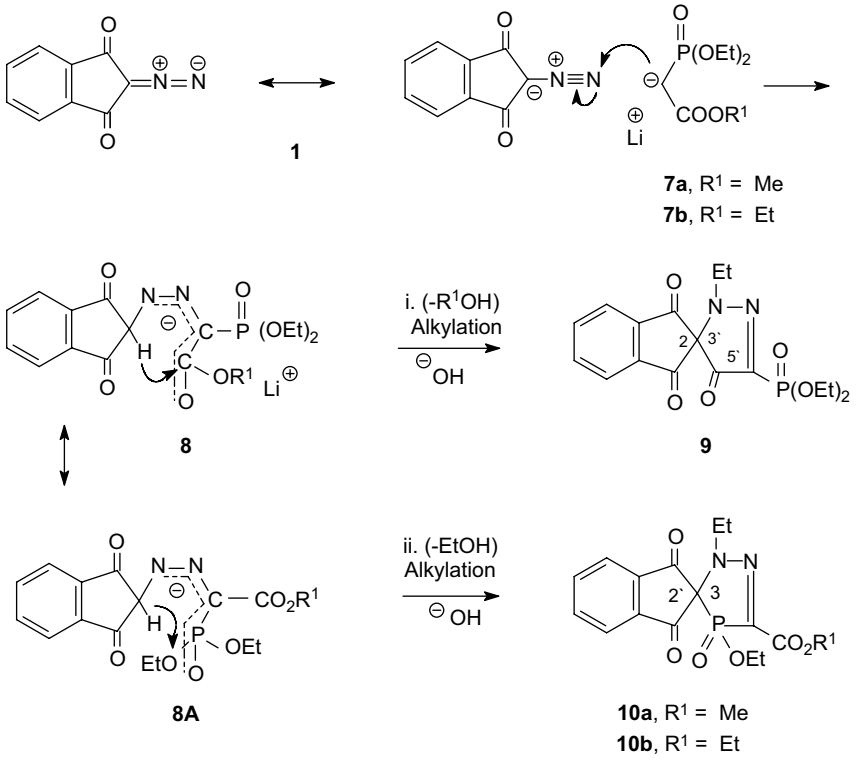
A noteworthy contrast exists between the present behavior of WH-reagent **2** toward the diazo compound **1** (Scheme 2), and that reported previously [1] for the resonance-stabilized ylide, cyanomethylenetriphenylphosphorane toward the same substrate whereby condensed pyridazine-**A** and oxadiazine-**B** derivatives were the reaction products (Scheme 1 – i).

On the other hand, by analogous procedure we obtained pyrazolinyl phosphonate **9** (27% yield) and diazaphosphole **10a** (44% yield) from the reaction of **1** with methyl diethyl phosphonoacetate (**7a**). Compound **9** (21% yield) along with the parallel diazaphosphole **10b** (46% yield) was also isolated when **1** was caused to react with triethyl phosphonoacetate (**7b**) under similar conditions. Structures **9** and **10** were substantiated on the basis of their elemental analyses, IR, ^{31}P, ^1H, ^{13}C NMR and mass spectral data.

Compound **9** [δ_p, (d_6-DMSO) = 29.7 ppm] was formulated as diethyl (2′-ethyl-1,3,4′-trioxo-1,2′,3,4′-tetrahydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate for the following reasons: The IR absorption spectrum of compound **9** in KBr, lacked the intense band in the 2110–2070 cm^{-1} region; characteristic for the diazo-group stretching vibration [17]. However, the spectrum exhibited the presence of stretching vibration bands at 1755, 1722 cm^{-1} that assigned to 1- and 3-carbonyl groups, thus excluding any cyclization reaction including these moieties. Other bands displayed at 1715 (4′-C=O), 1605 (–C=N), 1256 (P=O), and at 1087 (P–O–C) cm^{-1}. The ^1H NMR spectrum (d_6-DMSO) of **9** gave signals at δ 1.22 (dt, $J = 6.6$, $^4J_{P-H} = 4.6$ Hz, 6H, H_3C–C–O–P), and at 4.08 (dq, $^3J_{P-H} = 11.8$ Hz, 4H, H_2COP) due to the phosphonate species [$P(OCH_2CH_3)_2$]. The *N*-ethyl moiety was located at 0.88 (t, $J_{HH} = 6.6$ Hz, 3H, H_3C–C–N) and at 3.45 (q, $J_{HH} = 6.6$ Hz, 2H, H_2C-N). Its ^{13}C NMR spectrum (d_6-DMSO) showed the phosphonate carbon atom (5′-*C*–P) signal at 132.8 (d, $^1J = 98.5$ Hz). Among others, two signals were observed at δ 77.6 (d, $^3J_{P-C} = 14.6$ Hz), and at 182.4 (d, $^2J_{P-C} = 38.6$ Hz), assignable to spiro *C*(3′) and *C*(4′)=O, respectively.

Compound **10a** ($\delta_p = 13.6$ ppm) showed in its ^1H NMR spectrum (d_6-DMSO) the ethyl group of the phosphor ester at δ 1.26 (dt, $J_{HH} = 6.5$, $^4J_{P-H} = 4.3$ Hz, 3H, H_3C–C–O–P), and at 4.14 (dq, $^3J_{P-H} = 12.3$ Hz, 2H, H_2COP). The *N*-ethyl group was located at 0.89 (t, $J_{HH} = 6.8$ Hz, 3H, H_3C–C–N), and at 3.52 (q, $J_{HH} = 7.5$ Hz, 2H, H_2C–N) ppm. The spiro-carbon signal in the ^{13}C NMR spectrum (d_6-DMSO) is observed by 36.8 ppm (d, $^1Jp{-}c = 108$ Hz). The *C*-5 atom in the ^{13}C NMR is given as a doublet at 139.6 ($^1Jp{-}c = 98.5$ Hz), and the ester carbonyl function is given at 154.4 ppm. The EI-MS spectrum of **10a** and **b** demonstrated the existence of the weak molecular ion peak [M^+]. The fragmentation ions were consistent with the structure and can be clearly assigned. According to Scheme 3, the isolated products **9** and **10** might be formed through addition-cyclization reaction of **1** with the carbanion species [27]. Thus, the initial key intermediate **8** resulted from the addition reaction between **1** and the carbanion **7a** or **b**. Intramolecular cyclization of **8** and *N*-alkylation afforded the phosphonate **9**, accompanied with elimination of an alcohol molecule (R^1OH). On the other hand, the collapse of the phosphonate moiety in the tautomer **8A**, extrusion of an ethyl alcohol molecule [19] and *N*-alkylation gave diazaphosphole **10a** or **b**.

Under comparable two-phase reaction condition, diethyl (methylthio)methylphosphonate (**11**) behaved differently than **2**, **7a** and **b** toward **1**. In the reaction of **11** with **1**, the time taken for its complete consumption was only 10 h (TLC). After usual working up, 4-ethoxy-2-ethyl-5-(methylthio)-2,4-dihydrospiro[1,2,4-diazaphosphole-3,2′-indene]-1′,3′-dione-4-oxide (13, 49% yield) along with 1-ethyl 3-(methylthio)



Scheme 3.

indeno-[2,1-*e*][4,1,2]oxadiazin-9 (1*H*)-one (12, 17% yield) were isolated (Scheme 4).

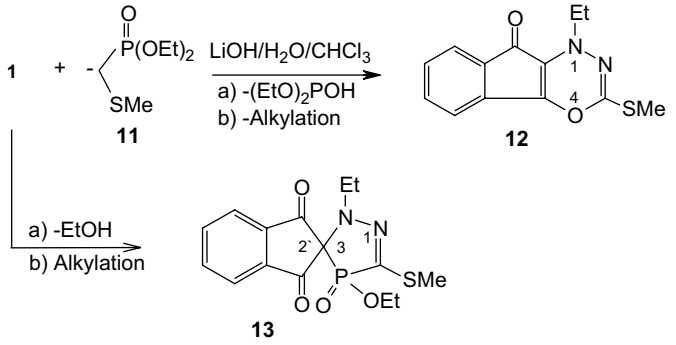
The constitution of the isolated products **12** and **13** is in accord with their elemental analyses, molecular weight determination (MS), and the spectral data. Compound **13** ($\delta_p = 10.82$ ppm) is given in the IR spectrum a sharp strong band at 1275 cm^{-1} assigned to P═O. This absorption band of the phosphorus-oxide is very characteristic for cyclic-phosphole systems as it is described in the literature [26]. The N═C−S stretching is located at 1420 cm^{-1}. There are two types of ethyl-protons in the ^1H NMR spectrum assigned for POC_2H_5 and N-C_2H_5. The thiomethyl-protons are given a doublet at 2.63 ppm ($^4J_{P-H} = 3.8$ Hz). The *C*-3 and *C*-5 signals in the ^{13}C NMR spectrum are given two doublets at 38.6 ppm ($^1J_{P-C} = 102.7$ Hz), and at 173.5 ppm ($^1J_{P-C} = 88.3$ Hz), respectively.

Next, in a systematic study, the reaction of diazoketone **1** with diethyl vinylphosphonate (**14**) was proceeded, under phase-transfer catalysis conditions ($LiOH/H_2O/CHCl_3$). Chromatographic separation of the product mixture produced diethyl (2′-ethyl-1,3-dioxo-1,2′,3,4′-tetrahydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate (16, 72% yield), advantageously (Scheme 5).

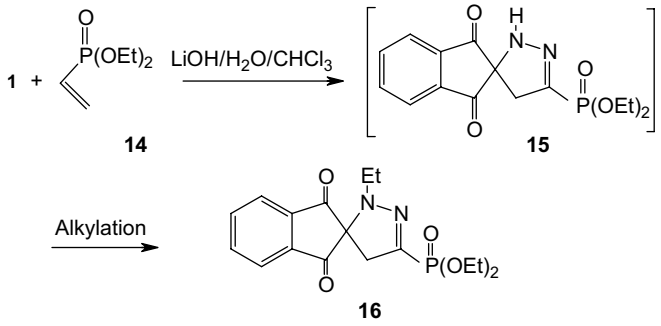
The structures suggested for all new compounds are in good agreement with their analytical and spectral data (Section 5).

3. Pharmacological evaluation

All of the synthesized phosphorus containing compounds, **4**, **5**, **9**, **10a**,**b**, **13**, **16**, and unphosphorylated oxadiazine **12** were tested [28] for their antimicrobial activities at a concentration 1 mg/disc. Streptomycin and mycostatin were used as



Scheme 4.



Scheme 5.

the reference compounds for antimicrobial and antifungal activities, respectively. *Bacillus tumefaciens*, *Staphylococcus aureus* and *Klebsiella pneumoniae* (bacteria) or *Aspergillus niger*, *Aspergillus flavus*, *Penicillium crysogenous* (fungi) were used as the tested organisms. Results have been recorded in the form of inhibition zone (diameter mm) and activity index in Table 1.

The data included in Table 1 indicates the high potency of heterocycle phosphor esters rather than the unphosphorylated. Further the phosphole derivatives **5**, **10a**, **10b**, and **13** are more active as compared to the phosphonate compounds and which indicates that phosphorus-containing five membered heterocyclic increases the activity. In addition, the preliminary results achieved have led us to conclude that this type of compounds should be studied in more detail for their applications in diverse areas, nevertheless, toxicity of these phosphorus compounds should also be tested.

4. Conclusion

The above four reactions illustrate the similarities and the dissimilarities between the behavior of phosphonyl carbanions with diazoketone **1** and the previously reported [1] behavior of phosphonium salts toward the same substrate **1**. In the latter case, the phosphonium salts reacted with **1** *via* different routes (see Scheme 1), and that the preferred reaction path depended strongly on the nature of the substituents attached to the ylidic carbon. On the other hand, regiospecific 1,3-dipolar addition leading to spiro-pyrazoline derivatives occurred when WH-reagents were applied to **1** in the present study. Finally, the observed *N*-alkylation process in Schemes 2–5 is in agreement with the reported [20–25] affection of phosphonyl carbanions as alkylating agents in their reactions.

5. Experimental section

All melting points are measured on an Electrothermal melting point apparatus. The IR spectra were recorded on a Perkin Elmer 317 Grating IR spectrophotometer, using KBr pellets. The ^{1}H and ^{13}C NMR spectra were measured on a Joel E.C.A-500 MHz instrument using $SiMe_4$ as an internal reference. The ^{31}P NMR spectra were recorded with the same instrument, relative to external H_3PO_4 (85%). The mass spectra were performed on a Joel JMS-A X 500 spectrometer. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques. TLC: Merck 0.2 mm silica gel 60 F154 anal aluminum plates. Column chromatography (CC): silica gel (Kieselgel 60 mesh, particle size 0.2–0.5 mm; E. Merck, Darmstadt). The substrate 2-diazonio-1,3-dioxo-2,3-dihydro-1*H*-inden-2-ide (**1**) was prepared according to the reported method [29].

5.1. Reaction of 2-diazonio-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (*1*) with diethyl cyanomethylphosphonate (*2*)

*Synthesis of compounds **4** and **5***. A solution of 0.7 g of **1** (4.07 mmol) and 0.73 g of **2** (4.12 mmol) in 25 ml $CHCl_3$ was treated with 15 ml aqueous LiOH solution (0.5 M). The reaction mixture was heated under reflux for ≈30 h (TLC control), the crude mixture was concentrated, poured into 100 ml of distilled H_2O, acidified with conc HCl and extracted with $CHCl_3$ (2 × 100 ml). The combined organic extracts were washed with 50 ml of distilled H_2O and dried. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (*n*-hexane/AcOEt) to give compounds **5** and **4**, respectively.

4-Ethoxy-2-ethyl-1′,3′-dioxo-1′,2,3′,4-tetrahydrospiro-[1,2,4-diazaphosphole-3,2′-indene]-5-carbonitrile-4-oxide (**5**) was obtained (*n*-hexane/AcOEt, 3:7, v/v), as yellow crystals (445 mg, 33% yield), mp 163–165 °C (from CH_2Cl_2); IR $\bar{\nu}$: 2218 (CN), 1782, 1721 (1′-, 3′-C=O), 1600 (C=N–), 1265 (P=O), 1044 (P–O–C) cm^{-1}; ^{1}H NMR (d_6-DMSO): δ 0.88 (t, $J = 7.7$ Hz, 3H, H_3CC–N), 1.22 (dt, $J_{H-H} = 6.8$, $^{4}J_{P-H} = 4.4$, 3H, H_3CC–O), 3.48 (q, $J = 7.7$ Hz, 2H, CH_2N), 4.08 (dq, $J_{H-H} = 6.8$, $^{3}J_{P-H} = 4.7$ Hz, 2H, H_2COP), 7.55, 7.88 (2d, $J_{H-H} = 7.2$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR (d_6-DMSO): δ 14.5, 15.8 (*C*H_3C–N, *C*H_3C–O), 38.6 (d, $^{1}J_{P-C} = 96.5$ Hz, 3-*C*, spiro), 47.6 (*C*H_2N), 61.4 (*C*H_2OP), 109.8 (d, $^{1}J_{P-C} = 68.6$ Hz, 5-*C*), 120.1 (*C*N), 123.4, 126.9, 135.8, 143.3 (*C*-Ar), 185.3, 187.6 (3′-, 1′-C=O) ppm; ^{31}P NMR (d_6-DMSO): $\delta_p = 11.2$ ppm; EI-MS: *m/z* (%) = 331 (15) [M^+], 305 ($M^+ - CN$, 18), 302 [$M^+ - (C_2H_5)$, 34], 273 [$M^+ - 2\ (C_2H_5)$, 66], 247 (273–CN, 100), 144 (29), 77 (41). $C_{15}H_{14}N_3O_4P$ (331.28): calcd C 54.38, H 4.26, N 12.68, P 9.35; found: C 54.44, H 4.18, N 12.57, P 9.43.

Table 1
Antimicrobial activity of compounds **4**, **5**, **9**, **10a**,**b**, **12**, **13** and **16**

Microorganisms		Phosphonates				Phospholes			
		4	**9**	**16**	**12**	**5**	**10a**	**10b**	**13**
B. tumefaciens	IZ (AI)	8.4 (0.75)	7.6 (0.57)	9.8 (0.84)	5.6 (0.55)	10 (0.89)	12.2 (0.9)	11 (0.78)	12.6 0.92
S. aureus	IZ (AI)	7.2 (052)	7.6 (0.83)	8 (0.61)	5.9 (0.26)	10 (0.92)	9 (0.85)	8.5 (0.88)	12.8 (1.16)
K. pneumoniae	IZ (AI)	6 (0.47)	8.2 (0.63)	7.6 (1.0)	5.1 (0.32)	12 (1.16)	10.3 (1.04)	11.3 (0.8)	10.5 (0.81)
A. niger	IZ (AI)	5.4 (0.73)	6.1 (0.73)	4.3 (0.66)	4.9 (1.31)	9 (1.14)	8.4 (1.18)	7.4 (1.23)	8 (1.14)
A. flavus	IZ (AI)	6.3 (0.78)	7.4 (0.88)	5 (0.62)	6.2 (0.41)	11.3 (1.15)	9 (1.12)	9.6 (1.35)	9.8 (1.36)
P. crysogenous	IZ (AI)	5.2 (0.71	5.9 (1.06)	9 (0.71)	5.6 (0.54)	8 (1.0)	7.9 (1.31)	7.8 (1.42)	9.2 (1.32)

IZ: inhibition zone (in mm).
AI: activity index of the tested compounds/inhibition zone of the standard.

Diethyl (4′-amino-1,3-dioxo-1,3-dihydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate (**4**) was obtained (eluent, AcOEt, 100%), as orange crystals (540 mg, 38% yield), mp 210–212 °C (from acetone); IR $\overline{\nu}$: 3344 (NH_2), 1784, 1717 (1-, 3-C=O), 1445 (–N=N–), 1224 (P=O, bonded), 1087 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (dt, $J_{H-H} = 6.8$, $^4J_{P-H} = 4.2$ Hz, 6H, $2 \times H_3C$–C–O), 4.17 (dq, $J_{H-H} = 6.8$, $^3J_{P-H} = 4.8$ Hz, 4H, $2 \times H_2CO$), 6.35 (br s, 1H, H^AN, NH_2), 7.55, 7.88 (2d, $J_{H-H} = 7.4$ Hz, 4H, *H*-Ar), 9.71 (br s, 1H, H^BN, NH_2) ppm; ^{13}C NMR ($CDCl_3$): δ 16.14 (CH_3C–O), 62.18 (CH_2O), 108.5 (d, $^3J_{P-C} = 8.3$ Hz, 3′-*C*, spiro), 132.6 (d, $^2J_{P-C} = 37$ Hz, 4′-*C*), 124.5, 126.2, 135.8, 146.4 (*C*-Ar), 157.3 (d, $^1J_{P-C} = 197.8$ Hz, 5′-*C*-P), 183.1, 188.7 (3-, 1-*C*–O) ppm; ^{31}P NMR ($CDCl_3$): $\delta_p = 29.7$ ppm; EI-MS: *m/z* (%) = 349 (15) [M^+], 348 (23), 293 [$M^+ - 2(C_2H_5)$, 34], 265 (293 – N_2, 100), 137 (33), 77 (46). $C_{15}H_{16}N_3O_5P$ (349.3): calcd C 51.58, H 4.62, N 12.02, P 8.87; found: C 51.66, H 4.55, N 12.13, P 8.83.

5.2. Reaction of diazoketone *1* with diethyl phosphonoacetates *7a* and *b*

*Synthesis of compounds **9**, **10a**,**b***. A solution of 0.7 g of **1** (4.07 mmol) and 4.12 mmol of **7a** (or of **7b**) in 25 ml $CHCl_3$ was treated with 15 ml aqueous LiOH solution (0.5 M). The reaction mixture was heated under reflux for ≈35 h (TLC control). After the usual workup, the residue was chromatographed with *n*-hexane/AcOEt to give **9** and **10a** or **9** and **10b**.

5.3. Reaction of *1* with methyl diethyl phosphonoacetate (*7a*) afforded *10a* and *9*

Methyl 4-ethoxy-2-ethyl-1′,3′-dioxo-1′,2,3′,4-tetrahydrospiro[1,2,4-diazaphosphole-3,2′-indene]-5-carboxylate-4-oxide (**10a**) was obtained (*n*-hexane/AcOEt, 7:3 v/v), as orange crystals (650 mg, 44% yield), mp 188–190 °C (from EtOH); IR $\overline{\nu}$: 1784, 1728 (1′-, 3′-C=O), 1715 (C=O, ester), 1605 (C=N), 1256 (P=O), 1087 (P–O–C) cm^{-1}; ^1H NMR (d_6-DMSO): δ 0.89 (t, $J = 6.8$ Hz, 3H, H_3CC–N), 1.26 (dt, $J_{H-H} = 6.5$, $^4J_{P-H} = 4.3$ Hz, 3H, H_3CC–OP), 3.52 (q, $J = 7.5$ Hz, 2H, CH_2N), 3.77 (s, 3H, CH_3O, ester), 4.14 (dq, $J_{H-H} = 6.5$, $^3J_{P-H} = 5.8$ Hz, 2H, H_2COP), 7.48, 7.88 (2d, $J_{H-H} = 7.5$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR (d_6-DMSO): δ 14.3, 16.4 (CH_3C–N, CH_3C–O), 36.8 (d, $^1J_{P-C} = 108$ Hz, 3-*C*, spiro), 48.2 (CH_2N), 52.8 (CH_3O, ester), 62.4 (CH_2OP), 125.5, 126.3, 135.8, 144.3, 148.7 (*C*-Ar), 139.6 (d, $^1J_{P-C} = 98.5$ Hz, 5-*C*), 154.4 (*C*=O, ester), 184.3, 187.6 (1′-, 3′-C=O) ppm; ^{31}P NMR (d_6-DMSO): $\delta_p = 13.6$ ppm; EI-MS: *m/z* (%) = 364 (16) [M^+], 349 (23), 320 (23), 291 (100), 232 (43), 77 (66). $C_{16}H_{17}N_{32}O_6P$ (364.3): calcd C 52.75, H 4.70, N 7.70, P 8.50; found: C 52.66, H 4.65, N 7.63, P 8.58.

Diethyl (2′-ethyl-1,3,4′-trioxo-1,2′,3,4′-tetrahydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate (**9**) was obtained (AcOEt, 100%), as reddish brown crystals (415 mg, 27% yield), mp 282–284 °C (from EtOH); IR $\overline{\nu}$: 1755, 1722 (1-, 3-C=O), 1715 (4′-C=O), 1605 (C=N), 1256 (P=O), 1087 (P–O–C) cm^{-1}; ^1H NMR (d_6-DMSO): δ 0.88 (t, $J = 6.6$ Hz, 3H, H_3CC–N), 1.22 (dt, $J_{H-H} = 6.6$, $^4J_{P-H} = 4.6$, 6H, H_3C–C–OP), 3.45 (q, $J = 6.6$ Hz, 2H, CH_2N), 4.08 (dq, $J_{H-H} = 6.6$, $^3J_{P-H} = 5.2$ Hz, 4H, H_2COP), 7.48, 7.78 (2d, $J_{H-H} = 7.4$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR (d_6-DMSO): δ 12.7, 16.2 (CH_3C–N, CH_3C–O), 45.8 (CH_2N), 62.4 (CH_2OP), 77.6 (d, $^3J_{P-C} = 14.6$ Hz, 3′-*C*, spiro), 125.5, 126.3, 134.8, 144.3 (*C*-Ar), 132.8 (d, $^1J_{P-C} = 98.5$ Hz, 5′-*C*), 182.4 (d, $^2J_{P-C} = 38.6$ Hz, 4′-*C*=O), 197.6 (1-, 3-C=O) ppm; ^{31}P NMR (d_6-DMSO): $\delta_p = 29.7$ ppm; EI-MS: *m/z* (%) = 378 (22) [M^+], 349 (25), 320 (13), 291 (40), 202 (100), 174 (35), 146 (65), 77 (32). $C_{17}H_{19}N_2O_6P$ (378): calcd C 53.97, H 5.06, N 7.40, P 8.19; found: C 53.93, H 5.14, N 7.33, P 8.25.

5.4. Reaction of *1* with of triethyl phosphonoacetate (*7b*) afforded *10b* and *9*

Ethyl 4-ethoxy-2-ethyl-1′,3′-dioxo-1′,2,3′,4-tetrahydrospiro[1,2,4-diazaphosphole-3,2′-indene]-5-carboxylate-4-oxide (**10b**) was obtained (*n*-hexane/AcOEt, 7:3, v/v), as orange crystals (0.7 g, 46% yield), mp 168–170 °C (from MeCN); $\overline{\nu}$: 1758, 1717 (1′-, 3′-C=O), 1710 (C=O, ester), 1586 (C=N), 1262 (P=O), 1084 (P–O–C) cm^{-1}; ^1H NMR (d_6-DMSO): δ 0.89 (t, $J = 6.8$ Hz, 3H, H_3CC–N), 1.06 (t, $J = 7.2$ Hz, 3H, H_3CC–O, ester), 1.26 (dt, $J_{H-H} = 6.5$, $^4J_{P-H} = 4.3$, 3H, H_3CC–O), 3.52 (q, $J = 6.8$ Hz, 2H, CH_2N), 3.84 (s, 2H, H_2CO, ester), 4.04 (dq, $J_{H-H} = 6.5$, $^3J_{P-H} = 5.0$ Hz, 2H, H_2COP), 7.48, 7.88 (2d, $J_{H-H} = 7.4$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR (d_6-DMSO): δ 14.3, 15.7, 16.4 (CH_3C–N, CH_3C–OP, CH_3C–O, ester), 36.8 (d, $^1J_{P-C} = 108$ Hz, 3-*C*, spiro), 48.2 (CH_2N), 52.8 (CH_2O, ester), 62.4 (CH_2OP), 126.3, 135.8, 144.3, 148.7 (*C*-Ar), 139.5 (d, $^1J_{P-C} = 96.8$ Hz, 5-*C*), 154.4 (*C*=O, ester), 184.3, 187.6 (1′-, 3′-*C*=O) ppm; ^{31}P NMR (d_6-DMSO): $\delta_p = 12.6$ ppm; EI-MS: *m/z* (%) = 378 (16) [M^+], 349 (23), 320 (23), 291 (100), 232 (43), 77 (66). $C_{17}H_{19}N_2O_6P$ (378.3): calcd C 53.97, H 5.06, N 7.40, P 8.19; found: C 54.06, H 5.12, N 7.45, P 8.26.

Elution with ethyl acetate yielded 320 mg of reddish brown crystals of compound **9** (21% yield), mp 282–284 °C (from EtOH), and characterized.

5.5. Reaction of diazoketone *1* with diethyl (methylthio)methylphosphonate (*11*)

*Synthesis of compounds **12** and **13***. A solution of 0.7 g of **1** (4.07 mmol) and 0.83 g of WH-reagent **11** (4.2 mmol) in 25 ml $CHCl_3$ was treated with 15 ml aqueous LiOH solution (0.5 M). The reaction mixture was heated under reflux for ≈10 h. After the usual workup, the residue was chromatographed with *n*-hexane/AcOEt to give **13** and **12**, respectively.

4-Ethoxy-2-ethyl-5-(methylthio)-2,4-dihydrospiro[1,2,4-diazaphosphole-3,2′-indene]-1′,3′-dione-4-oxide (**13**) was obtained (*n*-hexane/AcOEt, 2:8, v/v), as orange crystals (1.2 g, 49% yield), mp 123–125 °C (from CH_2Cl_2); $\overline{\nu}$: 1777, 17167 (1′-, 3′-C=O), 1595 (C=N), 1420 (N=C–S), 1275 (P=O),

1068 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (t, $J = 6.5$ Hz, 3H, H_3CC–N), 1.26 (dt, $J_{H-H} = 6.5$, $^4J_{P-H} = 4.3$, 3H, H_3CC–O), 2.63 (d, $^4J_{P-H} = 3.8$ Hz, 3H, H_3CS), 3.52 (q, $J = 6.5$ Hz, 2H, CH_2N), 4.05 (dq, dt, $J_{H-H} = 6.5$, $^3J_{P-H} = 5.3$ Hz, 2H, H_2COP), 7.46, 7.78 (2d, $J_{H-H} = 7.5$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR ($CDCl_3$): δ 14.3, 15.1, 16.04 (CH_3C–N, CH_3S, CH_3C–OP,), 38.6 (d, $^1J_{P-C} = 102.7$ Hz, 3-*C*, spiro), 48.2 (CH_2N), 62.5 (CH_2OP), 124.2, 125.5, 135.8, 144.3 (*C*-Ar), 173.5 (d, $^1J_{P-C} = 88.3$ Hz, 5-*C*), 184.3, 187.6 (1′-, 3′-*C*=O) ppm; ^{31}P NMR ($CDCl_3$): $\delta_p = 10.82$ ppm; EI-MS: *m/z* (%) = 352 (18) [M^+], 337 (20), 323 (42), 305 (29), 247 (100), 107 (80), 77 (53). $C_{15}H_{17}N_2O_4PS$ (352.3): calcd C 51.13, H 4.86, N 7.95, P 8.79, S 9.10; found: C 51.21, H 4.92, N 7.88, P 8.75, S 9.03.

1-Ethyl 3-(methylthio)indeno[2,1-*e*][4,1,2]oxadiazine-9(1*H*)-one (**12**) was obtained (AcOEt, 100%), as straw yellow crystals (180 mg, 17% yield), mp 208–210 °C (from EtOH); $\overline{\nu}$: 1723 (1-C=O), 1598 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (t, $J = 7.5$ Hz, 3H, H_3CC–N), 2.74 (s, 3H, H_3C-S), 3.42 (q, $J = 7.5$ Hz, 2H, CH_2N), 7.55, 7.88 (2d, $J_{H-H} = 6.5$ Hz, 3H, *H*-Ar), 8.32 (dd, $J = 2$, 7 Hz, 1H, *peri-H*) ppm; ^{13}C NMR ($CDCl_3$): δ 13.9, 14.6 (CH_3S and CH_3C–N), 46.4 (CH_2N), 121.4, 124.5, 126.3, 133.8, 139.6 (*C*-Ar), 151.3 (3-*C*), 185.3 (9-*C*=O) ppm; EI-MS: *m/z* (%) = 260 (24) [M^+], 219 (13), 184 (100), 144 (50), 77 (32); $C_{13}H_{12}N_2O_2S$ (260.32): calcd C 59.98, H 4.65, N 10.76, S 13.32; found: C 60.06, H 4.58, N 10.73, S 13.42.

5.6. Reaction of diazoketone *1* with diethyl vinylphosphonate (*14*)

Synthesis of compound ***16***. A solution of 0.7 g of **1** (4.07 mmol) and 1.3 g of WH-reagent **14** (8.2 mmol) 25 ml $CHCl_3$ was treated with 15 ml aqueous LiOH solution (0.5 M). The reaction mixture was heated under reflux for ≈30 h. After the usual workup, the residue was chromatographed with *n*-hexane/AcOEt to give compound **16**.

Diethyl (2′-ethyl-1,3-dioxo-1,2′,3,4′-tetrahydrospiro[indene-2,3′-pyrazol]-5′-yl)phosphonate (**16**) was obtained (*n*-hexane/AcOEt, 3:7, v/v), as yellow needles (533 mg, 72% yield), mp 178–180 °C (from $CHCl_3$); IR $\overline{\nu}$: 1777, 1728 (1-, 3-C=O), 1600 (C=N), 1254 (P=O), 1084 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, $J = 6.8$ Hz, 3H, H_3CC–N), 1.22 (dt, $J_{H-H} = 7.2$, $^4J_{P-H} = 3.8$ Hz, 6H, $2 \times H_3CC$–O), 2.38 (d, $^3J_{P-H} = 13.8$ Hz, 2H, 4′-CH_2), 3.46 (q, $J = 6.8$ Hz, 2H, CH_2N), 4.13 (dq, $J_{H-H} = 7.2$, $^3J_{P-H} = 5.5$ Hz, 4H, $2 \times H_2CO$), 7.48, 7.74 (2d, $J_{H-H} = 7.5$ Hz, 4H, *H*-Ar) ppm; ^{13}C NMR ($CDCl_3$): δ 13.8, 15.9 (CH_3C–N, CH_3C–OP), 28.6 (d, $^2J_{P-C} = 33.8$ Hz, 4′-CH_2), 45.8 (CH_2N), 62.2 (CH_2O), 71.8 (d, $^3J_{P-C} = 18.3$ Hz, 3′-*C*, spiro), 124.5, 126.2, 143.4 (*C*-Ar), 135.8 (d, $^1J_{P-C} = 176.8$ Hz, 5′-*C*), 198.3 (1-, 3-*C*=O) ppm; ^{31}P NMR ($CDCl_3$): $\delta_p = 24.7$ ppm; EI-MS: *m/z* (%) = 364 (9) [M^+], 363 (18), 335 (43), 306 (37), 277 (100), 198 (46), 144 (62), 137 (55), 77 (33). $C_{17}H_{21}N_2O_5P$ (364.4): calcd C 56.04, H 5.80, N 7.69, P 8.50; found: C 56.15, H 5.73, N 7.63, P 8.58.

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