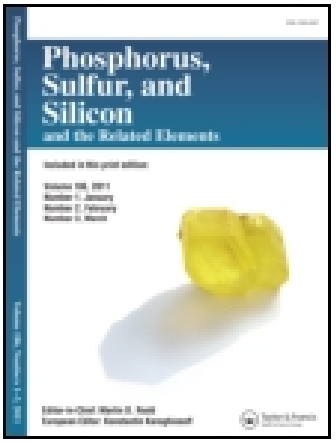

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Reactions of 1,1′-(Azodicarbonyl)Dipiperidine with Organophosphorus Reagents

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DOI: 10.1080/10426507.2011.586386

REACTIONS OF 1,1′-(AZODICARBONYL)DIPIPERIDINE WITH ORGANOPHOSPHORUS REAGENTS

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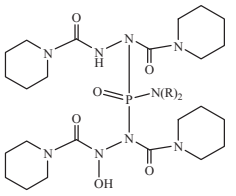
GRAPHICAL ABSTRACT



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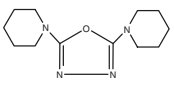

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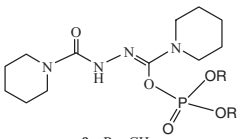
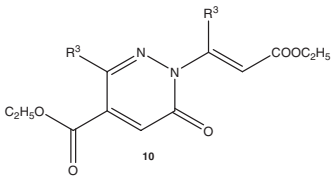


9a, R = CH_3
b, R = C_2H_5
c, R = $CH(CH_3)_2$



10

Abstract *1,1′-(Azodicarbonyl)dipiperidine reacts with tris(dimethylamino)phosphine, trialkyl phosphites, phosphorus ylides, and Lawesson's reagents to give the phosphorodihydrazidic amide, oxadiazole, dihydropyridazine, ethylenic, and thicarbonyl products, respectively. The antibacterial and antifungal activities for the new compounds are reported.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource: Biological Evaluation.*

Keywords Alkyl phosphites; 1,1′-(azodicarbonyl)dipiperidine; Lawesson's reagents; tris(dialkylamino)phosphines; ylides

INTRODUCTION

Our previous work reported that the new bioactive heterocyclic phosphorus substances synthesized from oxazolones possessed antischistosomal activity.[1] In addition, we

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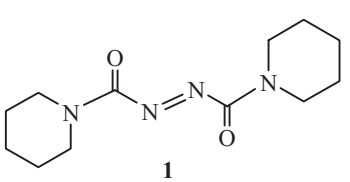
have found that some of our newly prepared heterocyclic oxaphospholes exhibit antibacterial and antifungal activities.[2] Moreover, it has been reported that different biological and pharmacological activities are well known for substituted diazines and related compounds.[3–8] In continuation of our previous work in organophosphorus chemistry,[1,2,9–11] we have now synthesized new heterocyclic phosphorus compounds incorporating important nuclei in the search for possible bactericidal and fungicidal activities.

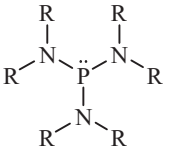
RESULTS AND DISCUSSION

Chemistry

In connection with a previous communication,[12] we report now on the reactions of 1,1′-(azodicarbonyl)dipiperidine (**1**) with tris(dialkylamino)phosphines **2a**,**2b**, trialkyl phosphites **3a–c**, phosphorus ylides **4a**,**4b**, and Lawesson's reagents **5a**,**5b** (Scheme 1).

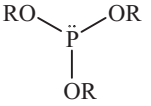


1



2a, R = CH_3

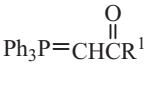
b, R = C_2H_5



3a, R = CH_3

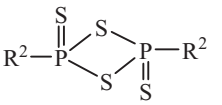
b, R = C_2H_5

c, R = $CH(CH_3)_2$



4a, $R^1 = OC_2H_5$

b, $R^1 = OC(CH_3)_3$



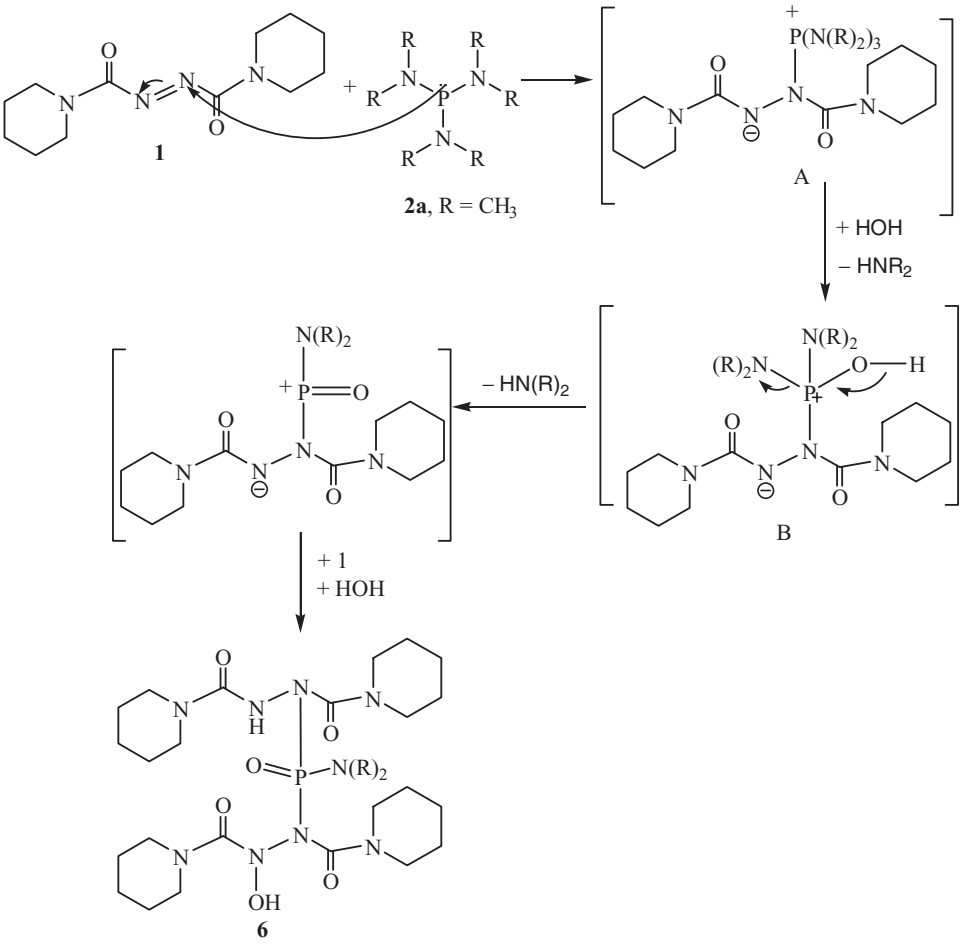
5a, $R^2 = C_6H_4\text{-}OCH_3\text{-}p$

b, $R^2 = S\text{-}C_6H_5$

Scheme 1

We have found that when one mole equivalent of tris(dialkylamino)phosphine **2a** reacted with two mole equivalents of 1,1′-(azadicarbonyl)dipiperidine (**1**), in refluxing toluene, compound **6** was isolated in a 68% yield (Scheme 2). Product **6** as a pure compound exhibited a sharp melting point. Structure elucidation of *N′,N″,N‴,N⁗*-tetrapiperidinylcarbonyl-*N‴*-hydroxy-*N,N*-dimethylphosphorodihydrazidic amide **(6)** was substantiated on the basis of its elemental analyses, IR, ^1H, ^{13}C, ^{31}P NMR, and mass spectral data (cf. Experimental section).

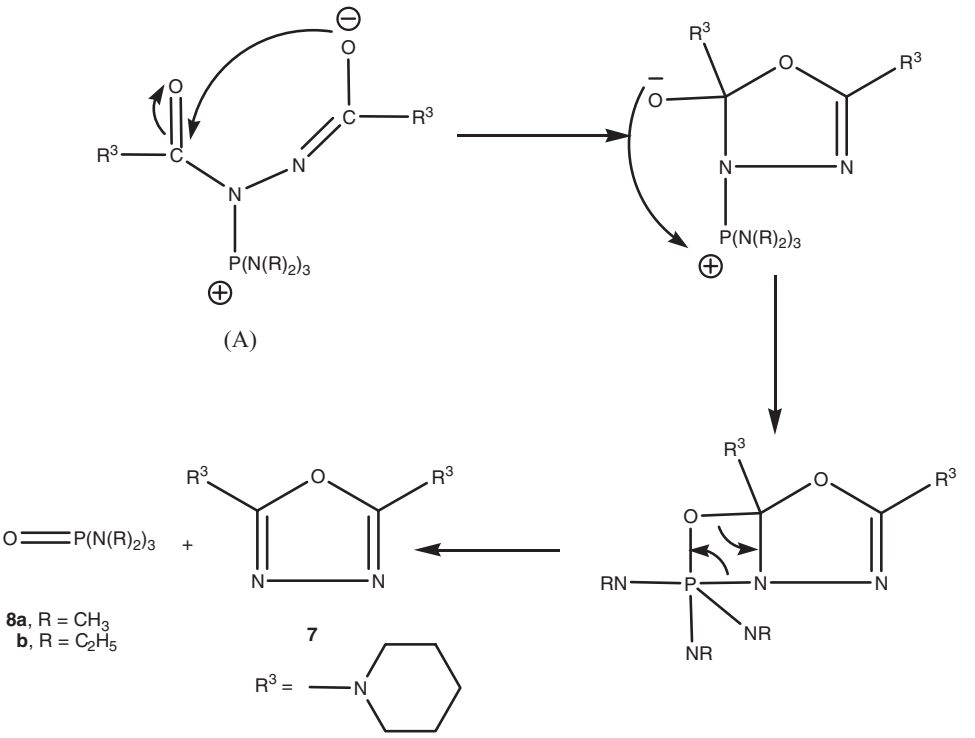
We propose the reaction course depicted in Scheme 2 for the formation of **6**. Thus, initial attack of aminophosphine **2a** on the most reactive center in **1** leads to the formation of the dipolar adduct (A), which collapses to the most stable form **6** through rapid hydrolysis of (A) (by the presence of unavoidable moisture) to give intermediate (B), which undergoes further decomposition together with addition of another molecule of **1** to yield product **6**.[2,13]



Scheme 2

On the other hand, when 1,1′-(azadicarbonyl)dipiperidine (**1**) was allowed to react with tris(dialkylamino)phosphine **2a** in the absence of solvent at room temperature for 15 min, colourless product **7** was obtained in an 85% yield together with tris(dialkylamino)phosphine oxide **8a** (Scheme 3). It is worth mentioning that when 1,1′-(azodicarbonyl)dipiperidine (**1**) was allowed to react with tris(dialkylamino)phosphine (**2b**) in the absence of solvent at room temperature for 10 min, the same product **7** was obtained in an 80% yield. Compound **7** was chromatographically pure and possessed a sharp melting point. Structural support for 2,5-di(piperidin-1-yl)-1,3,4-oxadiazole (**7**) was based on its analysis, IR, ^{1}H, ^{13}C NMR, and mass spectral data (cf. Experimental section). In order to identify unambiguously the structure of the reaction product (**7**), an X-ray structure determination[14–18] of crystalline **7** (Table 1) was performed (Figure 1).

Oxadiazole derivative **7** was probably obtained through a new competitive side reaction pathway, in which the betaine structure produced in the first step of the reaction is cyclized intramolecularly under drastic conditions as shown in Scheme 3.[19] 2,5-di(piperidin-1-yl)-1,3,4-oxadiazole was previously obtained from the reaction of azo compounds with tributyl phosphine (TBP).[19]



Scheme 3

Furthermore, this study was extended to include the behavior of 1,1′-(azodicarbonyl) dipiperidine (**1**) toward trialkyl phosphites **3**. Thus, we found that the reaction of **1** with trimethyl phosphite (**3a**) in dry toluene proceeded at the reflux temperature to give a chromatographically pure 1:1 adduct formulated as dimethyl (piperidin-1-yl)(piperidine-1-carboylimino)methyl phosphate **9a**. The structure of **9a** was deduced from its elemental

Table 1 Compound 7: Selected bond length (Å) and angles (°)

Selected bond	Bond length (bond angle)	Selected bond	Bond length (bond angle)
O1−C6	1.377(5)	C11−C16	1.471(6)
O1−C8	1.365(6)	C12−C15	1.502(7)
N2−C8	1.370(6)	C13−C16	1.511(8)
N2−C9	1.514(8)	C14−C17	1.506(9)
N2−C12	1.470(7)	C15−C17	1.520(8)
N3−N4	1.427(6)	C6−O1−C8	101.6(3)
N3−C6	1.273(6)	C8−N2−C9	112.9(4)
N4−C8	1.288(6)	C9−N2−C12	115.0(4)
N5−C6	1.368(6)	N4−N3−C6	106.1(4)
°N5−C13	1.467(6)	N3−N4−C8	105.5(4)
C7−C10	1.509(7)	C6−N5−C10	117.6(4)
C7−C11	1.504(7)	C6−N5−C13	114.5(4)
C9−C14	1.506(7)	O1−C6−N3	113.4(4)

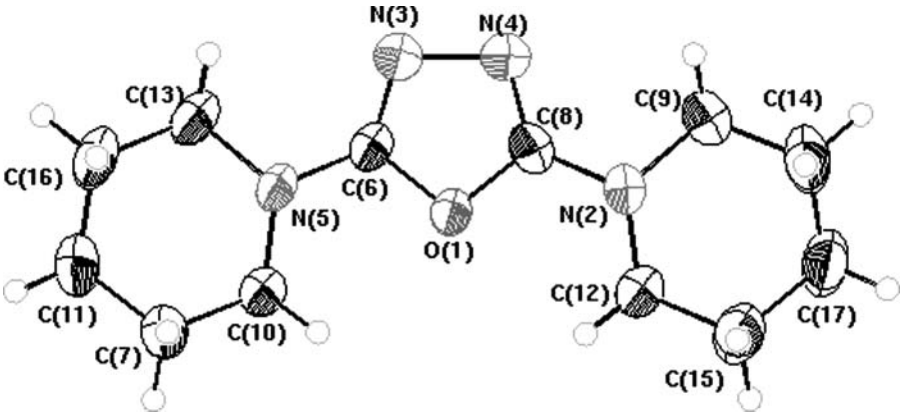
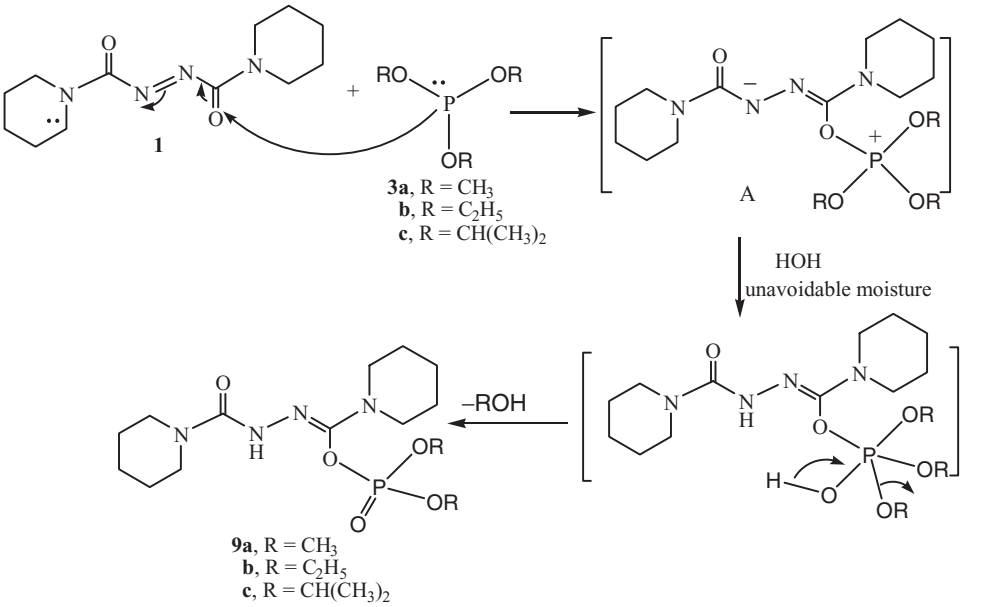


Figure 1 X-ray structure of compound **7**.

analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data (cf. Experimental section). Similarly, **3b** and **3c** react with **1** to give the dialkyl phosphates **9b** and **9c**, respectively, in good yields (Scheme 4). Structure assignments for **9b** and **9c** were substantiated on the basis of their elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data (cf. Experimental section).

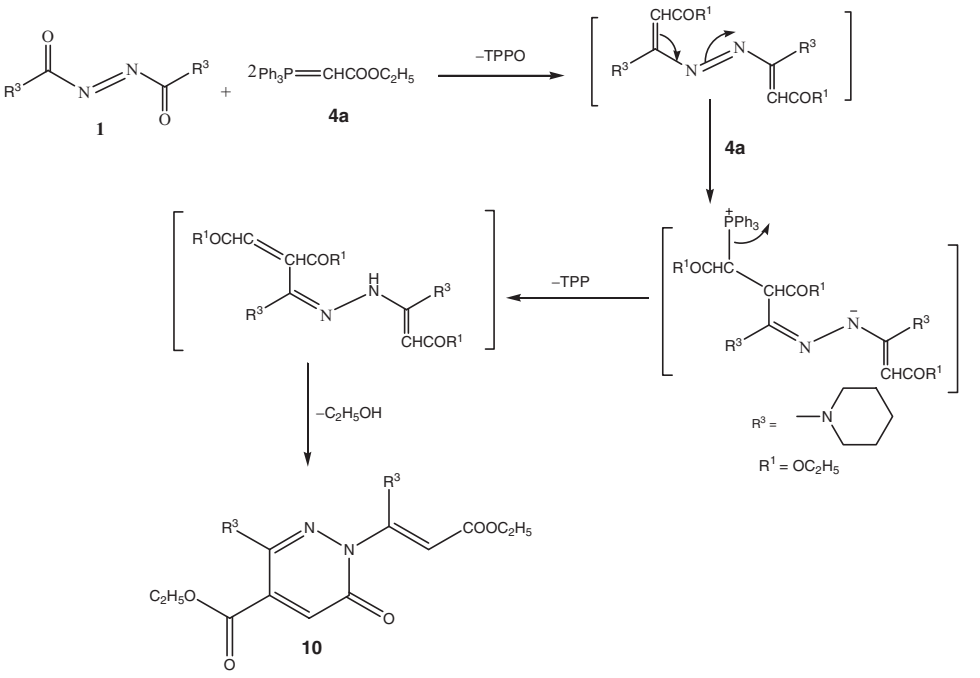


Scheme 4

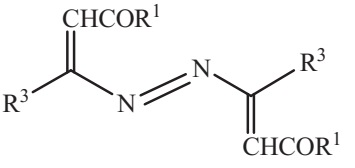
A possible explanation for the course of the reaction of trialkylphosphites **3a–c** with **1** is shown in Scheme 4. The reaction was assigned to proceed through an initial attack of the phosphorus reagents **3a–c** at the most reactive center in **1** and led to the formation of dipolar adduct (**A**). The reaction was accompanied with rapid hydrolysis by the presence

of unavoidable moisture and elimination of one molecule of alcohol under the applied reaction conditions to afford the dialkylphosphate products **9a–c**.

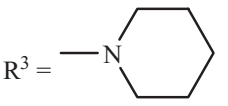
The reactions of **1** with phosphonium ylides **4a** and **4b** were also investigated. We found that 1,1′-(azodicarbonyl)dipiperidine (**1**) reacted with three mole equivalents of **4a** in refluxing toluene in the presence of a few drops of DMF to give product **10** in a 65% yield. Triphenylphosphine and triphenylphosphine oxide were also isolated from the reaction media. The structure of product **10** was assigned on the basis of IR, ^{1}H, ^{13}C NMR, and mass spectral data (cf. Experimental section). A possible explanation of the course of the reaction of phosphonium ylide **4a** with **1** is shown in Scheme 5. The reaction is assumed to proceed through olefination of the two carbonyl groups in **1** by the Wittig reagent **4a**, followed by addition of another molecule of phosphonium ylide **4a**



Scheme 5



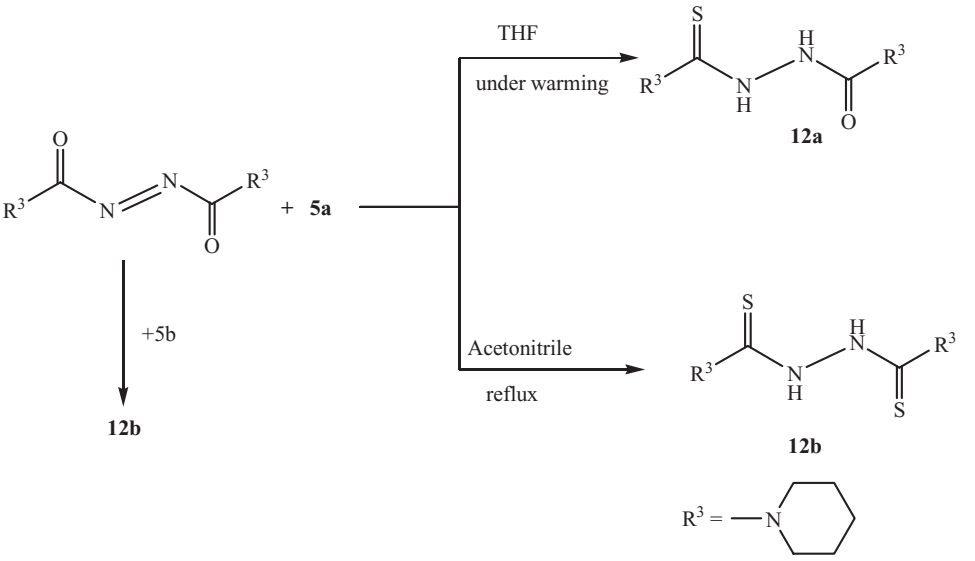
11

$R^3 =$  , $R^1 = OC(CH_3)_3$

Compound 11

and elimination of one molecule of alcohol under the applied reaction conditions to afford **10** (Scheme 5). On the other hand, when **1** was treated with two mole equivalents of **4b** in refluxing toluene in the presence of a few drops of DMF, the stable olefinic product **11** was isolated together with triphenylphosphine oxide. The compound *Tert*-butyl-3,3′(diazene-1,2-diyl)bis(3-piperidin-1-yl)acrylate **(11)** was chromatographically pure and exhibited a sharp melting point. Structure elucidation of product **11** was confirmed by analytical results and spectral data (see the Experimental section).

This study was further extended to include the reaction of Lawesson's reagents **5a**,**b** with 1,1′-(azodicarbonyl)dipiperidine (**1**). We have found that, when one mole of **1** was allowed to react with half an equivalent of **5a** in dry tetrahydrofuran under warming for 1 h, product **12a** was isolated in an 80% yield. Moreover, when one mole of **1** reacted with one equivalent of **5a** in refluxing acetonitrile for 1 h, **12b** was isolated in an 85% yield. On the other hand, 1,1′-(azodicarbonyl)dipiperidine **1** reacted with one equivalent of Japanese reagent (JP) **5b** in dry toluene at room temperature, to yield **12b** that was isolated in an 80% yield (Scheme 6).



Scheme 6

Previously, it has been reported that when *N*′-(piperidine-1-carbonyl)piperidine-1-carbohydrazide **1** was allowed to react with **5a** in refluxing xylene for 1 h, a complex mixture of products was produced.[20]

CONCLUSION

From the results of the present investigation, it can be concluded that the reaction of 1,1′-(azodicarbonyl)dipiperidine (**1**) with tris(dialkylamino)phosphines **2**, trialkyl phosphites **3**, phosphonium ylides **4**, and Lawesson's reagents **5** led to different products, depending on the nature of the phosphorus reagents as well as on the stability of the addition products. The significance of these findings lies in the discovery of a new pattern of attack by tris(dialkylamino)phosphines and in the establishment of a new method for

the synthesis of tetrapiperdinylcarbonyl-*N‴*-hydroxy-*N,N*-dimethylphosphorodihydrazidic amide, piperidine carboylimino phosphate, and dihydropyridazine derivatives.

EXPERIMENTAL

Melting points were determined in open glass capillaries using an Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex, UK) and were uncorrected. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infracord Spectrophotometer model 157(Grating). The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO as solvents on a Joel-500 MHz spectrometer, and the chemical shifts were recorded in δ values relative to TMS. The ^{31}P NMR (125 MHz) spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4 standard). The mass spectra were performed at 70 eV on a Shimadzu GCS-OP 1000 Ex spectrometer provided with a data system. Elemental analyses were performed using an Elmenter Varu EL Germany Instrument.

Reaction of Tris(Dimethylamino)Phosphine (2a) with 1,1′-(Azodicarbonyl)Dipiperidine (1)

Tris(dimethylamino)phosphine **2a**, 0.24 g (1 mmol) was added dropwise to a solution of compound **1** 0.5 g (2 mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 4 h. After evaporation of the volatile material under reduced pressure, the residue was washed several times with petroleum ether (b.r. 60 °C–80 °C) and crystallized from ethyl acetate to give 6 *N′,N″,N‴,N⁗*-tetrapiperdinylcarbonyl-*N‴*-hydroxy-*N,N*dimethylphosphorodihydrazidic amide (**6,** $C_{26}H_{48}N_9O_6P$).

(6): Yield 68%, mp 175 °C–176 °C (ethyl acetate). IR [ν, cm^{-1}, KBr]: 3318 (NH), 3320 (OH), 1650 (C=O), 1655 (C=O), 1320, 860 (P−N$(CH_3)_2$),[21] 1240 (P=O).[22] ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.56 (d, 24H, CH_2−Pip.), 2.67 (d, 6H, $^{3}J_{HP} = 10.05$ Hz, P−N$(CH_3)_2$), 3.38 (d, 16H, CH_2−Pip.), 6.76 and 6.79 (2s, 2H, 1NH, 1OH, exchangeable with D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 24.4 (s, 4CH_2−Pip.) 25.6 (s, 8CH_2−Pip.), 37.8 (d, $^{2}J_{CP} = 25.50$, O=P−N$(CH_3)_2$), 45.0 (s, CH_2−Pip.), 158.4 (d, $^{3}J_{CP} = 12$ Hz, C=O), 158.0 (d, $^{3}J_{CP} = 12$ Hz, C=O), 159.5 (d, $^{2}J_{CP} = 35.50$ Hz, O=C−N−P). ^{31}P NMR (δ ppm, $CDCl_3$): 26.24.[23] MS *m/z* (%): 614 [M^+] (Field Ionization Method). Anal. Calcd for $C_{26}H_{48}N_9O_6P$ (613.69): C, 50.89; H, 7.88; N, 20.54; P, 5.05. Found: C, 51.27; H, 8.12; N, 21.03; P, 5.20.

Reaction of Tris(Dialkylamino)Phosphine (2a) and/or (2b) with 1,1′-(Azodicarbonyl)Dipiperidine (1)

A mixture of **1** (0.25 g, 1 mmol) and excess of tris(dialkylamino)phosphine **2a** and/or **2b** was stirred at room temperature for 10–15 min. The reaction mixture was evaporated under reduced pressure. The residue was washed several times with petroleum ether (b.r. 60 °C–80 °C) to give 2,5-di(piperidin-1-yl)-1,3,4-oxadiazole (**7**, $C_{12}H_{20}N_4O$). The compound was crystallized from petroleum ether (b.r. 60 °C–80 °C) and was separated as colorless crystals, yield 80% and mp 75 °C–76 °C. IR [ν, cm^{-1}, KBr]: 1645 (C=N). ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.62 (m, 12H, CH_2−Pip.), 3.30 (m, 8H, CH_2−Pip.). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 24.2 (s, 4CH_2, pip.), 24.8 (s, 2CH_2, pip.), 47.3 (CH_2, pip.), 160.6 (C=N). MS *m/z* (%) 236 [M^+] (80). Anal. Calcd for $C_{12}H_{20}N_4O$ (236.31):

Table 2 Crystal data and experimental parameters used for the intensity data

Compound	7
Empirical formula	$C_{12}H_{20}N_4O$
Formula weight	236.319
Crystal system/space group	Triclinic
a/Å	6.3488(5)
b/Å	8.7559(8)
c/Å	12.1159(14)
α/Å	101.085(3)
β/Å	90.657(4)
γ/Å	105.527(4)
V/Å^3	635.42(11)
Z	2
D_x (Mg/cm^{-3})	1.235
μ (mm^{-1})	0.08
Color/Shape	Colorless/prismatic
Temp (K)	298
Theta range for collection	2.910–28.283
Reflection collected	3432
Independent reflections	2949
Data/restraints/parameters	154
R (gt)	0.066
Final *R* indices[1<3 (I)]	R_{int} 0.098

C, 60.99; H, 8.53; N, 23.71. Found: C, 60.97; H, 8.55; N, 23.79. Tris(dialkylamino)phosphine oxide **8a** and/or **8b** were also isolated from the reaction mixture and identified.

X-Ray Crystallographic Study[14–18]

A single crystal of (**7**) was grown by crystallization from petroleum ether (b.r. 40 °C–60 °C). The crystal structure was solved and refined, using maxus (Nonius, Deflt and Mac Science, Japan). MoK$_\alpha$ ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection. A summary of the crystal analysis parameters is given in the Table 2. CCDC 780686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data request/cif.

Reaction of Trimethyl Phosphite (3a) with 1,1′-(Azodicarbonyl)Dipiperidine (1)

Trimethyl phosphite (**3a**) (0.12 g, 1 mmol) was added dropwise to a solution of compound **1** (0.25 g, 1 mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 1 h. After evaporation of the volatile material under reduced pressure, the residue was washed several times with petroleum ether (40 °C–60 °C) to give product **9a** [dimethyl (piperidin-1-yl)(piperidine-1-caboylimino)methyl phosphate] (**9a,** $C_{14}H_{27}N_4O_5P$).

Crystallized from ethyl acetate, product **9a** was separated as colorless crystals, yield 65% and mp 126 °C–127 °C. IR [ν, cm^{-1}, KBr]: 1260 (P=O), 1628 (C=O), and 3315 (NH). ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.57 (m, 12H, CH_2—Pip.), 3.40 (m, 8H, CH_2—Pip.), 3.83 (d, 6H $^3J_{HP} = 11.50$ Hz, $P(OCH_3)_2$, 6.60 (s, NH, exchangeable with

D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 24.6 (s, 4$\underline{C}H_2$—Pip.), 25.4 (s, 2$\underline{C}H_2$—Pip.), 44.6 (s, 2$\underline{C}H_2$—Pip.), 47.2 (s, 2$\underline{C}H_2$—Pip.), 53.7 (d, $^2J_{CP} = 29.30$, O=P $(OCH_3)_2$), 158.4 (C=N), 160.0 (C=O). ^{31}P NMR (δ ppm, $CDCl_3$): 2.8. MS *m/z* (%) 362 [M^+] (75). Anal. Calcd for $C_{14}H_{27}N_4O_5P$ (362.63): C, 46.40; H, 7.51; N, 15.46; P, 8.55. Found: C, 46.47; H, 7.55; N, 15.45; P, 8.54.

Reaction of Triethyl Phosphite (3b) with 1,1′-(Azodicarbonyl)Dipiperidine (1)

Triethyl phosphite (**3b**) (0.16 g, 1 mmol) was added dropwise to a solution of compound **1** (0.25 g, 1 mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 4 h. After evaporation of the volatile materials under reduced pressure, the residue was washed several times with Petroleum ether (b.r. 40 °C–60 °C) to give product **9b**, [diethyl (piperidin-1-yl)(piperidine-1-caboylimino)methyl phosphate] (**9b**, $C_{16}H_{31}N_4O_5P$).

Crystallized from ethyl acetate, **9b** was separated as colorless crystals**,** yield 60% and mp 139 °C–140 °C. IR [*v*, cm^{-1}, KBr]: 1250 (P=O), 1620 (C=O), 3308 (NH). ^1H NMR (500 MHz, δ ppm, $CDCl_3$): 1.38 (t, 6H, (O)P(OCH_2—$\underline{CH_3}$)$_2$), 1.57 (m, 12H, CH_2—Pip.), 3.30 (m, 8H CH_2—Pip.), 3.90 (m, 4H, (O)P(O$\underline{CH_2}$—CH_3)$_2$), 6.80 (s, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 21.9 (d, $^3J_{cp} = 6.1$ Hz, P—O—CH_2—CH_3), 24.8 (s, 4$\underline{C}H_2$ pip.), 25.5 (s, 2$\underline{C}H_2$ pip.), 47.3 ($\underline{C}H_2$ pip.), 51.3 (d, $^2J_{cp} = 8.5$ Hz P—O—CH_2), 158.1 (C=N), 160.6 (C=O). ^{31}P NMR (δ ppm, $CDCl_3$): −0.21. MS *m/z* (%) 390 [M^+] (60). Anal Calcd for $C_{16}H_{31}N_4O_5P$ (390.41): C, 49.22; H, 8.00; N, 14.35; P, 7.93. Found: C, 49.23; H, 8.03; N, 14.53; P, 7.96.

Reaction of Triisopropyl Phosphite (3c) with 1,1′-(Azodicarbonyl)Dipiperidine (1)

Triisopropyl phosphite (**3c**) (0.2 g, 1 mmol) was added dropwise to a solution of compound **1** (0.25 g, 1 mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 4 h. After evaporation of the volatile materials under reduced pressure, the residue was washed several times with petroleum ether (b.r. 40 °C–60 °C) to give product **9c** [diisopropyl (piperidin-1-yl)(piperidine-1-caboylimino)methyl phosphate] (**9c**, $C_{18}H_{35}N_4O_5P$).

Crystallized from ethyl acetate, **9c** was separated as colorless crystals, yield 65% and mp 143 °C–144 °C. IR [*v*, cm^{-1}, KBr]: 1233 (P=O), 1628 (C=O), 997 (P(O—*i*Pr)$_2$), 3314 (NH). ^1H NMR (500 MHz, δ ppm, $CDCl_3$): 1.25 (m, 12H, (O)P(O—*i*Pr)$_2$), 1.59 (m, 12H, CH_2—Pip.), 3.30 (m, 8H CH_2—Pip.), 4.74, 4.35 (2m, 2H, *i*Pr), 6.60 (s, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 22.8 (O—$CH(CH_3)_2$); 23.9 (4$\underline{C}H_2$, pip.), 24.8 (2$\underline{C}H_2$, pip.), 45.0 (2$\underline{C}H_2$, pip.), 47.40 (2$\underline{C}H_2$, pip.), 51.2 (d, $^2J_{CP} = 7.6$ Hz, P($OCH(CH_3)_2$), 158.1 (C=N), 160.5 (C=O). ^{31}P NMR (δ ppm, $CDCl_3$): −2.15. MS *m/z* (%) 418 [M^+] (30). Anal. Calcd. for $C_{18}H_{35}N_4O_5P$ (418.47): C, 51.66; H, 8.43; N, 13.39; P, 7.40. Found: C, 51.68; H, 8.47; N, 13.40; P, 7.42.

Reaction of Phosphonium Ylide 4a with 1,1′-(Azodicarbonyl)Dipiperidine 1

To a mixture of 1.05 g **4a** (3 mmol) and 0.25 g (1 mmol) of **1** in dry toluene (40 mL), a few drops of DMF were added. The reaction mixture was refluxed for 15 h. The volatile material was evaporated under reduced pressure. The residue was subjected to silica gel

column chromatography to give ethyl 1-(3-ethoxy-3-oxo-1-(piperidin-1-yl)prop-1-enyl)-6-oxo-3-(piperidin-1-yl)-1,6-dihydropyridazine-4-carboxylate **(10,** $C_{22}H_{32}N_4O_5$**)**.

Eluent: petroleum ether/ethyl acetate (90/10, v/v), **10** was separated as colorless crystals, yield 55% and mp 29 °C–30 °C (petroleum ether/ethyl acetate). IR [ν, cm^{-1}, KBr]: 1624 (C=O cyclic), 1707 (C=O ester). ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.22 (2t, 16H, CH_3 ethyl), 1.28 (m, 12H, CH_2—Pip.), 3.05 (m, 8H, CH_2—Pip.), 4.18 (m, 4H, CH_2 ethyl), 5.30 (s, $CHCOOC_2H_5$), 7.60 (s, CH cyclic). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 14.3 (CH_3), 22.7 (4$\underline{C}H_2$, pip.), 27.7 (2$\underline{C}H_2$, pip.), 47.5 (C_5H_{10}), 60.2 (CH_2 ethyl), 77.2 (C=C), 128.7 (C—C cyclic), 143.4 (C=O cyclic), 150.0 (C=N), 163.1 (C=O, cyclic), 166.4 (C=O ester); 167.5 (C=O). MS *m/z* (%) 432 [M^+] (50). Anal. Calcd for $C_{22}H_{32}N_4O_5$ (432.51): C, 61.09; H, 7.46; N, 12.95. Found: C, 61.12; H, 7.49; N, 12.93. Triphenylphosphine and triphenylphosphine oxide were also isolated and identified.

Reaction of Phosphonium Ylide 4b with 1,1′-(Azodicarbonyl)Dipiperidine (1)

To a mixture of 0.76 g of **4b** (2 mmol) and 0.25 g (1 mmol) of **1** in dry toluene (40 mL), a few drops of DMF were added. The reaction mixture was refluxed for 2 h. The volatile material was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give product **11** [tert-butyl-3, 3′-(diazene-1,2-diyl)bis(3-(piperidin-1-yl)acrylate] (**11**, $C_{24}H_{40}N_4O_4$).

Eluent: petroleum ether/ethyl acetate (90/10, v/v), **11** was separated as colorless crystals, yield 60% and mp 35 °C–36 °C. IR [ν, cm^{-1}, KBr]: 1575 (N=N), 1628 (C=C), 1710 (C=O ester). ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.24 (m, 18H, 2–$C(CH_3)_3$), 1.55 (m, 12H, CH_2—Pip.), 3.10 (m, 8H,CH_2—Pip.), 5.37, 5.34 (2s, 2H, two = CH). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 14.2 ($CH_3)_3$); 28.3 (4CH_2, pip.), 29.7 (2CH_2, pip.), 45.0 (2CH_2, pip.), 49.1 (2CH_2, pip.), 102.0 ($\underline{C}$H), 143.6 ($\underline{C}$=CH), 163.1 (C=O ester). MS *m/z* (%) 448 [M^+] (65). Anal. Calcd for $C_{24}H_{40}N_4O_4$ (448.6): C, 64.26; H, 8.99; N, 12.49. Found: C, 64.29; H, 9.27; N, 12.85. Triphenylphosphine oxide was also isolated.

Reaction of Lawesson's Reagent (5a) with 1,1′-(Azodicarbonyl)Dipiperidine (1) in Tetrahydrofuran

A mixture of 0.2 g (0.5 mmol) of **5a** and 0.2 g (1 mmol) of **1** was gently heated for 1 h in rigorously dried tetrahydrofuran. The volatile material was evaporated under reduced pressure. The residue was washed several times with petroleum ether (b.r. 40 °C–60 °C) to give product **12a [***N′*-(piperidine-1-carbothioyl) piperidine-1-carbohydrazide] (**12a,** $C_{12}H_{22}N_4OS$).

Crystallized from *n*-hexane to give **12a** which was separated as colorless crystals**,** yield 80% and mp 180 °C–181 °C. IR [ν, cm^{-1}, KBr]: 1255 (C=S), 1632 (C=O), 3236 (NHC=S), 3434 (NHC=O). ^{1}H NMR (500 MHz, δ ppm, $CDCl_3$): 1.58 (m, 12H, CH_2—Pip.), 3.38 (m, 8H, CH_2—Pip.), 6.6 (s, 2H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 24.4 (4CH_2, pip.), 25.5 (2CH_2, pip.), 47.0 (2CH_2, pip.), 49.1 (2CH_2, pip.), 158.1 (C=O), 182.0 (C=S). MS *m/z* (%): 270 [M^+] (75). Anal. Calcd for $C_{12}H_{22}N_4OS$ (270.39): C, 53.30; H, 8.20; N, 20.72; S, 11.86. Found: C, 53.35; H, 8.28; N, 20.75; S, 11.88.

Reaction of Lawesson's Reagent (5a) with 1,1′-(Azodicarbonyl)Dipiperidine (1) in Acetonitrile

A mixture of 0.4 g (1 mmol) of **5a** and 0.25 g (1mmol) of compound **1** was refluxed in dry acetonitrile for 1 h. The volatile material was evaporated under reduced pressure. The residue was washed several times with petroleum ether (b.r. 60 °C–80 °C) to give product [**12b** N′-(piperidine-1-carbothioyl) piperidine-1-carbothiohydrazide] (**12b**, $C_{12}H_{22}N_4S_2$).

Crystallized from ethyl acetate **12b** as colorless crystals, yield 85%, mp 167 °C–168 °C. IR [ν, cm^{-1}, KBr]: 1200 (C=S), 3201 (NHC=S). ^1H NMR (500 MHz, δ ppm, $CDCl_3$): 1.80 (m, 12H, CH_2—Pip.), 3.34 (m, 8H, CH_2—Pip.), 7.3 (s, 2H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, δ ppm, $CDCl_3$): 24.3 ($4CH_2$, pip.), 25.4 ($2CH_2$, pip.), 44.9 (CH_2, pip.), 188.1 (C=S). MS *m/z* (%): 286 [M^+] (45). Anal Calcd for $C_{12}H_{22}N_4S_2$ (286.46): C, 50.31; H, 7.74; N, 19.56; S, 22.39. Found: C, 50.34; H, 7.76; N, 19.53; S, 22.37.

N′-(Piperidine-1-Carbothioyl) Piperidine-1-Carbothiohydrazide (12b, $C_{12}H_{22}N_4S_2$)

A mixture of 0.4 g (1 mmol) of **5b** and 0.25 g (1 mmol) of compound **1** was stirred in dry toluene for 1 h at room temperature. The volatile materials were evaporated under reduced pressure. The residue was washed several times with petroleum ether (b.r. 60 °C–80 °C) to give the same product **12b** (mixed mp and comparative IR spectra).

Biological Screening

The antibacterial and antifungal activities were carried out in the Microbial Chemistry Department, National Research Centre, using the diffusion plate method.[24–27] The Supplemental Materials contain a summary of the results. The obtained results were compared with reference antibiotics[24–27] that were purchased from Egyptian markets.

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