Synthesis of Various Schiff Bases Containing Isoxazole Ring and Their Applications with Thioglycollic Acid and Diverse Phosphorus Reagents

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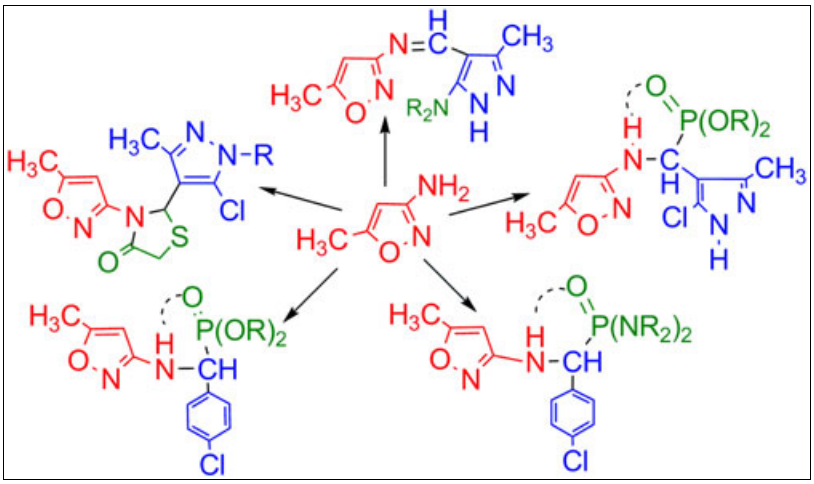


A series of Schiff bases bearing isoxazole and pyrazole rings were synthesized. Application of thioglycollic acid on two selective synthesized Schiff bases afforded the corresponding thiazolidin-4-one derivatives. On the other hand, following the multicomponents one-pot Kabachnik– Fields reaction, the Schiff base generated *in situ* from 4-chlorobenzaldehyde and 5-methyl isoxazol-3-amine was trapped by phosphorus reagents to produce the corresponding amino phosphonates in moderate yields. However, the latter products could also be obtained in better yields (≥78%) by directly applying the dialkylphosphites to a selective synthesized Schiff base. Similarly, a series of α-aminophosphonates could be obtained from 5-chloro-3-methyl-1*H*-pyrazol-4-carbaldehyde, 5-methylisoxazol-3-amine, and phosphorus reagents. Moreover, applying hexaalkyl triamido phosphites to the *N*-(4-chlorobenzylidene)-5-methylisoxazol-3-amine in ethanol afforded methylphosphonic diamide derivatives, whereas *N*-((5-chloro-3-methyl-1*H*-pyrazol-4-yl)methylene)-5-methylisoxazol-3-amine underwent dechlorination through reaction with hexaalkyl triamido phosphites to give the respective amine derivatives.

INTRODUCTION

Literature survey revealed that isoxazole rings have been widely used as key building blocks for drugs; their derivatives are endowed with broad spectrum of pharmacological properties including hypoglycemic, analgesic, anti-inflammatory, anti-bacterial, anti-HIVs, and anti-cancer activities [1–5]. In addition, pyrazole derivatives have received considerable attention owing to their diverse chemotherapeutic potentials including versatile anti-neoplastic activities [6–13]. Many of these compounds are demonstrated as anti-leukemic [6,7], anti-tumor [8,9], and anti-proliferative [10,11] agents, in addition to their capability to exert remarkable anti-cancer effects through inhibiting different types of enzymes that play important roles in cell division [12,13].

The chemistry of substituted heterocyclic phosphor esters has attracted many attention because of their unique structural features and diverse applications in biological systems [14].

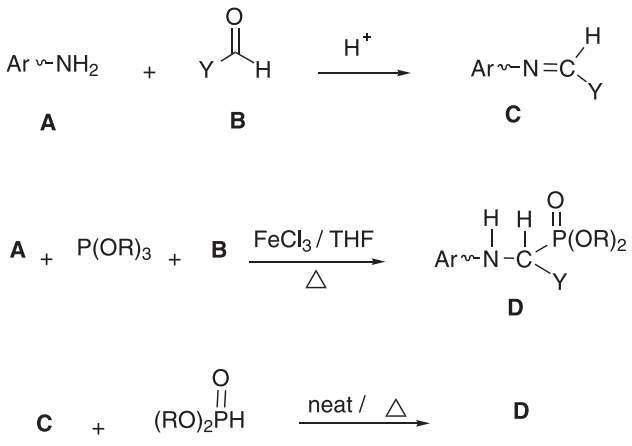
α-Aminophosphonates constitute an important class of compounds that attract medicinal chemists because of their wide use in drug development; they can serve as both hyperglycemic and hypoglycemic agents in different concentrations [15,16], anti-tumor agents [17,18], pharmacogenic agents [19], and as inhibitors of serine hydrolases [20].

We now report on multicomponent reactions with three or more reactants combined in a one-pot procedure to give a single product. Accordingly, efficient synthesis of α-aminophosphonates from selected amine, aldehyde, and phosphorus reagents including trialkylphosphites, dialkylphosphites, or hexaalkyl triamidophosphites could be achieved following the previously reported method [21–25] using 10% $FeCl_3$ in tetrahydrofuran (THF)

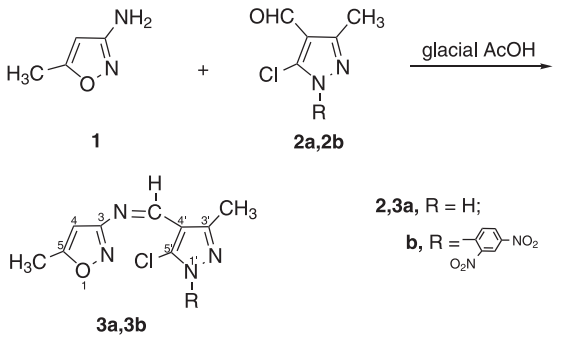
solution to facilitate the Mannich-type reaction of aldehyde, amine, and phosphorus reagent.

Appling hexaalkyl triamidophosphites to the Schiff bases in different solvents afforded phosphorylating and amine- induced dephosphorylating derivatives.

Scheme 1. General pathway for synthesis of Schiff bases and phosohonate products.



Scheme 2. Synthesis of Schiff bases **3a**, **3b**.



RESULTS AND DISCUSSION

We adopted the multicomponent reactions in a one-pot synthesis of the target α-aminophosphonate by mixing stoichiometric amounts of an amine with appropriate aldehyde, and the phosphorus reagents trialkylphosphites or dialkylphosphites as displayed in Scheme 1.

The required carbaldehydes **2a** and **2b** were obtained in moderate yields (~43%), via Vilsmeier–Haack reaction of 3-methyl-1*H*-pyrazole-5(4*H*)-one or 1-aryl-3-methyl-1*H*-pyrazole-5(4*H*)-one [26].

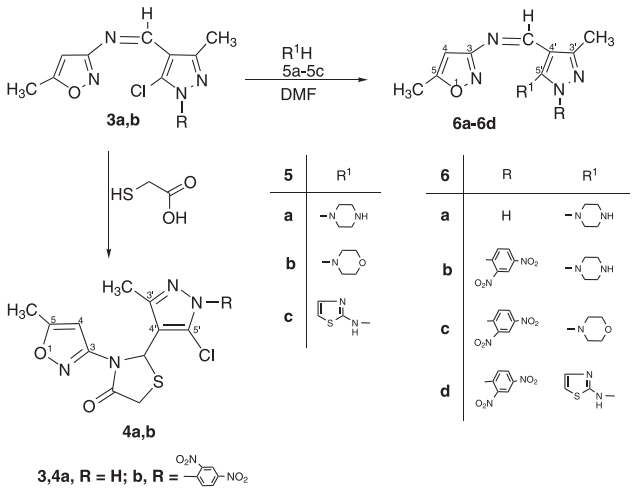
Condensation of carbaldehydes **2a** or **2b** with 3-amino-5-methylisoxazole (**1**) in the presence of glacial acetic acid, afforded the corresponding methylisoxazol-amines **3a** or **3b** as shown in Scheme 2. The structure suggested for **3a** and **3b** are in good agreement with their analytical and spectral data.

When compound **3a** or **3b** was reacted with thioglycollic acid in dry benzene, the thiazolidine-4-ones **4a** or **4b** was produced (Scheme 3). The ^{1}H nmr spectrum of compound **4a** revealed the presence of a broad singlet at $\delta = 10.90$ ppm (NH), D_2O exchangeable while ei-ms of compound **4b** showed *m/z* 464 (M^+).

When compound **3a** was allowed to react with piperazine **5a** in DMF under reflux, the corresponding Schiff base **6a** was produced. Moreover, compound **3b** was allowed to react with piperazine, morpholine, and 2-aminothiazol **5a–5c** under the same reaction conditions to obtain the corresponding Schiff base **6b–6d** as shown in Scheme 3. The spectroscopic data of compound **6a** was in good agreement with the assigned structure.

The required aminophosphonates **9a–9c** were obtained as colorless crystals by mixing the amine **1** with aldehyde **8** in THF solution containing 10% $FeCl_3$. TAPs **7a–7c** were then added at r.t, followed by heating under reflux for ~8h (Scheme 4).

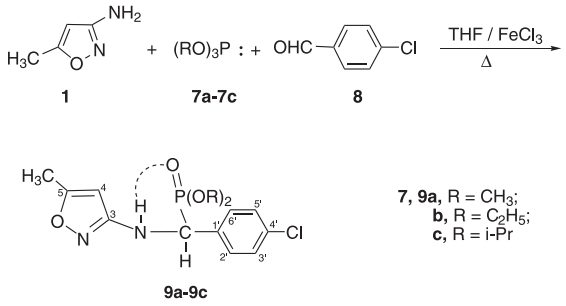
Scheme 3. Synthesis of thiazolidine-4-ones **4a**, **4b** and Schiff bases **6a–6d**.



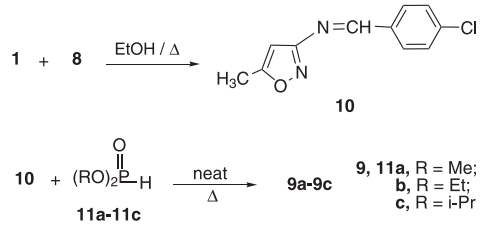
5	R^1
a	piperazine
b	morpholine
c	2-aminothiazole

6	R	R^1
a	H	piperazine
b	2,4-dinitrophenyl	piperazine
c	2,4-dinitrophenyl	morpholine
d	2,4-dinitrophenyl	2-aminothiazole

Scheme 4. Synthesis of α-aminophosphonates **9a–9c** via TAPs.



Scheme 5. Synthesis of α-aminophosphonates **9a–9c** via DAPs.

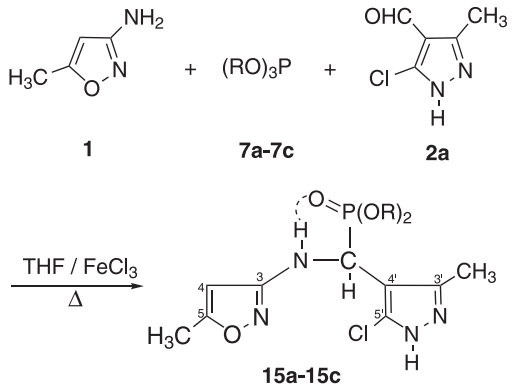


Structural reasoning for **9** are as follows: compatible elementary and molecular weight determinations (ms) were gained for **9a–9c**. Positive chemical shifts were recorded for **9a** ($\delta = 23.80$ ppm) [^{31}P- nmr spectrum (vs 85% H_3PO_4)], confirming the presence of P-C linkage (phosphonate group).

The ir spectrum (KBr, cm^{-1}) of dimethyl (4-chlorophenyl) (5-methylisoxazol-3-ylamino)methylphosphonate (**9a**) taken as a representative example showed the P=O stretching band at 1226 (P=O, bonded) cm^{-1}; this could be explained by a preferred conformation of intramolecular hydrogen bonding between the NH proton and the P=O moiety.

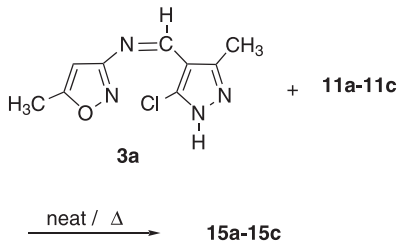
Apparently, the asymmetry of the molecule because of the presence of a stereocenter would render the two methoxyl groups diastereotropic, and hence, anisochronous is resulting in the observed splitting pattern [27].

Scheme 7. Synthesis of α-aminophosphonates **15a–15c** via TAPs.



7,15 a, R = Me; **b**, R = Et; **c**, R = i-Pr

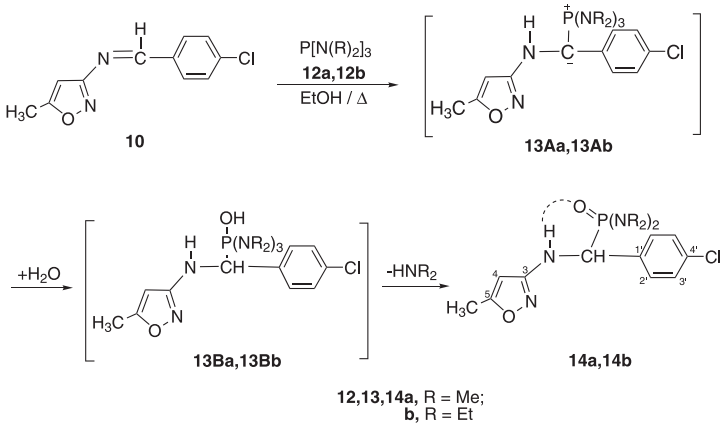
Scheme 8. Synthesis of α-aminophosphonates **15a–15c** via DAPs.



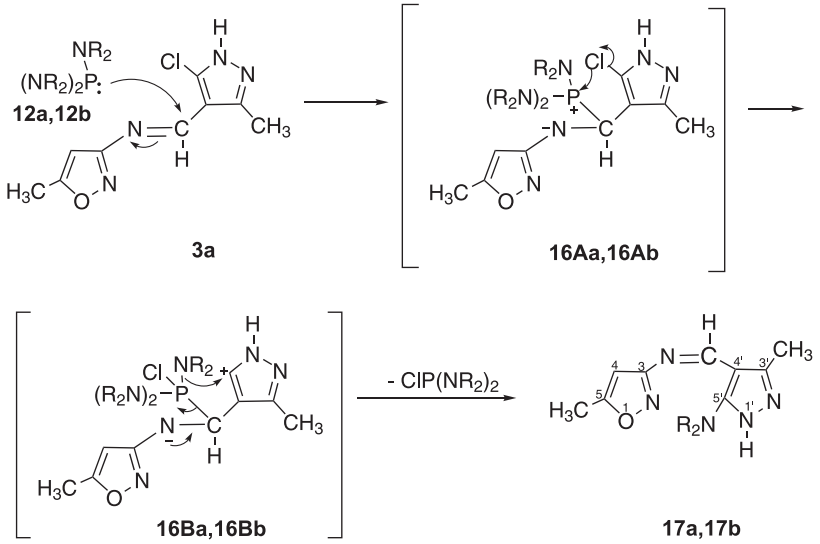
11, 15a, R = Me; **b,** R = Et; **c,** R = i-Pr

The possible explanation for the mechanism of the reaction is proposed according to the Kabachnik–Fields reaction [28,29]. The first step may involve condensation between aldehyde and amine in the presence of $FeCl_3$

Scheme 6. Synthesis of tetraalkylphosphonic diamide derivatives **14a**,**14b**.



Scheme 9. Synthesis of dialkylamino derivatives **17a** and **17b**.



12,16,17a, R = Me; **b** R = Et

and formation of the intermediate Schiff base **10**, followed by addition of the phosphorus reagent **7a–7c** to produce **9a–9c**. The formation of dialkyl and not trialkyl adduct is acceptable since in the presence of acidic medium ($FeCl_3$), TAPs are hydrolyzed to their DAP counterparts.

In favor of this mechanism compounds **9a–9c** were independently synthesized in higher yields (~74%) and characterized (Scheme 5). Thus, **9a–9c** could be obtained by treating *N*-(4-chlorobenzylidene)-5-methylisoxazol-3-amine (**10**) with DAPs **11a–11c** at 100°C in absence of solvent to give colorless phosphonate 1:1 adducts for which structures **9a–9c** are, respectively, assigned.

On the other hand, when Schiff base **10** was allowed to react with hexaalkyl triamidophosphites **12a** or **12b** in boiling ethanol, the corresponding tetraalkylphosphonic diamide derivatives **14a** or **14b** were isolated in ~62% yield. Satisfactory elementary analyses and molecular weight determinations confirmed structure **14**.

Obviously, compounds **14a** or **14b** were formed through an initial addition of the aminophosphine **12a** or **12b** to the Schiff base **10** giving rise to the phosphonium dipolar ion intermediates **13A**. Stabilization of **13A** was attained by its reaction with fortuitous water to give the intermediates **13B** and an extrusion of dialkylamine moiety leading to **14a** or **14b** [30]; the reaction mechanism is depicted in Scheme 6.

In the same sense, the target α-aminophosphonates **15a–15c** could be obtained in moderate yield (≥50%) by mixing the amine **1** with the aldehyde **2a** in THF solution containing 10% $FeCl_3$. TAPs **7a–7c** were then added at r. t., followed by heating under reflux for ~10 h (Scheme 7).

Similarly, compounds **15a–c** were separated in good yields and identified (mp, mixed m.ps. comparative ir and ms spectra) by treating **3a** with DAPs **11a–11c** at 100°C in absence of solvent (Scheme 8). The structures suggested for all new compounds are in good agreement with their analytical and spectral data (refer to experimental section).

The behavior of compound **3a** toward hexaalkyl triamidophosphites **12a** and **12b** was also investigated. The reaction proceeded in THF at reflux temperature to give products devoid of phosphorus **17a** and **17b**.

The reaction mechanism is depicted in Scheme 9. Initial nucleophilic attack by the phosphine-phosphorus atom on **3a** would produce a betaine of a structure like **16A** [31]. By virtue of the great affinity of phosphonium ions to halides [32] would facilitate formation of transient betaine of type **16B**. The latter in which phosphorus can act as a good leaving group because of its bulkiness, **16B**, decomposes to afford **17a** or **17b**.

Analytical and spectroscopic data recorded for compounds **17a** and **17b** afford a strong support for the postulated mechanism.

CONCLUSIONS

It was an attractive challenge in this work to synthesize novel molecules carrying the isoxazole moiety in combination with different side chains and with pyrazole ring aiming to obtain potent biological drugs. We also report a one pot synthesis of aminophosphonates via Kabachnik–Fields reaction, starting from substituted amines and aldehyde derivatives in the presence of phosphorus reagents. These targeted products were resynthesized in better yields by directly applying phosphorus reagents on synthesized Schiff bases.

Finally, hexaalkyl triamidophosphites used as aminating agent and induce chlorine displacement to yield the respective 5-(dialkylamino)- derivatives.

EXPERIMENTAL

General. Melting points were determined with an open capillary tube on an electrothermal (variable heater, Stuart, UK) melting point apparatus and were uncorrected. The ir spectra were recorded on a JASCO FT- ir 6100 using KBr disk (Jasco, Japan). The nmr spectra were measured with a Jeol E.C.A-500 MHz (^{13}C: 125.4 MHz, ^{1}H: 500.7 MHz, ^{31}P: 200.7 MHz) spectrometer (Jeol, Japan). ^{1}H and ^{13}C nmr spectra were recorded with trimethylsilane as internal standard in $CDCl_3$ and/or DMSO. ^{31}P nmr spectra were recorded with H_3PO_4 (85%) as external reference. Chemical shifts (δ) are given in parts per million. The mass spectra were performed at 70 eV on an ms-50 Kratos (A.E.I.) spectrometer (Kratos, UK). The appropriate precautions in handling moisture-sensitive compounds were observed. The purity of all new samples was verified by microchemical analysis (C/H/N/S) and spectroscopy. Solvents were dried by standard techniques. All chemicals used were purchased from Aldrich. TLC: Merck 0.2 mm silica gel 60 F154 anal aluminum plates. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using Elemental Analyessystem GMbH-vario EL III Elemental Analyzer Germany. The known Schiff base **10** was obtained using the procedure reported by Rajanarendar *et.al.* [33].

General procedure for synthesis of carbaldehydes 2a and 2b. To ice cold dimethylformamide (400 mmol) was added dropwise with stirring phosphorus oxychloride (400 mmol) over a period of 30 min, stirring was continued for further 45 min, and the reaction mixture was kept at 0°C. 3-Methyl-1*H*-pyrazole-5(4*H*)-one (7.8 g, 80 mmol) or 1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-4 (5H)-one (21.1 g, 80 mmol) was then added, and the reaction mixture was allowed to attain room temperature. The mixture was then heated at 90°C for 4–6 h (TLC), allowed to cool and poured onto a mixture of crushed ice and water. The precipitates obtained were filtered, dried, and crystallized from ethanol to obtain the required 5-chloro -4-carbaldehydes **2a** or **2b**.

5-Chloro-3-methyl-1H-pyrazole-4-carbaldehyde (2a). Straw yellow solid, yield 45%, 5.17 g, mp 200–202°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3345 (NH), 1725 (O=C). ^{1}H nmr (DMSO-d_6): δ_H 2.52 (3H, s, CH_3), 10.82 (1H, s(br), NH, $D_2O_{exchangeable}$), 10.2(1H, s, HCO). ^{13}C nmr (DMSO-d_6): δ_C 12.8 (CH_3), 110.9, 142.8, 147.7 (C(4), C(5), C(3)), 181.2 (CHO). ei-ms, *m/z* (%) = 144 (M^+, 30). *Anal*. Calcd for $C_5H_5ClN_2O$ (144.56): C, 41.54; H, 3.49; N, 19.38%. Found: C, 41.71; H, 3.35; N, 19.21%.

5-chloro-1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (2b). Yellowish brown solid, yield 41%, 10.17 g, mp 280–283°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3100 (CH_{arom}), 1725 (O=C). ^{1}H nmr (DMSO-d_6): δ_H 2.59 (3H, s, CH_3), 7.27–7.52 (2H, 2d, J_{HH} 7.8 Hz, ArH), 8.33 (1H, s, ArH), 10.8 (1H, s, HCO). ^{13}C nmr (DMSO-d_6): δ_C 13.5 (CH_3), 113.1, 140.2, 145.2 (C(4), C(5), C(3)), 124.9, 126.8, 134.7, 136.8, 145.1, 146.9 (ArC), 180.6 (CHO). ei-ms, *m/z* (%) = 310 (M^+, 25). *Anal*. Calcd for $C_{11}H_7ClN_4O_5$ (310.65): C, 42.53; H, 2.27; N, 18.04%. Found: C, 42.68; H, 2.12; N, 17.84%.

General procedure for synthesis of compounds 3a and 3b. A mixture of 3-amino-5-methylisoxazole (**1**) (4.90 g, 50 mmol) and 5-Chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde (**2a**, 50 mmol, 7.20 g), 5-chloro-1-(2,4-dinitrophenyl)-3-methyl-1*H*-pyrazole-4-carbaldehyde (**2b**, 50 mmol, 15.55 g) in glacial acetic acid (100 mL) was refluxed for 18–20 h (TLC). After cooling, the formed precipitate was filtered, washed with petroleum ether 60–80 and crystallized from ethanol to afford Schiff bases **3a** or **3b**.

N-[(5-Chloro-3-methyl-1H-pyrazol-4-yl)methylene]-5-methylisoxazol-3-amine (3a). Yellowish brown solid, yield 40%, 4.45 g, mp 158–160°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3345 (w, NH), 1624 (N=CH). ^{1}H nmr (DMSO-d_6): δ_H 2.18 (3H, s, CH_3-pyrazole), 2.38 (3H, s, CH_3-isoxazole), 6.58 (1H, s, H-isoxazole), 8.41(1H, s, CH=N), 10.82 (1H, s(br), NH, $D_2O_{exchangeable}$). ^{13}C nmr (DMSO-d_6): δ_C 13.1 (Me-isoxazole), 13.8 (Me-pyrazole), 86.9, 143.1, 165.1 (C(4), C(3), C(5)-isoxazole), 96.8, 145.0, 146.2 [C(4′), C(3′), C(5′)-pyrazole], 153.2 (HC=N). ei-ms, *m/z* (%) = 224 (M^+, 35). *Anal*. Calcd for $C_9H_9ClN_4O$ (224.65): C, 48.12; H, 4.04; N, 24.94%. Found: C, 48.28; H, 3.88; N, 24.80%.

N-{[5-Chloro-1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-4-yl]methylene}-5-methylisoxazol-3-amine (3b). Yellowish brown solid, yield 40%, 7.80 g, mp 233–235°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3100 (CH_{arom}), 1628 (N=CH). ^{1}H nmr (DMSO-d_6): δ_H 2.19 (3H, s, CH_3-pyrazole), 2.40 (3H, s, CH_3-isoxazole), 6.55 (1H, s, H-isoxazole), 7.30–7.51 (2H, 2d, J_{HH} 7.4 Hz, ArH), 8.30 (1H, s, ArH), 8.49 (1H, s, CH=N). ^{13}C nmr (DMSO-d_6): δ_C 12.9 (Me-isoxazole), 13.3 (Me-pyrazole), 90.2, 145.9, 164.1 (C(4), C(3), C(5) -isoxazole), 99.8, 144.1, 146.3 (C(4′), C (3′), C(5′)-pyrazole), 122.8, 125.1, 135.8, 136.1, 144.3, 146.1 (ArC), 153.9 (HC=N). ei-ms, *m/z* (%) = 390 (M^+, 30). *Anal*. Calcd for $C_{15}H_{11}ClN_6O_5$ (390.74): C, 46.11; H, 2.84; N, 21.51%. Found: C, 46.22; H, 2.65; N, 21.39%.

General procedure for synthesis thiazolidinones 4a, 4b. A mixture of compound **3a** (0.44 g, 2 mmol) or **3b** (0.78 g, 2 mmol) and thioglycolic acid (0.2 mL, 2 mmol) in dry benzene (20 mL) was heated under reflux for 10–20 h. The solvent was evaporated under reduced pressure, and the formed residue was treated with diluted solution of sodium carbonate (10%). The formed precipitate was filtered, dried, and crystallized from ethanol to give **4a** or **4b.**

2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-3-(5-methylisoxazol-3-yl)-1,3-thiazolidin-4-one (4a). Straw yellow solid, yield 50%, 0.27 g, mp 211–213°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3230 (NH), 1725 (CO). ^1H nmr (DMSO-d_6): δ_H 2.15 (3H, s, CH_3-pyrazole), 2.28 (3H, s, CH_3-isoxazole), 3.60 (2H, s, CH_2-thiazolidine), 5.30 (1H, s, H- thiazolidine), 6.63 (1H, s, H-isoxazole), 10.90 (1H, s(br) NH, $D_2O_{exchangeable}$). ^{13}C nmr (DMSO-d_6): δ_C 12.9 (Me-isoxazole), 13.3 (Me-pyrazole), 36.5 (CH_2- thiazolidine), 58.4(CH- thiazolidine), 89.5, 142.3, 165.1 (C(4), C(3), C(5) -isoxazole), 99.1, 143.1, 145.1 (C(4′), C(3′), C(5′)-pyrazole), 173.5 (C=O). ei-ms, *m/z* (%) = 298 (M^+, 25). *Anal*. Calcd for $C_{11}H_{11}ClN_4O_2S$ (298.75): C, 44.22; H, 3.71; N, 18.75; S, 10.73%. Found: C, 44.31; H, 3.59; N, 18.65; S, 10.81%.

2-[5-Chloro-1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-4-yl]-3-(5-methylisoxazol-3-yl)-1,3-thiazolidin-4-one (4b). Yellowish brown solid, yield 40%, 0.38 g, mp >300°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3100 (CH_{arom}), 1720 (CO). ^1H nmr (DMSO-d_6): δ_H 2.25 (3H, s, CH_3-pyrazol), 2.68 (3H, s, CH_3-isoxazole), 3.64 (2H, s, CH_2-thiazolidine), 5.28 (1H, s, H-thiazolidine), 6.61 (1H, s, H-isoxazole), 7.31–7.49 (2H, 2d, J_{HH} 7.4 Hz, ArH), 8.32 (1H, s, ArH). ^{13}C nmr (DMSO-d_6): δ_C 12.9 (Me-isoxazole), 13.3 (Me-pyrazol), 36.1 (CH_2- thiazolidine), 57.4(CH-thiazolidine), 86.9, 144.3, 165.4 (C(4), C(3), C(5)-isoxazole), 100.2, 144.2, 145.6 (C(4′), C(3′), C(5′)-pyrazole), 123.6, 124.8, 135.6, 136.2, 143.1, 145.8 (ArC), 174.2 (C=O). ei-ms, *m/z* (%) = 464 (M^+, 20). *Anal*. Calcd for $C_{17}H_{13}ClN_6O_6S$ (464.84): C, 43.93; H, 2.82; N, 18.08; S, 6.90%. Found: C, 44.02; H, 2.68; N, 18.01; S, 6.96%.

General procedure for synthesis of methylene-isoxazoles 6a–6d. A mixture of 5 mmol of compound **3a** (1.12 g) or **3b** (1.95 g) **a**nd different amines, namely piperazine, morpholine, or 2-aminothiazole (**5a–5c**) (5 mmol) in dry DMF (20 mL) was refluxed for 36 h. The reaction mixture followed by TLC. After complete the reaction, cool and poured onto ice/cold water. The formed precipitate was filtered, dried, and crystallized from ethanol to give **6a–6d**.

5-Methyl-N-[(3-methyl-5-piperazin-1-yl-1H-pyrazol-4-yl)methylene]isoxazol-3-amine (6a). Yellowish brown solid, yield 45%, 0.62 g, mp 187–189°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3440, 3376 (2NH), 1622 (N=CH). ^1H nmr (DMSO-d_6): δ_H 2.35 (3H, s, CH_3-pyrazol), 2.58 (3H, s, CH_3-isoxazole), 2.95–3.09 (8H, m, CH_2-piperazine), 6.31 (1H, s, H-isoxazole), 8.32 (1H, s, CH=N), 9.92, 9.99 (2H, 2s(br), 2NH, $D_2O_{exchangeable}$). ^{13}C nmr (DMSO-d_6): δ_C 12.9 (Me-isoxazole), 13.4 (Me-pyrazole), 44.2, 48.1(4C-piperazine), 90.2, 144.0, 166.2 (C(4), C(3), C(5)-isoxazole), 99.9, 145.1, 146.7 (C(4′), C(3′), C(5′)-pyrazole), 155.5 (HC=N). ei-ms, *m/z* (%) = 274 (M^+, 22). *Anal*. Calcd for $C_{13}H_{18}N_6O$ (274.32): C, 56.92; H, 6.61; N, 30.64%. Found: C, 56.99; H, 6.45; N, 30.54%.

N-((1-(2,4-dinitrophenyl)-3-methyl-5-(piperazin-1-yl)-1H-pyrazol-4-yl)methylene)-5-methylisoxazol-3-amine (6b). Pale brown solid, yield 47%, 1.03 g, mp >300°C (from acetic acid); ir (KBr, ν_{max}, cm^{-1}): 3200 (NH), 3100 (CH_{arom}), 1626 (N=CH). ^1H nmr (DMSO-d_6): δ_H 2.32 (3H, s, CH_3-pyrazole), 2.56 (3H, s, CH_3-isoxazole), 2.94–3.11 (8H, m, CH_2- piperazine), 6.30 (1H, s, H-isoxazole), 7.25,7.48 (2H, 2d, J_{HH} 7.8 Hz, ArH), 8.22 (1H, s, CH=N), 8.34 (1H, s, ArH), 9.90 (1H, s(br), NH, $D_2O_{exchangeable}$). ^{13}C nmr (DMSO-d_6): δ_C 12.5 (Me-isoxazole), 13.6 (Me-pyrazole), 43.6, 47.4(4C-piperazine), 89.7, 145.4, 165.9 (C(4), C(3), C(5)-isoxazole), 100.2, 148.3, 150.2 (C(4′), C (3′), C(5′)-pyrazole), 122.3, 124.7, 135.3, 139.1, 142.8, 144.2 (ArC), 151.7 (HC=N). ei-ms, *m/z* (%) = 441 ($M^+ + 1$, 36). *Anal*. Calcd for $C_{19}H_{20}N_8O_5$ (440.41): C, 51.82; H, 4.58; N, 25.44%. Found: C, 52.01; H, 4.37; N, 25.23%.

N-((1-(2,4-dinitrophenyl)-3-methyl-5-morpholino-1H-pyrazol-4-yl)methylene)-5-methylisoxazol-3-amine (6c). Beige color solid, yield 40%, 0.88 g, mp 119–121°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3100 (CH_{arom}), 1620 (N=CH). ^1H nmr (DMSO-d_6): δ_H 2.45 (3H, s, CH_3-pyrazole), 2.55 (3H, s, CH_3-isoxazole), 3.24–3.49 (8H, m, CH_2-morpholine), 6.25 (1H, s, H-isoxazole), 7.30, 7.53 (2H, 2d, J_{HH} 7.4 Hz, ArH), 8.20 (1H, s, CH=N), 8.32 (1H, s, ArH). ^{13}C nmr (DMSO-d_6): δ_C 12.8 (Me-isoxazole), 13.3 (Me-pyrazole), 49.3, 64.2(4C-morpholine), 92.1, 144.2, 166.3 (C(4), C(3), C (5)-isoxazole), 101.2, 147.0, 151.1 (C(4′), C(3′), C(5′)-pyrazole), 123.3, 124.6, 134.8, 136.2, 144.4, 145.6 (ArC), 153.8 (HC=N). ei-ms, *m/z* (%) = 441 (M^+, 20). *Anal*. Calcd for $C_{19}H_{19}N_7O_6$ (441.40): C, 51.70; H, 4.34; N, 22.21%. Found: C, 51.82; H, 4.27; N, 22.11%.

N-{[1-(2,4-dinitrophenyl)-3-methyl-5-(1,3-thiazol-2-ylamino)-1H-pyrazol-4- yl]methylene}-5-methylisoxazol-3-amine (6d). Yellowish brown solid, yield 45%, 1.02 g, mp >300°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3150 (NH), 3095 (CH_{arom}), 1625 (N=CH). ^1H nmr (DMSO-d_6): δ_H 2.51 (3H, s, CH_3-pyrazole), 2.56 (3H, s, CH_3-isoxazole), 6.58 (1H, s, H-isoxazole), 7.95–8.56 (6H, m, H-thiazole, CH=N and ArH), 9.31 (1H, s(br), NH, $D_2O_{exchangeable}$). ^{13}C nmr (DMSO-d_6): δ_C 13.0 (Me-isoxazole), 13.3 (Me-pyrazole), 91.2, 147.1, 166.7 (C(4), C(3), C(5)-isoxazole), 99.9, 147.8 150.1 (C(4′), C(3′), C(5′)-pyrazole), 115.2, 132.2, 158.4 (3C- thiazole), 122.6, 125.1, 132.6, 135.7, 145.2, 148.0 (ArC), 154.1 (HC=N). ei-ms, *m/z* (%) = 454 (M^+, 15). *Anal*. Calcd for $C_{18}H_{14}N_8O_5S$ (454.42): C, 47.58; H, 3.11; N, 24.66, S, 7.06%. Found: C, 47.65; H, 3.02; N, 24.58, S, 7.11%.

General procedure for the one-pot preparation of 9a–9c. A stirred mixture of 0.8 g 4-chlorobenzaldehyde (**8**, 5.6 mmol), 0.55 g 3-amino-5-methylisoxazole (**1**, 5.6 mmol), and trimethyl (**7a**), triethyl (**7b**), or triisopropylphosphite (**7c**) (6 mmol) in 10 mL THF containing 10% $FeCl_3$ was heated under reflux for 5–8 h. After completion of the reaction

(TLC), 10 mL AcOEt was added to the mixture. The organic phase was separated, washed with 20 mL distilled water, and dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum, and the residue was crystallized from the proper solvent to give compounds **9a–9c**.

Dimethyl (4-chlorophenyl)(5-methylisoxazol-3-ylamino) methylphosphonate (9a). White solid, yield 57%, 1.07 g, mp 115–117°C (from cyclohexane); ir (KBr, ν_{max}, cm^{-1}): 3340 (NH), 1226 (P=O, bonded), 1110 (P-O-C). ^1H nmr ($CDCl_3$): δ_H 2.21 (3H, s, CH_3), 3.44, 3.77 (6H, 2d, $^3J_{PH}$ 10.6 Hz, 2(H_3CO)P), 5.17 (1H, d, $^2J_{PH}$ 22.9 Hz, HCP), 5.54 (1H, s, H-isoxazole), 7.55 and 7.78 (4H, 2d, J_{HH} 8.6 Hz, ArH), 8.57(1H, br, NH). ^{13}C nmr ($CDCl_3$): δ_C 12.3 (Me-isoxazole), 52.4 (d, $^1J_{PC}$ 158.2 Hz, C-P), 53.8 (d, $^2J_{PC}$ 15.8 Hz, $(MeO)_2P$), 88.5, 155.2 (C(4), C(5)-isoxazole), 122.8, 128.8 (C(3′), C(5′), C(4′)-Ar), 129.2(d, $^3J_{PC}$ 10.6 Hz, C(2′), C(6′)-Ar), 134.7(d, $^2J_{PC}$ 11.2 Hz, C (1′)-Ar), 135.6 (d, $^3J_{PC}$ 8.6 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 23.80. MS, *m/z* (%) = 330 (M^+, 10). *Anal.* Calcd for $C_{13}H_{16}ClN_2O_4P$ (330.70): C, 47.21; H, 4.88; N, 8.47%. Found: C, 47.35; H, 4.72; N, 8.35%.

Diethyl (4-chlorophenyl)(5-methylisoxazol-3-ylamino) methylphosphonate (9b). White solid, yield 60%, 1.22 g, mp 148–150°C (from MeCN); ir (KBr, ν_{max}, cm^{-1}): 3350 (NH), 1225 (P=O, bonded), 1129 (P-O-C). ^1H nmr ($CDCl_3$): δ_H 1.12, 1.29 (6H, 2dt, J_{HH} 7.6, $^4J_{PH}$ 4.8 Hz, 2(H_3CCOP)), 2.26 (3H, s, CH_3), 3.75, 4.16 (4H, 2dq, J_{HH} 7.6, $^3J_{PH}$ 8.6 Hz, 2(H_2COP)), 5.20 (1H, d, $^2J_{PH}$ 22.9 Hz, HCP), 5.59 (1H, s, H-isoxazole), 7.28 and 7.53 (4H, 2d, J_{HH} 7.6 Hz, ArH), 8.54 (1H, br, NH). ^{13}C nmr ($CDCl_3$): δ_C 12.8 (Me-isoxazole), 16.3 (d, $^3J_{PC}$ 8.2 Hz, 2(CH_3COP)), 54.9 (d, $^1J_{PC}$ 169.4 Hz, C-P), 62.3 (d, $^2J_{PC}$ 8.9 Hz, 2(CH_2OP)), 85.1, 157.1 (C (4), C(5)-isoxazole), 124.1, 130.2 (C(3′), C(5′), C(4′)-Ar), 128.3 (d, $^3J_{PC}$ 9.8 Hz, C(2′), C(6′)-Ar), 133.9 (d, $^2J_{PC}$ 10.4 Hz, C(1′)-Ar), 136.1 (d, $^3J_{PC}$ 8.2 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 25.6. MS, *m/z* (%) = 358 (M^+, 10). *Anal.* Calcd for $C_{15}H_{20}ClN_2O_4P$ (358.76): C, 50.22; H, 5.62; N, 7.81%. Found: C, 50.35; H, 5.49; N, 7.96%.

Diisopropyl(4-chlorophenyl)(5-methylisoxazol-3-ylamino) methylphosphonate (9c). White solid, yield 55%, 1.21 g, mp 170–172°C (from $CHCl_3$); ir (KBr, ν_{max}, cm^{-1}): 3345 (NH), 1224 (P=O, bonded), 1110 (P-O-C). ^1H nmr ($CDCl_3$): δ_H 1.11, 1.33 (12H, 2dd, J_{HH} 7.2, $^4J_{PH}$ 5.8 Hz, 4(H_3CCOP)), 2.28 (3H, s, CH_3), 4.62, 4.81 (2H, 2 m, 2HCOP), 5.18 (1H, d, $^2J_{PH}$ 20.6 Hz, HCP), 5.56 (1H, s, H-isoxazole), 7.56 and 7.77 (4H, 2d, J_{HH} 8.6 Hz, ArH), 8.56 (1H, br, NH). ^{13}C nmr ($CDCl_3$): δ_C 13.2 (Me-isoxazole), 23.9 (d, $^3J_{PC}$ 8.4 Hz, CH_3COP), 57.4 (d, $^1J_{PC}$ 164.4 Hz, C-P), 77.6 (d, $^2J_{PC}$ 9.8 Hz, CHOP), 86.2, 156.3 (C(4), C(5)-isoxazole), 126.0, 129.3 (C(3′), C(5′), C(4′)-Ar), 128.9 (d, $^3J_{PC}$ 10.4 Hz, C(2′), C(6′)-Ar), 134.1 (d, $^2J_{PC}$ 11.6 Hz, C(1′)-Ar), 135.9 (d, $^3J_{PC}$ 8.8 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 27.4. MS, *m/z* (%) = 386 (M^+, 11). *Anal.* Calcd for $C_{17}H_{24}ClN_2O_4P$ (386.81): C, 52.79; H, 6.25; N, 7.24%. Found: C, 52.98; H, 6.04; N, 7.15%.

Products **9a–9c** were obtained in good yield, **9a** (76%, 0.9 g), **9b** (72%, 0.93 g), **9c** (75%, 1.05 g) when dimethyl (**11a**), diethyl (**11b**), or diisopropyl phosphite (**11c**) were heated with Schiff base **10** in the absence of solvent at 100°C for 2–4 h. After removing the volatile materials *in vacuo*, the residue was triturated with light petroleum and left to cool. The solid formed was collected and crystallized from a suitable solvent. Compounds **9a–9c** were verified by mps, mixed mps, and comparative ir spectra with the previous obtained ones.

Synthesis of 14a and 14b by reaction of the Schiff base 10 with hexaalkyltriamidophosphites 12a and 12b. No reaction occurred when equimolar amounts of **10** and phosphine **12a** or **12b** were heated under reflux in THF (or benzene) even after 3 days, after which compound **10** was recovered practically unchanged in 87% yield. A stirred solution of 0.8 g **10** (3.6 mmol) and 3.6 mmol phosphine **12a** or **12b** in 25 mL ethyl alcohol was boiled under reflux for 28–30 h (TLC). The volatile materials were evaporated under vacuum; the residue was collected, washed with light petroleum, and crystallized from the proper solvent to give compounds **14a** and **14b**.

P-{(4-chlorophenyl)[(5-methylisoxazol-3-yl)amino]methyl}-N,N,N′,N′-tetramethylphosphonic diamide (14a). Yellow solid, yield 63%, 0.81 g, mp 190–192°C (from CH_2Cl_2); ir (KBr, ν_{max}, cm^{-1}): 3320 (NH), 1229 (P=O, bonded), 1320, 860 (P-N-Me). ^1H nmr ($CDCl_3$): δ_H 2.39 (3H, s, CH_3), 2.42, 2.48 (12H, 2d, $^3J_{PH}$ 10.4 Hz, $(Me_2N)_2$–P), 5.48 (1H, d, $^2J_{PH}$ 20.6 Hz, HCP), 6.21 (1H, s, H-isoxazole), 6.51 (1H, br, NH), 7.39 and 7.53 (4H, 2d, J_{HH} 7.8 Hz, ArH). ^{13}C nmr ($CDCl_3$): δ_C 13.6 (Me-isoxazole), 43.8 (d, $^2J_{PC}$ 27.4 Hz, CH_3NP), 52.4 (d, $^1J_{PC}$ 170.2 Hz, C-P), 84.2, 158.6 (C(4), C(5)-isoxazole), 126.5, 132.5 (C(3′), C(5′), C(4′)-Ar), 131.1(d, $^3J_{PC}$ 8.8 Hz, C(2′), C(6′)-Ar), 134.0 (d, $^2J_{PC}$ 14.1 Hz, C(1′)-Ar), 134.8 (d, $^3J_{PC}$ 8.4 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 33.4. MS, *m/z* (%) = 356 (M^+, 10). *Anal.* Calcd for $C_{15}H_{22}ClN_4O_2P$ (356.79): C, 50.50; H, 6.22; N, 15.70%. Found: C, 50.66; H, 6.01; N, 15.56%.

P-{(4-chlorophenyl)[(5-methylisoxazol-3-yl)amino]methyl}-N,N,N′,N′-tetraethylphosphonic diamide (14b). Yellow solid, yield 61%, 0.9 g, mp 170–172°C (from $CHCl_3$); ir (KBr, ν_{max}, cm^{-1}): 3335 (NH), 1230 (P=O, bonded), 1323, 865 (P-N-Et). ^1H nmr ($CDCl_3$): δ_H 1.09, 1.15 (6H, 2dt, J_{HH} 6.6, $^4J_{PH}$ 4.8 Hz, H_3CCNP), 2.41 (3H, s, CH_3), 2.89–3.00 (8H, m, $(CH_2N)_2$-P), 5.36 (1H, d, $^2J_{PH}$ 22.2 Hz, HCP), 6.29 (1H, s, H-isoxazole), 6.59 (1H, br, NH), 7.36 and 7.62 (4H, 2d, J_{HH} 7.6 Hz, ArH). ^{13}C nmr ($CDCl_3$): δ_C 11.8 (Me-isoxazole), 14.2 (MeCN), 38.8 (d, $^2J_{PC}$ 24.2 Hz, CH_2NP), 54.1 (d, $^1J_{PC}$ 164.8 Hz, C-P), 83.7, 159.4 (C(4), C(5)-isoxazole), 127.1, 132.8 (C(3′), C(5′), C(4′)-Ar), 132.7(d, $^3J_{PC}$ 9.2 Hz, C(2′), C(6′)-Ar),

133.2 (d, $^2J_{PC}$ 12.8 Hz, C(1′)-Ar), 134.7 (d, $^3J_{PC}$ 8.7 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 34.6. MS, *m/z* (%) = 412 (M^+, 9). *Anal.* Calcd for $C_{19}H_{30}ClN_4O_2P$ (412.89): C, 55.27; H, 7.32; N, 13.57%. Found: C, 55.39; H, 7.20; N, 13.45%.

General procedure for the synthesis of 15a–15c. A mixture of 0.8 g 5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde (**2a**, 5.53 mmol), 0.54 g 3-amino-5-methylisoxazole (**1**, 5.53 mmol), and trimethyl (**7a**), triethyl (**7b**), or triisopropyl phosphite (**7c**) (6 mmol) in 15 mL THF containing 10% $FeCl_3$ (or 2 mL glacial acetic acid) was heated under reflux for 6–8 h (TLC). The product mixture was extracted with 50 mL AcOEt, washed with 20 mL distilled water, and dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum, and the residue was crystallized from the proper solvent to give the corresponding phosphonates **15a–15c**.

Dimethyl{(5-chloro-3-methyl-1H-pyrazol-4-yl)[(5-methyl isoxazol-3-yl)amino]methyl}phosphonate (15a). Yellow solid, yield 55%, 1.02 g, mp 190–192°C (from EtOH); ir (KBr, ν_{max}, cm^{-1}): 3340, 3335 (2NH), 1226 (P=O, bonded), 1050 (P-O-C). ^{1}H nmr ($CDCl_3$): δ_H 2.19 (3H, s, CH_3-pyrazole), 2.49 (3H, s, CH_3-isoxazole), 3.60, 3.65 (6H, 2d, $^3J_{PH}$ 12 Hz, 2(H_3CO)P), 5.62 (1H, d, $^2J_{PH}$ 20.2 Hz, HCP), 5.82 (1H, s, H-isoxazole), 6.96, 7.81 (2H, 2br, 2NH). ^{13}C nmr ($CDCl_3$): δ_C 12.3 (Me-isoxazole), 13.2 (Me-pyrazole), 51.8 (d, $^1J_{PC}$ 160.6 Hz, C-P), 53.8 (d, $^2J_{PC}$ 18.2 Hz, $(MeO)_2$P), 84.2, 158.8 (C(4), C(5)-isoxazole), 110.8 (d, $^2J_{PC}$ 12.2 Hz, C(4′)-pyrazole), 126.5 (d, $^3J_{PC}$ 8.6 Hz, C(3′)-pyrazole), 130.7 (d, $^3J_{PC}$ 8.2 Hz, C (5′)-pyrazole), 134.1 (d, $^3J_{PC}$ 8.4 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 29.3. MS, *m/z* (%) = 334 (M^+, 13). *Anal.* Calcd for $C_{11}H_{16}ClN_4O_4P$ (334.70): C, 39.47; H, 4.82; N, 16.74%. Found: C, 39.52; H, 4.71; N, 16.61%.

Diethyl{(5-chloro-3-methyl-1H-pyrazol-4-yl)[(5-methyl isoxazol-3-yl)amino]methyl}phosphonate (15b). Straw yellow solid, yield 53%, 1.06 g, mp 224–226°C (from MeCN); ir (KBr, ν_{max}, cm^{-1}): 3346, 3338 (2NH), 1228 (P=O, bonded), 1066 (P-O-C). ^{1}H nmr ($CDCl_3$): δ_H 1.17, 1.67 (6H, 2dt, J_{HH} 7.2, $^4J_{PH}$ 4.6 Hz, 2H_3CCOP), 2.18 (3H, s, CH_3-pyrazole), 2.51 (3H, s, CH_3-isoxazole), 3.89, 4.03 (4H, 2m, 2H_2COP), 5.57 (1H, d, $^2J_{PH}$ 18.6 Hz, HCP), 5.65 (1H, s, H-isoxazole), 6.97, 7.79 (2H, 2br, 2NH). ^{13}C nmr ($CDCl_3$): δ_C 12.5 (Me-isoxazole), 13.6 (Me-pyrazole), 16.9 (d, $^3J_{PC}$ 6.6 Hz, CH_3COP), 52.2 (d, $^1J_{PC}$ 168.2 Hz, C-P), 64.4 (d, $^2J_{PC}$ 8.8 Hz, CH_2OP), 84.8, 158.1 (C(4), C(5)-isoxazole), 111.9 (d, $^2J_{PC}$ 10.8 Hz, C (4′)-pyrazole), 128.1 (d, $^3J_{PC}$ 8.8 Hz, C(3′)-pyrazole), 128.9 (d, $^3J_{PC}$ 8.5 Hz, C(5′)-pyrazole), 132.9 (d, $^3J_{PC}$ 8.6 Hz, C(3)-isoxazole).^{31}P nmr ($CDCl_3$): δ_P 24.5. MS, *m/z* (%) = 362 (M^+, 12). *Anal.* Calcd for $C_{13}H_{20}ClN_4O_4P$ (362.75): C, 43.04; H, 5.56; N, 15.45%. Found: C, 43.18; H, 5.42; N, 15.31%.

Diisopropyl{(5-chloro-3-methyl-1H-pyrazol-4-yl)[(5-methyl isoxazol-3-yl)amino]methyl}phosphonate (15c). Yellow solid, yield 50%, 1.08 g, mp 230–232°C (from acetone); ir (KBr, ν_{max}, cm^{-1}): 3360, 3300 (2NH), 1224 (P=O, bonded), 1022 (P-O-C). ^{1}H nmr ($CDCl_3$): δ_H 1.09, 1.19 (12H, 2dd, J_{HH} 6.9, $^4J_{PH}$ 6.4 Hz, 4H_3CCOP), 2.16 (3H, s, CH_3-pyrazole), 2.49 (3H, s, CH_3-isoxazole), 4.58–4.85 (2H, m, $^3J_{PH}$ 10.8 Hz, 2HCOP), 5.52 (1H, d, $^2J_{PH}$ 20.2 Hz, HCP), 6.01 (1H, s, H-isoxazole), 6.91, 7.72 (2H, 2br, 2NH). ^{13}C nmr ($CDCl_3$): δ_C 12.1 (Me-isoxazole), 13.2 (Me-pyrazole), 26.1 (d, $^3J_{PC}$ 10.2 Hz, CH_3COP), 56.8 (d, $^1J_{PC}$ 170.1 Hz, C-P), 78.1 (d, $^2J_{PC}$ 12.4 Hz, CHOP), 83.7, 158.9 (C(4), C(5)-isoxazole), 109.8 (d, $^2J_{PC}$ 11.2 Hz, C(4′)-pyrazole), 126.7 (d, $^3J_{PC}$ 8.2 Hz, C(3′)-pyrazole), 130.3 (d, $^3J_{PC}$ 8.4 Hz, C(5′)-pyrazole), 134.2 (d, $^3J_{PC}$ 8.2 Hz, C(3)-isoxazole). ^{31}P nmr ($CDCl_3$): δ_P 28.8. MS, *m/z* (%) = 390 (M^+, 12). *Anal.* Calcd for $C_{15}H_{24}ClN_4O_4P$ (390.80): C, 46.10; H, 6.19; N, 14.34%. Found: C, 46.22; H, 6.02; N, 14.21%.

Phosphonates **15a–15c** were obtained in higher yield, **15a** (73%, 0.87 g), **15b** (75%, 0.97 g), **15c** (70%, 0.97 g) and characterized by mps, mixed mps, and comparative ir spectra with the previous obtained ones. That was taken place by heating Schiff base **3a** with dimethyl (**11a**), diethyl (**11b**), or diisopropyl phosphite (**11c**) in the absence of solvent at 100°C for 4–6 h (TLC). After the usual working up, the residue was collected and crystallized from a proper solvent.

Reaction of 3a with hexaalkyltriamidophosphites 12a and 12b. General procedure: A mixture of **3a** (0.8 g, 3.56 mmol) and hexamethyl (**12a**) or hexaethyl triamidophosphite (**12b**) (4 mmol) in dry THF (50ml) was refluxed for 4–6 h (TLC). The solid formed was collected, and then crystallized from suitable solvent to give **17a** or **17b**.

N-((5-(dimethylamino)-3-methyl-1H-pyrazol-4-yl)methylene)-5-methylisoxazol-3-amine (17a). Pale yellow powder, yield 74%, 0.61 g, mp 185–187°C (from cyclohexane); ir (KBr, ν_{max}, cm^{-1}): 3400 (NH), 2942 ($N(CH_3)_2$), 1640 (N=CH). ^{1}H nmr ($CDCl_3$): δ_H 2.12 (3H, s, CH_3-pyrazole), 2.34 (3H, s, CH_3-isoxazole), 3.09 (6H, s, Me_2N), 6.11 (1H, s, H-isoxazole), 8.55 (1H, s, CH=N), 9.02 (1H, br, NH). ^{13}C nmr ($CDCl_3$): δ_C 12.3 (Me-isoxazole), 13.6 (Me-pyrazole), 41.7 (2MeN), 96.2, 131.9, 158.4 (C(4), C(3), C(5)-isoxazole), 108.5, 126.2, 135.6 [C(4′), C(3′), C(5′)-pyrazole), 154.8 (C=N). MS, *m/z* (%) = 233 (M^+, 45). *Anal.* Calcd for $C_{11}H_{15}N_5O$ (233.27): C, 56.64; H, 6.48; N, 30.02%. Found: C, 56.78; H, 6.32; N, 29.03%.

N-((5-(diethylamino)-3-methyl-1H-pyrazol-4-yl)methylene)-5-methylisoxazol-3-amine (17b). Pale yellow powder, yield 71%, 0.66 g, mp 198–200°C (from *n*-hexane); ir (KBr, ν_{max}, cm^{-1}): 3425 (NH), 2930 ($N(C_2H_5)_2$), 1635 (N=CH). ^{1}H nmr ($CDCl_3$): δ_H 0.09, 1.05 (6H, 2t, J_{HH} 6.8, H_3CCN), 2.11 (3H, s, CH_3-pyrazole), 2.31 (3H, s, CH_3-isoxazole), 2.79, 2.98 (4H, 2q, J_{HH} 6.8, CH_2N), 6.15

(1H, s, H-isoxazole), 8.59 (1H, s, CH=N), 8.99 (1H, br, NH). ^{13}C nmr ($CDCl_3$): δ_C 12.1 (2Me-CN), 13.2 (Me-isoxazole), 13.9 (Me-pyrazole), 46.6 ($2CH_2$-N), 98.0, 129.8, 159.1 (C(4), C(3), C(5)-isoxazole), 111.3, 124.6, 130.9 (C(4′), C(3′), C(5′)-pyrazole), 156.2 (C=N). MS, *m/z* (%) = 261 (M^+, 42). *Anal.* Calcd for $C_{13}H_{19}N_5O$ (261.32): C, 59.75; H, 7.33; N, 26.80 %. Found: C, 59.62; H, 7.21; N, 26.69 %.

REFERENCES AND NOTES

[1] Shin, K. D.; Lee, M. Y.; Shin, D. S.; Lee, S.; Son, K. H.; Koh, S.; Paik, Y. K.; Kwon, B. M.; Han, D. C. J Biol Chem 2005, 280, 41439.

[2] Simoni, D.; Roberti, M.; Paolo, I. F.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Alessandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. J Med Chem 2001, 44, 2308.

[3] Liu, X. H.; Cui, P.; Song, B. A.; Bhadury, P. S.; Zhu, H.,. L.; Wang, S. F. Bioorg Med Chem 2008, 16, 4075.

[4] Velaparthi, S.; Brunsteiner, M.; Uddin, R.; Wan, B.; Franzblau, S. G.; Petukhov, P. A. J Med Chem 2008, 51, 1999.

[5] Magedov, I. V.; Manpadi, M.; Van Slambrouck, S.; Steelant, W. F. A.; Rozhkova, E.; Przhevalískii, N. M.; Rogelj, S.; Kornienko, A. J Med Chem 2007, 50, 5183.

[6] Chou, L. C.; Huang, L. J.; Yang, J. S.; Lee, F. Y.; Teng, C. M.; Kuo, S. C. Bioorg Med Chem 2007, 15, 1732.

[7] Manetti, F.; Brullo, C.; Magnani, M.; Mosci, F.; Chelli, B.; Crespan, E.; Schenone, S.; Naldini, A.; Bruno, O.; Trincavelli, M. L.; Maga, G.; Carraro, F.; Martini, C.; Bondavalli, F.; Botta, M. J Med Chem. 2008, 51, 1252.

[8] Xia, Y.; Dong, Z. W.; Zhao, B. X.; Ge, X.; Meng, N.; Shin, D. S.; Miao, J. Y. Bioorg Med Chem 2007, 15, 6893.

[9] Xia, Y.; Fan, C. D.; Zhao, B. X.; Zhao, J.; Shin, D. S.; Miao, J. Y. Eur J Med Chem 2008, 43, 2347.

[10] Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Brullo, C.; Fossa, P.; Mosti, L.; Menozzi, G.; Carraro, F.; Naldini, A.; Bernini, C.; Manetti, F.; Botta, M. Bioorg Med Chem Lett 2004, 14, 2511.

[11] Daidone, G.; Raffa, D.; Maggio, B.; Valeria, R. M.; Plescia, F.; Schillaci, D. Eur J Med Chem 2004, 39, 219.

[12] Warshakoon, N. C.; Wu, S.; Boyer, A.; Kawamoto, R.; Renock, S.; Xu, K.; Pokross, M.; Evdokimov, A. G.; Zhou, S.; Winter, C.; Walter, R.; Mekel, M. Bioorg Med Chem Lett 2006, 16, 5687.

[13] Zhu, G. D.; Gong, J.; Gandhi, V. B.; Woods, K.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Stoll, V. S.; Mamo, M.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. Bioorg Med Chem 2007, 15, 2441.

[14] Quin, L. D. A guide to organophosphorus chemistry. Wiley-Interscience: New York, 2000.

[15] Westheimer, F. H., *et al.* Science 1987, 235, 1173.

[16] Kafarski, P.; Lejczak, B. Curr Med Chem Anticancer Agents 2001, 1, 301.

[17] Bloemink, M. J.; Diederen, J. J. H.; Dorenbos, J. P. Heetebrij, R. J.; Keppler, B. K. Eur J inorg chem 1999, 1999, 1655.

[18] Rao, X.; Song, Z.; He, L. Heteroatom Chem 2008, 19, 512.

[19] Makhaeva, G. F.; Malygin, V. V.; Aksinenko, A. Y.; Sokolov, V. B.; Strakhova, N. N.; Rasdolsky, A. N.; Richardson, R. J.; Martynov, I. V. Dokl Biochem Biophys 2005, 400, 92.

[20] Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. J Chem Soc Perkin Trans 1984, 1, 2845.

[21] Abdou, W. M.; Salem, M. A. I.; Barghash, R. F. Arkivoc 2007, 15, 45.

[22] Abdou, W. M.; Sediek, A. A.; Khidre, M. D. Monatsh Chem 2008, 139, 617.

[23] Abdou, W. M.; Shaddy, A. A. Lett Org Chem 2008, 5, 569.

[24] Abdou, W. M.; Khidre, M. D.; Khidre, R. E. Eur J Med Chem 2009, 44, 526.

[25] Abdou, W. M.; Shaddy, A. A.; Sediek, A. A. J Chem Res 2009, 8.

[26] Xiao, H. Q. Ouyang, G. P. Sun, X. D. Yao, X. D. Bao, G. Q. Qi, C. Z. Chin J Synth Chem 2005, 13, 600.

[27] Eliel, E. L.; Wilen, S. H. Stereochemistry of Organic Compounds; John Wiley and Sons Inc.: New York, 1994, p 486.

[28] Matveeva, E. D.; Zefirov, N. S. Dokl Chem 2008, 420, 137.

[29] Kaboudin, B. Phosphorus Sulfur Silicon Relat Elem 2002, 177, 1749.

[30] Abdou, W. M.; Barghash, R. F.; Bekheit, M. S. Monatsh Chem 2011, 142, 649.

[31] aArutgunam, A.; Gunar, V. I.; Zav'yalov, S. I. Izv Akad Nauk, SSSR Serkhim 1969, 12, 2857; Chem Abstr 1970, 72, 78979.

[32] Hudson, R. F. Structure and Mechanism in Organophosphorus Chemistry; Academic Press: London, 1965, pp 204–249.

[33] Rajanarendar, E.; Afzal, M. d.; Ramu, K. Indian J Chem Sect B 2003, 42, 927.