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NOVEL METHOD OF SYNTHESIS OF TRIAZOLYLAMIDINE AND IT'S CHARACTERIZATION WITH NMR AND XRAY DIFFRACTION. SYNTHESIS OF NOVEL 1,2,4-TRIAZOLO-1,3,5,2-TRIAZAPHOSPHORINE-2-OXIDE DERIVATIVES BY THE REACTION BETWEEN AMIDINE WITH OXIDE OF TRICHLOROPHOSPHINE OR HEXAMETHYLPHOSPHORAMIDE

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ABSTRACT
A serie of novel *N*,*N'*-disubstituted amidines derivatives were obtained in one step reaction of their corresponding imidates with primary alkyl or aryl amines in microwave and one of them was characterized by X ray diffraction.Then we have studied their reactivity with HMPA and $POCl_3$ in order to obtain new 1,3,5,2-triazaphosphorine-2-oxide. All of synthesized components were characterized by IR, ^{1}H NMR, ^{13}C NMR,^{31}P, elemental analysis and MS spectroscopy of some products.

KEYS WORDS: N-3-triazolyl amidine, Hexamethyl phosphoramide, phosphorylchloride, 1,2,4-triazolo-1,3,5,2-triazaphosphorine-2-oxide, NMR spectroscopy, X-ray crystallography.

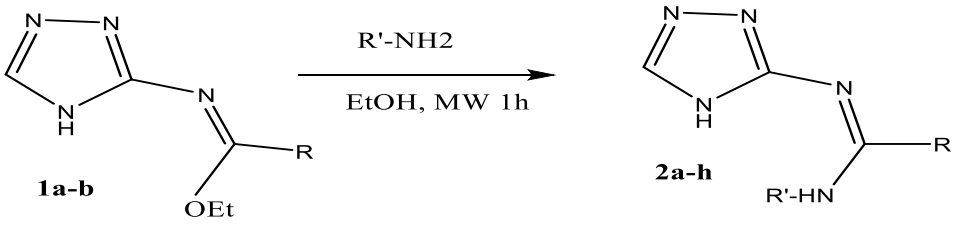
1. INTRODUCTION
Compounds containing 1,2,4-triazole nucleus exhibit antimicrobial[I], antiproliferative[II], antibacterial[III], and antitubercular[IV] properties. In agricultural field, it are recognized as potential antifungal [V] and herbicidal[VI]agents. In addition, the synthesis of amidines has received more attention due to the revelation of their biological properties. In fact, amidines derivatives exhibiting anti-HIV [VII,anti-inflammatory [VII,VIII], anticancer [IX], anti-resorptive[X], and anti-tumor [XI] activities have been reported in literature. Furthermore amidines are known to be useful synthetic building blocks especially in heterocyclic chemistry[XII]. Recent studies have demonstrated their capacity to fix carbon dioxide [XIII].The ethyl N-(1*H*-1,2,4-triazol-3-yl)-imidates derivatives have been synthesized[XIV]. In the present work, we focus our interest on the reactivity of these imidates with the primary amines in order to access to a novel series of *N*,*N'*-disubstitutedamidines and we characterized one of them by X ray diffraction. Our interest to triazaphosphorine is for their applications in many domains. They have anticancer activity and antitumor activity. [XV]. We study then the

reactivity of amidine with HMPA and POCl3 in order to synthesis new 1,3,5,2-triazaphosphorine-2-oxide that have not been studied before.

2.RESULTS AND DISCUSSION

2.1.**Synthesis of compound 2**

The new derivatives were prepared following the reaction sequences depicted in scheme 1. Imidates derivatives**1a,b** were obtained by the condensation of 3-amino-1,2,4-triazole with the appropriated orthoester in the presence of catalytic amount of glacial acetic acid and under reflux conditions as reported in literature [XIV-XV].The synthesized imidates derivatives were isolated in good yields 65-75%. The structures of iminoestersobtained were confirmed with IR, ^{1}H NMR, ^{13}C NMR.



Scheme 1: Synthesis method of amidines

The IR spectra of compounds **1a,b** shows the presence of an intense absorption band at 1670 cm^{-1}approximately. This characteristic absorption band was due to the functional group(>C=N-) formed. The broad absorption band observed in the IR spectra at 3100 cm^{-1}was attributed to NH group of the triazole ring.

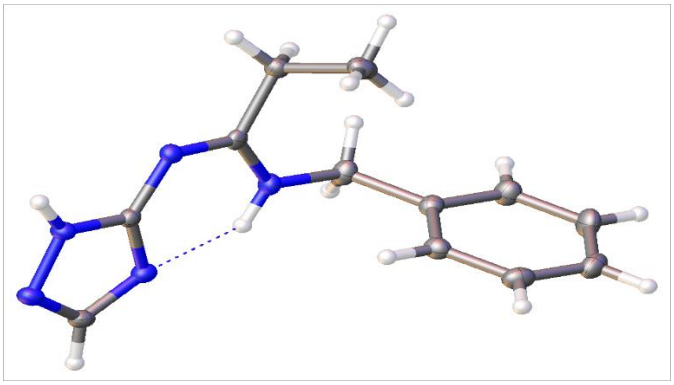
^{1}H NMR spectral data have confirmed the obtaining of desired chemical structures of compounds **1a,b**. In fact, the appearance of a triplet and quadruplet at *δ:* 4.18 and 1.25 ppm respectively confirmed the presence of ethoxy group in the obtained structures.

In second part of our study, we have synthesized a new series of *N,N'*-disubstitutedamidines2a-2h, obtained by the reaction of their corresponding iminoesters with a primary amines under mild conditions. The reaction was carried out in anhydrous ethanol in microwave for 1hour and the desired *N,N'*-disubstitutedamidinesderivatives were isolated in reasonable to good yields 55-86%.

In order to extend the scope of this method, we have used a wide variety of primary alkyl and aryl amines such as (O-toluidine, benzylamine, cyclopentylamine and propylamine) with iminoesters**1a,b** synthesized previously.

X-ray diffraction measurements were recorded at 293 temperature on EnrafNonius Mach III X-ray diffractometer using Ag K_{α}, radiation (λ = 0.5608A˚). Crystal data and experimental parameters used for intensity data collection of **1**; procedures and results of the structure determination were given in Table 1

The data collection parameters and crystallographic information for the crystal are summarized in Table 1.



Scheme 2: Ortep of compound 2e

Identification code	jml1524
Empirical formula	$C_{12}H_{15}N_5$
Formula weight	229.29
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	I2/c
a/Å	18.6412(8)
b/Å	5.8601(2)
c/Å	22.9827(8)
α/°	90.00
β/°	113.362(5)
γ/°	90.00
Volume/Å^3	2304.79(16)
Z	8
ρ_{calc}g/cm^3	1.322
μ/mm^{-1}	0.678
F(000)	976.0
Crystal size/mm^3	0.235 × 0.139 × 0.056
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.38 to 141.56
Index ranges	$-17 \leq h \leq 22$, $-7 \leq k \leq 6$, $-25 \leq l \leq 28$
Reflectionscollected	4066
Independent reflections	2168 [R_{int} = 0.0181, R_{sigma} = 0.0246]
Data/restraints/parameters	2168/0/163
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0392, wR_2 = 0.0982
Final R indexes [all data]	R_1 = 0.0444, wR_2 = 0.1037

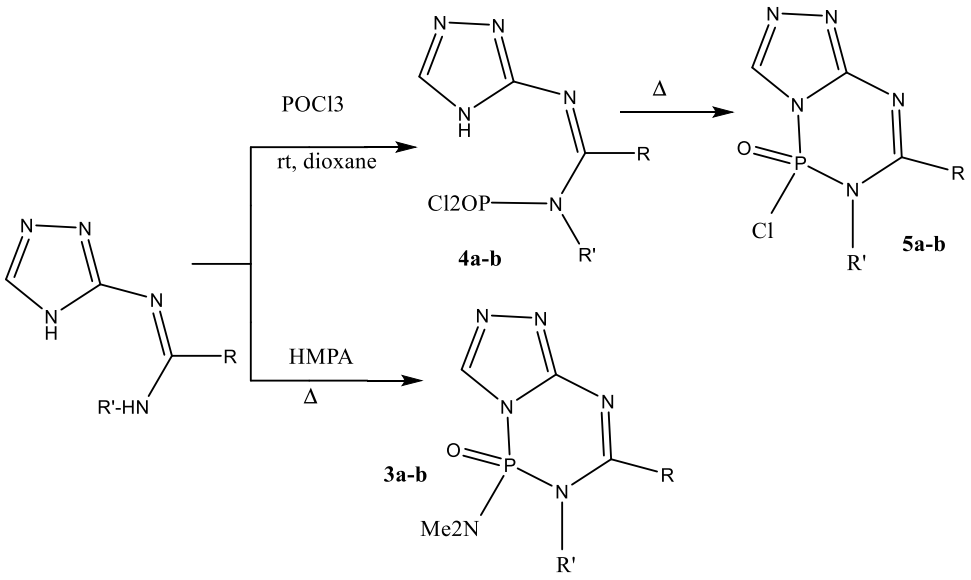
Table 1: Crystal data and structure refinement for jml1524.

3.2.Synthesis of of triazaphosphorine -2-oxide derivatives.

N-2-Triazol-3-yl amidines were synthesized by condensation of 3-amino-1,2,4-triazolyl iminoester with amine in microwave; the corresponding amidines were reacted with HMPA in

anhydrous toluene and $POCl_3$ in anhydrous dioxane, in order to obtain triazaphosphorine -2-oxide derivatives 3a-b and N-phosphoroamidotriazolylamidine4a-b respectively and when we heated compound 4, we have obtained trizaphosphorine5a-b.All phosphorus compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR and^{31}P and MS.

The reaction of amidines with an equimolecular amount of hexamethylphosphoramide (HMPA) in anhydrous toluene under reflux for 24 h afforded [1,2,4]triazolo-1,3,5,2-triazaphosphorin-2-oxide. The IR spectra of 3, exhibited absorption bands at 1285 (PO) and 1618 cm^{-1}, (C=N). The ^{1} H NMR spectrum of 3 displayed two multiplets in the region δ 2.6-2.7 ppm due to NMe_2 protons and the disappearance of an amino group in molecules 3a–3b that confirmed the formation of triazaphosphorin-2-oxide. The ^{13}C NMR spectra display the characteristic signals of all carbons.The ^{31} P NMR show one signal at □□ 25 ppm.



Scheme3:Synthesis of 3, 4,5

IR confirmed the formation of compounds **4**. The IR spectra of compound **4** showed the band of NH at the region of 3286 an the appearance of P=O at 1264cm^{-1}. The ^{1}H NMR and^{13} C NMR confirmed the formation of 4. The ^{31} P NMR spectrum shows one signal around □□ -17.7 ppm.

The reaction of amidine 2b or 2d with an equimolar amount of $POCl_3$ in anhydrous dioxaneat room temperature afforded N-phosphorotriazolylamidine 4a–4b, the heating of the intermediate 4, under reflux for 24 h gave the triazaphosphorine-2-chloride-2-oxide 5. The IR spectra of 4, showed absorption bands in the regions 1628–1622 (C=N) and 3450–3440 cm^{-1} (N–H). While the IR spectra of compound 5 show the de disappearance of NH band and appearance of vibration band at 1615 cm^{-1}(C=N). The ^{1} H NMR spectrum of 4 displayed a broadened singlet around δ : 9.83 ppm due to NH. However the ^{1}H NMR, ^{13}C and ^{31} P confirmed the formation of compound 5.(Scheme 3)

3. EXPERIMENTAL

All melting points were determined on a Kofler-type and are uncorrected. IR spectra were recorded on a Perkin-Elmer Fourier transform FT–IR spectrophotometer (4000–400 cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature (rt) in $CDCl_3$ or dimethylsulfoxide (DMSO-d6) at 300, 400, and at 75, 100, or 125 MHz, respectively, using solvent peaks [$CDCl_3$: 7.27 (D), 77.2 (C) ppm and DMSO-d_6 2.50 (D) and 39.7 (C) ppm] as internal reference. The assignment of chemical shifts is based on standard NMR experiments

(1H, 13C) using tetramethylsilane (TMS) as the internal standard.Multiplicities were represented by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).Elemental analyses (C, H, and N) were carried out on an Interscience Flash EA 1112 series (Thermo Finnigan, San Jose, CA, USA) elemental analyzer at the Spectropole, Faculte of Sciences, saint Jerome cite. High-resolution mass spectra (HRMS) were carried out with JEOL Gcmate spectrometer.

3.1. General procedure for formation of 2.

To 0.1 mol of iminoester(compounds 1 were synthesized according to the method cited in the article [15]) we added 0.1 mole of primary amine dissolved in few ethanol. The reaction was maintained in microwave for 1 hour.The disubstituted amidines derivatives were isolated in reasonable to good yields 65-86%.

***N*-(*o*-tolyl)-*N'*-(1*H*-1,2,4-triazol-3-yl)acetimidamide 2a**

White solid;Yield: 59%. M.p = 204°C; ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.91 (br s, 1H, NH_{ar}), 11.73 (s, 1H, NH), 7.32-7.17(m, 4H, H-Ar), 2.34 (s, 3H, H-1), 2.26 (s, 3H, H-11).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 162.0, 158.1, 148.5, 136.8, 134.7 , 131.1, 127.7, 127.4, 126.9, 21.0, 18.2 .HRMS: Calcd. for$C_{11}H_{13}N_5$: 215.1171, Found: 215.1170; I.R. ῡ (cm^{-1}):3261, 3170 (NH) and 1625 (>C=N-).

***N*-benzyl-*N'*-(1*H*-1,2,4-triazol-3-yl)acetimidamide 2b**

White solid; Yield:55%*;* M.p = 212°C*;* ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.34 (br s, 1H, NH_{ar}), 10.53 (s, 1H, NH), 7.73 (s, 1H, H-4), 7.40-7.29 (m, 5H, H-Ar), 4.60 (d, 2H, *J*= 6.2 Hz, H-5), 2.35 (s, 3H, H-1).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 163.0, 158.3,148.5, 137.5, 129.1, 127.8, 126.8, 47.6, 20.6; HRMS: Calcd. for$C_{11}H_{13}N_5$: 215.1171, Found: 215.1171.*;* I.R. ῡ (cm^{-1}):3272, 3172(NH) and 1626 (>C=N-).

***N*-cyclopentyl-*N'*-(1*H*-1,2,4-triazol-3-yl)acetimidamide 2g**

Brown solid; Yield: 60%; M.p = 128°C; ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.94 (br s, 1H, NH_{ar}), 10.15 (d, 1H, *J* = 7.5 Hz, NH), 7.72 (s, 1H), 4.01-3.93 (m, 1H), 2.37 (s, 3H), 2.07-2.01 (m, 2H), 1.88-1.77 (m, 2H), 1.71-1.58 (m, 4H).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 161.8, 158.4, 148.4 (C-7), 55.4, 34.2, 23.8, 20.7. HRMS: Calcd. for$C_9H_{15}N_5$: 193.1327, Found: 193.1327.I.R. ῡ (cm^{-1}):3260, 3179 (NH) and 1619 (>C=N-).

***N*-(*o*-tolyl)-*N'*-(1*H*-1,2,4-triazol-3-yl)propionimidamide 2d**

White solid ; Yield : 88; M.p = 184°C; ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.52 (br s, 1H, NH_{ar}), 11.71 (s, 1H, NH), 7.31-7.21 (m, 4H, H-Ar), 2.54 (q, 3H, *J* = 7.5 Hz,), 2.23 (s, 3H,), 1.24 (t, 3H, *J* = 7.6 Hz,).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 166.82, 158.5 ,148.5,136.8, 134.9, 131.1, 127.7, 127.6, 126.9, 26.8, 18.3, 12.3 .HRMS: Calcd. for$C_{12}H_{15}N_5$: 229.1327, Found: 229.1327.I.R. ῡ (cm^{-1}):3154(NH) and 1696 (>C=N-).

***N*-benzyl-*N'*-(1*H*-1,2,4-triazol-3-ylpropionimidamide 2e**

White solid; Yield:86%; M.p = 152°C**;** ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.72 (br s, 1H, NH_{ar}), 10.56 (t, 1H, *J* = 5.8 Hz, NH), 7.74 (s, 1H), 7.41-7.29 (m, 5H, H-Ar), 4.62 (d, 2H, *J*= 6.2), 2.65 (q, 2H, *J* = 7.7 Hz), 1.34 (t, 3H, *J* = 7.6 Hz).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 167.3, 158.5,148.5, 137.7 , 129.0, 127.8, 126.8, 47.1 , 26.8, 12.2 .HRMS: Calcd. For$C_{12}H_{15}N_5$: 229.1327, Found: 229.1328.I.R. ῡ (cm^{-1}):3278, 3180(NH) and 1624 (>C=N-).

***N*-cyclopentyl-*N'*-(1*H*-1,2,4-triazol-3-yl)propionimidamide 2f**

White solid; Yield: 55%.; M.p = 156°C. ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.92 (br s, 1H, NH_{ar}); 10.17 (d, 1H, *J* = 8.2 Hz, NH), 7.71 (s, 1H), 3.99 (m, 1H), 2.63 (q, 2H, *J* = 7.6 Hz), 2.06-1.99 (m, 2H), 1.83-1.80 (m, 2H), 1.66-1.59 (m, 4H), 1.35 (t, 3H, *J* = 7.67 Hz).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 166.3, 158.7, 148.3, 55.0, 34.4, 26.9, 23.7, 12.5.HRMS: Calcd. for$C_{10}H_{17}N_5$: 207.1484, Found: 207.1482.I.R. ῡ (cm^{-1}): 3256, 3170 (NH) and 1626 (>C=N-).

***N*-propyl-*N'*-(1*H*-1,2,4-triazol-3-yl)propionimidamide 2g**

Pale solid; Yield: 80%.;M.p = 88°C; ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm) 14.74 (br s, 1H, NH_{ar}), 10.07 (s, 1H, NH), 7.74 (s, 1H,), 3.34 (dd, 2H, *J* = 12.9 Hz, *J* = 6.9 Hz), 2.62 (q, 2H, *J* = 7.6 Hz,), 1.75-1.66 (m, 2H), 1.35 (t, 3H,*J* = 7.6 Hz,), 1.04 (t, 3H, *J* = 7.4 Hz).^{13}C NMR ($CDCl_3$, 100.6 MHz):δ (ppm) 167.0, 158.7, 148.3, 45.26, 26.8, 23.7, 12.2 , 11.5 .HRMS: Calcd. for$C_8H_{15}N_5$: 181.1327, Found: 181.0796.**;** I.R.ῡ (cm^{-1}): 3271, 3178 (NH) and 1614 (>C=N-).

***N*-pentyl-*N'*-(1*H*-1,2,4-triazol-3-yl)propionimidamide 2h**

White solid; Yield =60%,^{1}H NMR ($CDCl_3$+DMSO-d_6,(δ ppm)):0. 82(t, 3H), 2.1(q, 2H), 7.20 (s,1H) 9.43(s,1H), 6.30 (s,1H), 2.8 (m, 2H), 1.20 (m,2H), 1.32(m,2H), 1.30(m, 2H), 0.60(t,3H).^{13}C NMR: 10.59; 10.20; 10.25; 10.31; 25.32; 43.80; 22.50; 165.20; 156.80; 147.40;

3.2.General procedure for preparation of compound 3

We dissolved amidine 2a or 2h (0.1 mmol) in anhydrous toluene (40 ml) and we added dropwise the 0.12 mol of HMPA (dissolved in toluene).The mixture was heated under reflux for 24 and then left to cool. The solvent was evaporated under reduced pressure and the obtained solid 3 was filtered and crystallized in appropriate solvant.

3a: yield= 50%; IR ($\upsilon(cm^{-1})$), $\nu_{C=N}$=1618 cm^{-1}, $\nu_{p=o}$=1304 cm^{-1}; RMN^{1}H ($CDCl_3$+DMSO-d_6,(δ ppm)): 1.33(t, 3H), 2.42 (q,2H), 8.61(s,1H), 5.20(s, 2H), 7,20-7,75(m, $5H_{arom}$).^{13}C NMRδ ppm :10.10; 25.20, 36.70; 167.12; 159.82; 148.83;; 47.70125.20-129.80 ^{31}P NMR(δ ppm) : 26. Analcal ($C_{14}H_{19}N_6PO$) (%) C: 52.83; H : 5.97; N : 27.04. found C: 52.80; H : 5.96; N : 27.09

3b: Yield=30%, IR ($\upsilon(cm^{-1})$), $\nu_{C=N}$=1616 cm-1; $\nu_{p=o}$= 1285 cm^{-1}; RMN^{1}H ($CDCl_3$+DMSO-d_6,(δ ppm)):1.08(t, 3H), 2.40(q, 2H), 7.95(s, 1H),3.37(t,2H), 1.82(m,2H), 1.32(m, 2H), 1.20(m, 2H), 1.15(t,3H).^{13}C NMR: 10.11; 25.4; 36.9; 164.16; 160.2; 47.0; 35.75; 23.50; 10.32; 8.20. ^{31}P NMR(δ ppm : 26.1. Analcalfor $C_{10}H_{19}N_6PO$) (%) C: 44.44; H : 7.03; N : 31.11.found: C: 44.43; H : 7.04; N : 31.10

3.3.General procedure for synthesis of 4

We dissolved amidine 2b or 2d (0.1 mmol) in anhydrous dioxane (40 ml) and we added dropwise the $POCl_3$ (dissolved in dioxane).The mixture was left at room temperature 3 days . The solvent was evaporated under reduced pressure and the obtained solid 4 was filtered and crystallized in ethanol..

4a: Yield = 65%; IR (ν (cm^{-1})): $\nu_{C=N}$ = 1668cm^{-1}, ν_{NH} = 3286 cm^{-1}, $\nu_{P=O}$ = 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, (δ ppm)): a: 2,85(s, 3H), b: 8,31 (s, 1H), c: 9,15 (s, 1H), d: 3,80(s, 1H), e: 7,27-7,87 (m, $5H_{arom}$); ^{13} C NMR : 22.66; 164.49; 163.46; 155.58; 47.91; 127.38-134.61; ^{31}P NMR ($CDCl_3$+DMSO-d_6, (δ ppm)) : δ = -17,92.

4b: Yield = 57 %; ; IR (ν (cm^{-1})): $\nu_{C=N}$ = 1674 cm^{-1}, ν_{NH} = 3275 cm^{-1}, $\nu_{P=O}$ = 1261 cm^{-1}; ^{1}H NMR (DMSO-d_6, (δ ppm)): 2.51 (s, 3H); 8.78(s, 1H); 10.43(s, 1H); 3.52(t, 2H); 1.65(m, 2H), 0.93(t, 3H); ^{13} C NMR (δ ppm) : 21.25;164.16; 159.41; 148.44; 45.02; 23.75; 10.32 RMN ^{31}P(DMSO-d_6, (δ ppm)): δ = -17,74.

3.4.General procedure of synthesis of diazaphosphorine-2-chloride-2-oxide 5

We heated under reflux of dioxane the compounds 4 for 24h. The mixture was then left to cool. The solvent was evaporated under reduced pressure and the obtained solid 3 was filtered and crystallized in methanol.

5a: Yield = 65%; IR (ν (cm^{-1})): $\nu_{C=N}$ = 1620cm^{-1}, $\nu_{P=O}$ = 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, (δ ppm)): a: 2.75(s, 3H), 8,30 (s, 1H), 3.80(s, 1H), e: 7,20-7,77 (m, $5H_{arom}$); ^{13} C NMR, (δ ppm) : 22.50; 163.49; 162.46; 153.58; 46.91; 126.38-133.51; ^{31}P NMR ($CDCl_3$+DMSO-d_6, (δ ppm)) : δ = -24. Anal calfor $C_{10}H_{11}N_5POCl$ (%) C: 44.67; H : 3.72; N : 23.68. found : C: 44.60; H : 3.70; N : 23.65.

5b: Yield = 60 %; ; IR (ν (cm^{-1})): $\nu_{C=N}$ = 1674 cm^{-1}, $\nu_{P=O}$ = 1282 cm^{-1}; ^{1}H NMR (DMSO-d_6, (δ ppm)): 2.50 (s, 3H); 8.68(s, 1H); 3.52(t, 2H); 1.57(m, 2H), 0.90(t, 3H); ^{13} C NMR (δ ppm) :

21.20;164.10; 158.41; 147.34; 44.02; 23.65; 10.30 RMN ^{31}P(DMSO-$d_{6,}$ (δ ppm)): δ = -25. Anal calfor $C_9H_{15}N_5POCl$ (%) C: 39.20; H : 5.44; N : 25.40. found C: 39.19; H : 5.43; N : 25.41

4. CONCLUSION

In this work we have used new route to obtain a series of amidine that were synthesized using microwaveve that is an easy and fast method. This new method is believed to be the shortest and the most efficient synthetic route to 2. All product 2 were characterized by FTIR, ^{1}H NMR,^{13}C NMR and X-ray diffraction and obtained in high purity. Then we have study their reactivity via HMPA and $POCl_3$. The New[1,2,4]triazolo[1,3,5,2]triazaphosphorine-2-oxide and [1,2,4]triazolo[1,3,5,2]triazaphosphorine-2-chloride -2-oxide were successfully synthesized from amidines. All compounds were obtained with goodyield.

CONFLICT OF INTEREST The authors confirm that this article content has no conflict of interest.

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