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ONE STEP PROTOCOL AND GREEN SYNTHESIS OF 2-*N,N*-DIMETHYLAMINO-3-ALKYL(ARYL)-2-OXIDO-1-HYDRO -2-BENZO[1,3,2]DIAZAPHOSPHININE-4-ONE DERIVATIVES

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ABSTRACT. 2-*N,N*-dimethylamino-2-oxido-3-alkyl(aryl)-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2**) derivatives are synthesized by one pot reaction by reacting equimolar quantities of anthranilic acid, primary amine, and *N,N*-dimethylphosphoramic dichloride under reflux of ethanol with good yields. The structure of the compounds were established on the basis of their infrared, nuclear magnetic resonance spectral data (^{1}H NMR, ^{13}C NMR and ^{31}P NMR), mass spectrometry, and elemental analysis.

KEY WORDS: Anthranilic acid, *N,N*-Dimethylphosphoramic dichloride, Diazaphosphinine

INTRODUCTION

Organophosphorus compounds possess a broad spectrum of biological properties including antifungal and antibacterial activities [1]. Moreover, they have a great importance in agriculture as pesticide [2] and plant growth regulators [3]. The presence of nitrogen and carbamate moieties is responsible for their therapeutic activity [4-5]. Particularly, diazaphosphinine nucleus derivatives are a very important heterocyclic compound and their synthesis has attracted considerable attention because of not only biological interest but also their uses in organic chemistry [6-9]. These compounds have a wide range of activities like antiviral and antitumor agents [10-11]. They also increase the auxin and antioxidant activities [12, 13]. Furthermore, they are used as potential agents for cancer chemotherapy [14].

Thanks to the importance of 1,3,2-diazaphosphinine and their derivatives, several methods for their synthesis are developed [15-17]. According to the previous facts mentioned, the objective of the current paper is to synthetize new compounds containing diazaphosphinine nucleus in one pot. To meet this end, anthranilic acid was reacted with primary amine and *N,N*-dimethyl-phosphoramic dichloride under reflux of ethanol to afford diazaphosphnine **2**. In the present paper, the 1,3,2-diazaphosphinine were synthesized with good yields via an efficient method without toxic solvent and catalyst.

RESULTS AND DISCUSSION

The condensation of substituted amine with anthranilic acid and *N,N*-dimethylphosphoramic dichloride under reflux of EtOH, afford diazaphosphinine derivatives **2**. This protocol improves the yields of the products **2**. Thus, the monitoring of the progress, of the reaction is done by TLC. Hence, the reaction was finished after 24 h. Therefore, the structure of new compound **2** is performed by FTIR, ^{1}H NMR, ^{13}C NMR, GC-MS and elemental analysis.

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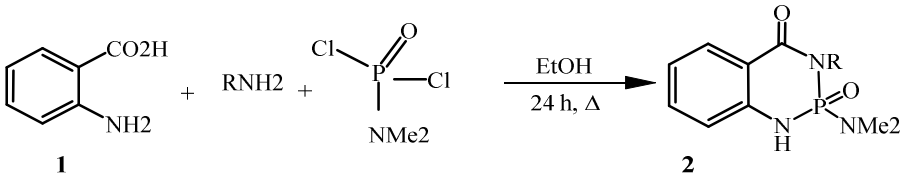


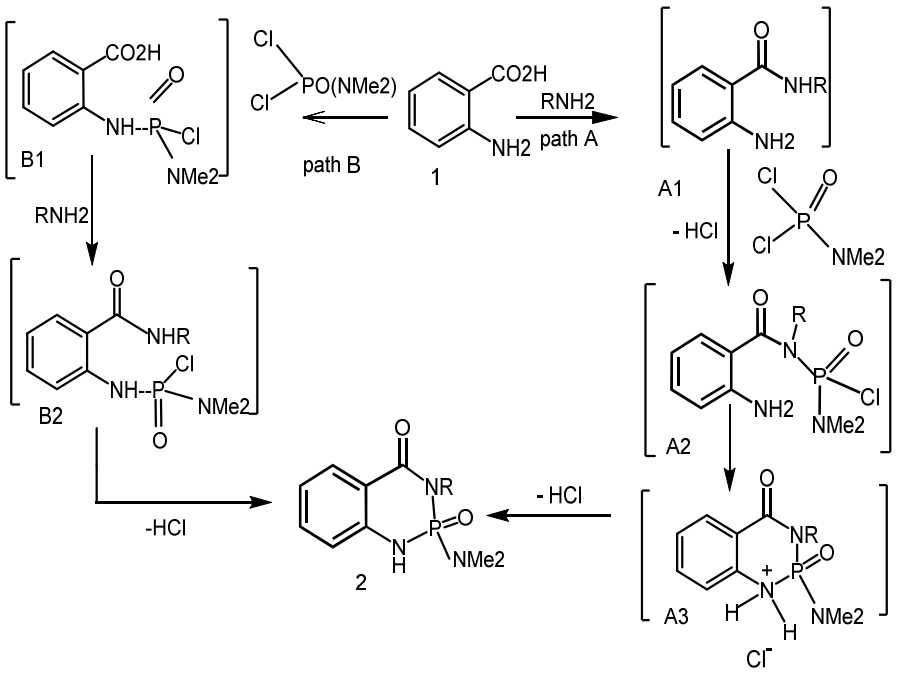
1 **2**

Scheme 1. Synthesis of 1,3,2-diazaphosphinine derivatives **2**.

2	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
R	Ph	o-Tolyl	Ph-CH_2	Me	C_5H_{11}	Neopentyl	decyl	C_5H_4N

The diazaphosphinine derivatives (**2**) were purified using column chromatography on silica gel with a mixture of hexane/EtOAc (8/2) and their structure are unambiguously confirmed by FTIR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, by elemental analysis and GCMS spectral data. The IR spectra of products **2** show the appearance of characteristic bands: at 3334-3449 cm^{-1} corresponding to -N-H group, the band at 1304 cm^{-1} is attributed to P=O, 1073 cm^{-1} to P-N and disappearance of the vibrations bands due to OH and NH_2. In addition, the ^{1}H NMR spectra confirm not only the formation of **2** but also indicates the presence of new signals of the two methyl group of NMe_2. For example, the ^{1}H NMR spectrum of **2c** reveals broad singlet at 4.7 ppm assigned to NH, as well as at 2.5 for the $N(CH_3)_2$ group that appears as two singlets though the aromatic protons appears as a range of 6.3-7.7 ppm. Hence the ^{13}C NMR of **2c** confirm the suggested structure, which shows the methyl carbon of NMe_2 group at 36.81 ppm whereas the C=O, C=C atoms appeared at 173 ppm and 150 ppm respectively, the peaks at 42 ppm corresponds to CH_2-N. The peaks at 115; 116; 126; 127; 128; 129; 131.1; 131.9; 134.1; 134.4; 135; 139 are attributed to C=C aromatic. The ^{31}P NMR spectrum shows one signal in the range of 25 ppm. The EI mass spectrum for compounds **2a**, **2b**, **2c**, **2d**, **2e**, and **2f** shows the presence of the following fragments (M^+ - (O=P-$N(CH_3)_2$)): (M^+ - 92).

The suggested mechanism is described in Scheme 2 and either path A or B can explain it. As far as path A is concerned, the first step of the mechanism is the nucleophilic attack of amine to acid group to afford the intermediate A1. The addition of the amide N-atom of amide A1 onto the phosphore group leads to intermediate A2, followed by the attack of the amine on the phosphore atom of the intermediate A2 leads to the formation of A3, which undergoes an intramolecular cyclization to give the compound **2** (path A). Nevertheless, for path B, the mechanism consists of the attack of amine of anthranilic acid onto phosphore group leading to B1 intermediate which is non-isolated. Then, the attack of primary amine on the phosphore atom of the intermediate B1 leads to B2, which by intracyclization allows to obtain product **2**. As we have not isolated any intermediate (A1, A2, A3, B1 and B2). Thus, we cannot conclude on the pathway of the mechanism.



Scheme 2. The suggested mechanism for the formation of **2**.

EXPERIMENTAL

IR spectra were recorded on Nicolet TR 200 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with $CDCl_3$ solvent containing TMS (tetramethylsilane) on a Brüker 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.47 MHz, ^{31}P: 121.49 MHz). The chemical shifts (δ) are reported in ppm relative to TMS (internal reference) and relative to 85% H_3PO_4 (external reference) for ^{31}P. For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, and m: multiplet. MS spectra were recorded on a JEOL JMS-GC mate II spectrophotometer (Faculty of Sciences Saint - Jérome). Elemental microanalysis were performed on a Perkin-Elmer analyzer apparatus (model 2400, series CHN, France).

*Synthesis of benzodiazaphosphinine derivatives **2***

A mixture of anthranilic acid (1 mmol), primary amine (1 mmol) and *N,N*-dimethylphosphoramic dichloride (1 mmol) in dry ethanol (10 mL) are heated under reflux for 24 h. The solvent is evaporated in vacuum and the resulting product is washed several times with petroleum ether. The pure product is isolated by column chromatography on silica gel (hexane/EtOAc (8/2)).

*2-N,N-Dimethylamino-2-oxido-3-phenyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2a**)*

Yield: 80% (m = 0.24 g). Yellow oil; Rf: 0.5; IR: ν cm^{-1}: 1689 (C=O); 3453 (NH_{free}); 3301 (NH_{asso}). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.5 (d, J = 7.2 Hz, 6H, O=P-N(CH_3)$_2$), 4.7 (broad s, H, NH), 6.3-7.8 (m, 8H, 8 H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.59, 111.58, 115.81, 116.44, 121.50, 123.18, 125.18, 128.06, 128.07, 128.83, 131.68, 133.21, 150.88, 170.00. ^{31}P NMR

($CDCl_3$, 121.49 MHz): 25.70. MS (m/z, %): $M^{+\cdot}$: 301 ($C_{15}H_{16}N_3PO_2$) (5%); 210 (M-Me_2NPO: 301-92) (20%); 212 (10%); 135(100%). Anal. calcd. for $C_{15}H_{16}N_3PO_2$ (301) %: C, 59.80; H, 5.31; N,13.95. Found: C, 59.78; H, 5.30; N, 13.92.

*2-N,N-Dimethylamino-2-oxido-3-o-tolyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2b**)*

Yield: 90% (0.27 g). Brown oil; Rf: 0.6; IR: ν cm^{-1}: 1690 (C=O); 3460 (NH $_{free}$); 3371 (NH $_{asso}$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.2 (s, 3 H, CH_3). 2.5 (d, 6.5 Hz, 6H, O=P-N(CH_3)$_2$), 5.1 (broad s, H, NH), 6.7-7.9 (m, 8H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.71, 36.7, 111.13, 114.90, 115.10, 116.90, 118.27, 126.90, 128.06, 129.40, 131.26, 133.41, 137.70, 150.31, 170.45.^{31}P NMR ($CDCl_3$, 121.49 MHz): 25.16. Anal. calcd. for $C_{16}H_{18}N_3PO_2$ (315) %: C, 60.95; H , 5.71; N ,13,33. Found: C, 60.93; H, 5.70; N, 13.30.

*2-N,N-Dimethylamino-2-oxido-3-Benzyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2c**)*

Yield: 80% (0.25 g). Orange oil; Rf: 0.5; IR: ν cm^{-1}: 1688 (C=O), 3455 (NH $_{free}$), 3370 (NH $_{asso}$). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.5 (d, J = 6.5 Hz, 6 H, O=P-N($C\underline{H}_3$)$_2$). 5.5 (s, 2H, N-CH_2), 3.7 (broad s, H, NH), 6.3-7.7 (m, 8H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.81, 43.5, 115.58, 115.81, 116.44, 116.90, 126.41, 126.98, 127.06, 128.69, 128.83, 131.75, 134.11, 149.75, 173.16.^{31}P NMR ($CDCl_3$, 121.49 MHz): 25.25. MS (m/z, %): 315($C_{16}H_{18}N_3PO_2$) (7.8%); 179(58%); 135 (100%). Anal. calcd. for $C_{16}H_{18}N_3PO_2$ (315) %: C, 60.95; H, 5.71; N, 13,33. Found: C, 60. 94; H, 5.69; N, 13.31.

*2-N,N-Dimethylamino-2-oxido-3-methyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2d**)*

Yield: 85% (0.20 g). Yellow oil; Rf: 0.6. IR: ν cm^{-1}: 1690 (C=O), 3451 (NH $_{free}$), 3299 (NH $_{asso}$). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.4 (m, J = 7.2 Hz, 9 H, O=P-N(CH_3)$_2$, NCH_3), 5.9 (broad s, H, NH), 6.0-7.4 (m, 4H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.59, 46.1, 110.80, 114.33, 115.99, 130.59, 132.14, 150.98, 170.00. ^{31}P NMR ($CDCl_3$, 121.49 MHz): 25.70. MS (m/z, %): 239 ($C_{10}H_{14}N_3PO_2$) (5%); 148(M-Me_2NPO: 239-91) (7.5%); 118 (100%). Anal. calcd. for $C_{10}H_{14}N_3PO_2$ (239) %: C, 50.20; H, 5.85; N, 17.57. Found: C, 50.18; H, 5.83; N, 17.55.

*2-N,N-Dimethylamino -2-oxido-3-pentyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2e**)*

Yield: 82% (0.24 g). Brown oil; Rf: 0.6; IR: ν cm^{-1}: 1690 (C=O), 3451 (NH $_{free}$), 3299 (NH $_{asso}$). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.5-2 (m, 9H, -C_5H_9), 3.4 (s, 2 H, N-CH_2), 6.3-7.8 (m, 5H, 4H_{arom} + NH); 2.6 (m, 2H + 6 H, O=P-N($C\underline{H}_3$)$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16, 21, 27, 46, 36.64, 116.24, 116.52, 116.65, 117.19, 132.26, 149.67, 173.96. ^{31}P NMR ($CDCl_3$, 121.49 MHz): 25.91. MS (m/z, %): 295 ($C_{14}H_{22}N_3PO_2$) (1.5%); 180(M-115) (79%); 179(M- 116) (95.0%); 118(M- 177) (100%). Anal. calcd. for $C_{14}H_{22}N_3PO_2$ (295) %: C, 56.94; H, 7.45; N, 14.23. Found C, 56.92; H, 7.42; N, 14.22.

*2-N,N-Dimethylamino-2-oxido-3-neopentyl-1-hydro-2-benzo[1,3,2]diazaphosphinin-4-one (**2f**)*

Yield: 92% (0.27 g). Yellow oil; Rf: 0.5; IR: ν cm^{-1}: 1688 (C=O), 3451 (NH $_{free}$), 3300 (NH $_{asso}$). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ: 6.7-7.9 (m, 4H, H_{arom}), 5.5 (broad s, H, NH), 2.9 (s, 2H, CH_2). 2.5 (mu, 15 H, O=P-N(CH_3)$_2$), 3 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.59, 111.50, 115.11, 116.99, 131.62, 134.51, 151.21, 170.18.^{31}P NMR ($CDCl_3$, 121.49 MHz): 25.50. MS (m/z, %): 295 ($C_{14}H_{22}N_3PO_2$) (6%); 179 (M-116) (80%); 135 (M-160) (95%); 118(100%). Anal. calcd. for $C_{14}H_{22}N_3PO_2$ (295) %: C, 56.94; H, 7.45 N, 14.23. Found C, 56.91; H, 7.40; N, 14.21.

*2-N,N-Dimethylamino-2-oxido -3-decyl-1-hydro-2-benzo[1,3,2]diazaphosphorin-4-one (**2g**)*

Yield: 90% (0.32 g). Brown oil. Rf: 0.5. IR: ν cm-^{1}: 1682 (C=O), 3451 (NH $_{free}$), 3300 cm^{-1} (NH $_{asso}$). ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 300 MHz): δ = 6.7-7.6 (m, 4H, Harom), δ = 4.4 (s, 1H, NH),). 2.6 (d, J = 7.2 Hz, 6 H, O=P-N(CH_3)$_2$); 2.69 (t, J = 6.9Hz, 2H, N-CH_2); 1.28 (mu, 14H (7 CH_2-C), 0.9 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 75 MHz): δ = 14.1, 22.7, 26.7, 28, 29.6, 40, 116.4, 117.9, 118.9, 128.3, 132.9, 145.5, 160.1. ^{31}P NMR (DMSO-d_6 + $CDCl_3$, 121.49 MHz): 25.60. MS (m/z, %): 365($C_{19}H_{32}N_3PO_2$) (5%); 148(M-Me_2NPO: 239-91) (7.5%); 118 (100%). Anal. calcd. for $C_{19}H_{32}N_2PO_2$ (365) %: C, 62.46; H, 8.67; N, 11.50. Found: C, 62.45; H, 8.65; N, 11.52.

*2-N,N-Dimethylamino-2-oxido -3-(pyridin-2-yl)-1-hydro-2-benzo[1,3,2]diazaphosphorin-4-one (**2h**)*

Yield: 88% (0.26 g). Yellow oil. Rf: 0.6. IR: ν cm^{-1}: 1680 (C=O), 3456 (NH $_{free}$), 3300 (NH $_{asso}$). ^{1}H NMR (DMSO + $CDCl_3$, 300 MHz); δ = 6.2-8.4 (m, 9H, H_{arom} +H_{Py} +NH), 2.5 (d, J = 7.2 Hz, 6 H, O=P-N(CH_3)$_2$). ^{13}C NMR (DMSO + $CDCl_3$; 75 MHz): 109.76, 112.03, 112.46, 115.09, 131.33, 132.73, 138.53, 143.57, 150.28, 157.68, 171.7; ^{31}P NMR (DMSO + $CDCl_3$; 121.49 MHz) δ ppm: 25.55. Anal. calcd. for $C_{14}H_{15}N_4PO_2$ (302) %: C, 55.62; H, 4.96; N, 18.54. Found: C, 55.63; H, 4.95; N, 18.53.

CONCLUSION

In summary, a series of diazaphosphinine **2** are successfully synthesized using one pot synthesis. The green synthesis of diazaphosphinines derivatives **2** is high yielding and product isolation is very straightforward without using any catalyst. Over all compounds are identified by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, GCMS and elemental analysis.

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