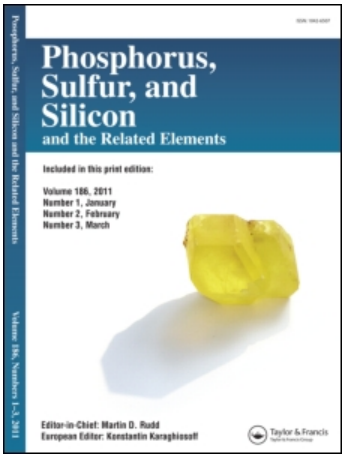

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SYNTHESIS AND REACTVITY OF *N*-[*N*-PHOSPHORAMIDO-1*H*-BENZIMIDAZOL-2-YL] IMIDATES

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SYNTHESIS AND REACTVITY OF *N*-[*N*-PHOSPHORAMIDO-1*H*-BENZIMIDAZOL-2-YL] IMIDATES

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N-*(-1*H-*Benzimidazol-2-yl) imidates* ***1a–c*** *react with chlorophosphoramide to give the* N-*[-1-*N,N,N′,N′*-tetramethylphosphoramidoyl-1*H-*benzimidazol-2-yl]-imidates* ***2a–c*** *or with dichlorophosphoramide to yield the bis[(*N*-1-benzimidazol-2-yl)-imidate] phosphoramide derivatives* ***3a–b****. The reaction of compounds* ***2a–c*** *toward primary amines is studied. The obtained amidine derivatives* ***4a–b*** *were unambiguously characterized by different spectroscopic techniques (IR,* ^{1}H*,* ^{13}C*, and* ^{31}P *NMR, and in some cases MS).*

Keywords: *N*-Benzimidazol-2-yl imidates; *N*-[-1-*N*,*N*,*N*′,*N*′-tetramethylphosphoramido-1*H*-benzimidazol-2-yl] imidates; bis[(*N*-1-benzimidazol-2-yl)-imidate] phosphoramides; *N*-[*N*-1-phosphoramido-benzimidazol-2-yl] amidines; chlorophosphoramide; dichlorophosphoramide

INTRODUCTION

In recent years several papers have been devoted to the synthesis of benzimidazolyl derivatives because they are widely used as anxiolytics, antineoplastics, and antimicrobial agents.[1–7] However, few papers concern benzimidazolyl compounds associated to phosphorus groups.[8–13]

In the last few years, we focused our attention[12–14] on the study of *N*-benzimidazol-2-yl imidates **1**, which contain two reactive centers:

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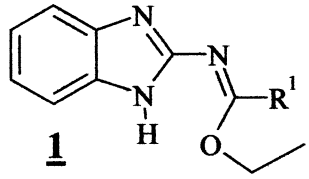
the imidic carbon and the imidazolic nitrogen (Scheme 1). Theses compounds are versatile synthetic intermediates in heterocyclic chemistry. In this article, the functionalization of these imidates by a phosphoramide moiety on the imidazolic nitrogen is reported. The reactivity of the resulting imidates **2** toward primary amines is also studied.



1

SCHEME 1

RESULTS AND DISCUSSION

Synthesis of *N*-[*N*-1-phosphoramidoyl-benzimidazol-2-yl] Imidates 2

The *N*-benzimidazol-2-yl imidates **1** react with sodium hydride to give the anionic intermediates **A**. These anions react easily with *N*,*N*,*N*′,*N*′-tetramethylchlorophosphoramide to yield the corresponding imidates **2**. However, if these anionic intermediates **A** are treated by dichlorodimethylaminophosphoramide $Cl_2(NMe_2)P{=}O$ in 1:1 molar ratio, only derivatives **3** were obtained as a result of a double nucleophilic substitution on the phosphorus atom instead of the expected monochlorinated substrate **2**′ (Scheme 2).

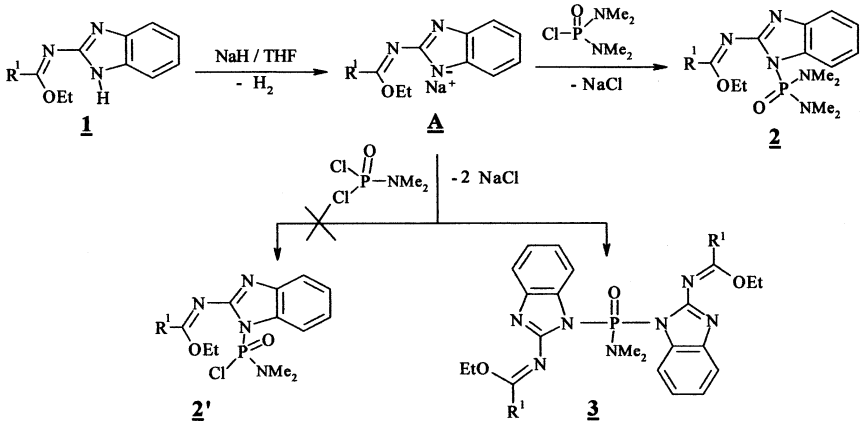
The imidates **2** were characterized by the analysis of their NMR, IR, and MS spectra.

IR Spectroscopy

The IR spectra show the absence of the characteristic stretching band of the imidazolic function N—H and the shift of the absorption of C=N band to lower frequencies. In fact, the C=N band frequency is approximately equal to 1650 cm^{-1} for the imidates **1** and it is about 1635 cm^{-1} for the products **2** and **3**. This decrease is due to the inductive effect of the $(Me_2N)_2$ P=O group.

NMR Spectroscopy

The analysis of the ^1H NMR spectra points out the absence of the characteristic peak of the mobile proton of the imidazolic group and

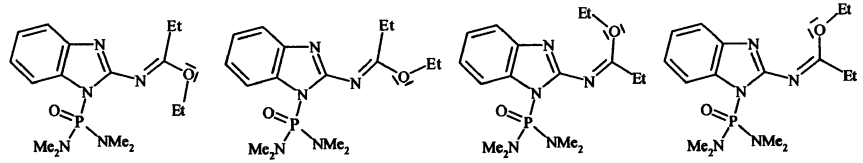


substrate	2a	2b	2c	3a	3b
R^1	CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5

SCHEME 2

the presence of a doublet at 2.7 ppm assigned to the methyl protons of the introduced phosphoramide moiety. This is confirmed by the peaks at 36 ppm on the ^{13}C NMR spectra; the introduction of the phosphoramide group do not affect the other proton groups and carbons shifts.

The presence of only one peak at about 12 ppm for imidates **2** in the ^{31}P NMR spectra is in agreement with the existence of only one of the four theoretical possible isomers (Scheme 3).[15,16]



SCHEME 3

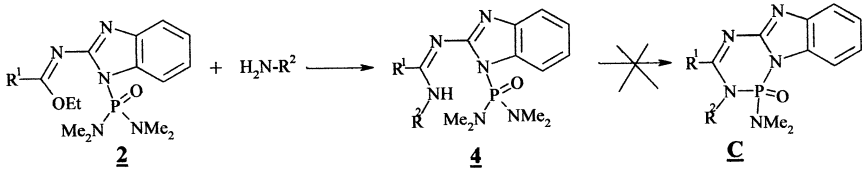
MS

EI mass spectrum for the imidate **2b** shows the presence of the following fragments: the molecular peak M^+(m/z = 351, 64%), the peak $(M + H\text{-}(Me_2N)_2PO)^+$ (m/z = 217, 60%) due to the elimination of the

phosphoramide moiety and the basis peak $((Me_2N)_2PO)^+$ (m/z = 135, 100%) for the phosphoramide group.

Synthesis of Amidines 4

The new imidates **2** have two electrophilic centers in positions 1 and 5, so they may form heterocyclic phosphorus compounds by reaction with various binucleophilic derivatives. Thus, in the presence of primary amines, the imidates **2** give the corresponding amidines **4** by the substitution of the ethoxy group by the amine function. By heating under reflux in several higher boiling solvents like dioxane, toluene, or xylene, the resulting products do not give the triazaphosphorines **C** (Scheme 4). If the refluxing time exceeds 48 h, decomposition of the resulting amidines occurs. In addition, the action of strong bases like n-butyl lithium, sodium hydride, and potassium tert-butoxide was also unsuccessful.



substrate	4a	4b	4c	4d	4e	4f	4g	4h
R^1	Me	Me	Et	Et	Et	Et	Ph	Ph
R^2	Bn	*s*-Bu	Bn	Py	*n*-Bu	Ph	Bn	Ph

Bn: benzyl; *s*-Bu: 2-methylpropyl; Py: 3-pyridinyl

SCHEME 4

The amidines **4** have been characterized by the analysis of their IR, NMR, and MS spectra.

IR Spectroscopy

The IR spectra show a strong stretching vibration band at about 3335 cm^{-1} assigned to the amidinic N–H bond and a second absorption at approximately 1615–1620 cm^{-1}, characterizing the stretching vibration of the amidinic C=N function.

NMR Spectroscopy

The substitution of the ethoxy moiety by the amine group NHR^2 is confirmed, in the ^1H NMR spectra, by the absence of the proton signals of the ethoxy group and the presence of those related to the amine protons. This is confirmed by the ^{13}C NMR spectra. In the ^{31}P NMR spectra there is no significant difference between the shifts of the phosphorus in the imidates **2** and the amidines **4**.

MS

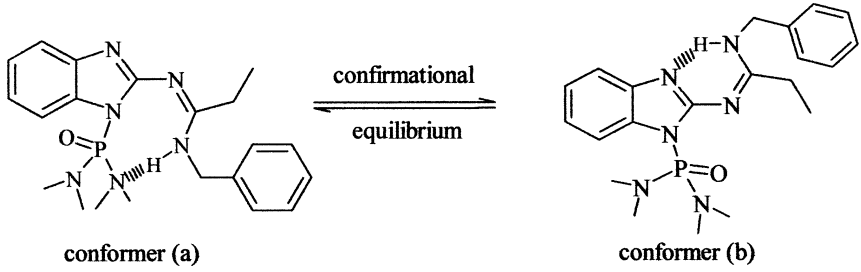
All the CI mass spectra exhibit the peaks M^+, $(M + H)^+$, and $(M + 2H)^+$, and some common fragments due to the elimination of the phosphoramide moiety $(Me_2N)_2$ P=O (m/z = 135); Other fragments related to the R^2 group of the amine are also observed, such as for butyl, phenyl, and benzyl.

Quantum Chemistry Study

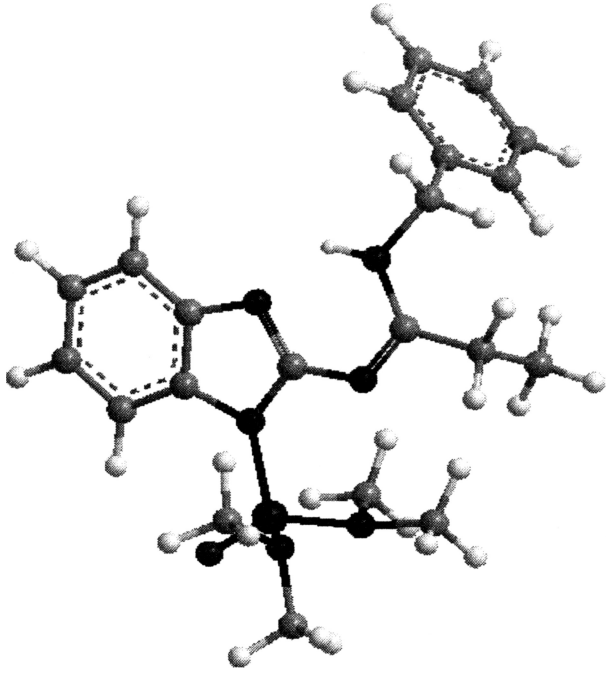
In order to explain why amidines **4** do not give the corresponding triazaphosphorines **C**, we have performed quantum calculations using AM1[17] then PM3[18] semiempirical methods on MOPAC[19] and GAMESS[20] programs to optimize the geometry and to calculate the charge of the reactive centers.

The calculated charges on the amidinic nitrogen and the phosphorus atom were, respectively, −0.22e and 2.13e for the substrate **4c**; thus a nucleophilic substitution on the phosphorus atom by the amidinic nitrogen may occur. Nevertheless, the more stable conformation for amidine **4c** corresponds to the conformer (b) (Scheme 5) as it was illustrated for the substrate **4c** in Scheme 6.

Also, we noticed that the phosphorus atom does not belong to the same level that contains the benzimidazole moiety; the dihedral angle between the two levels is about 12.7°. The strained geometry of these compounds does not allow any cyclization reaction.



SCHEME 5



SCHEME 6 Optimized geometry for the amidine **4c**.

CONCLUSION

In this work, we were able to introduce a second electrophilic center on *N*-benzimidazolyl imidates **1**. The reaction of imidates with dichlorophosphoramide give bis[(*N*-1-benzimidazol-2-yl)-imidate] phosphoramide derivatives **3**. Their reactions with primary amines yield the *N*-1-benzimidazol-2-yl amidines **4**, which are stable enough to be isolated and fully characterized. All attempts for the amidines cyclization were unsuccessful.

EXPERIMENTAL SECTION

Apparatus

Melting points were determined on an Electrothermal 9100 apparatus, and they are uncorrected. The IR spectra were recorded in chloroform or in KBr disks on a Perkin-Elmer spectrophotometer Paragon 1000 PC. Mass spectra were recorded on a JEOL MS 700 system in chemical

ionization mode using NH_3 or in MAT Finnigan 90 apparatus for EI MS. The ^1H, ^{13}C, and ^{31}P NMR were recorded either in $CDCl_3$ solution or in DMSO-d_6 solution on a Bruker AC 300 MHz spectrometer operating at 300 MHz for the proton, 75 MHz for ^{13}C, and 121 MHz for ^{31}P. Chemical shifts were in ppm using tetramethylsilane (TMS) as an internal standard for the ^1H and ^{13}C NMR and H_3PO_4 85% for ^{31}P NMR spectra as an external standard. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; br, board; mu, multiplet.

Synthesis of Imidates 2

To a stirred suspension of sodium hydride (15 mmole) in 15 ml of anhydrous tetrahydrofuran (THF), under an inert nitrogen atmosphere and cooled with an ice–salt bath ($\theta \sim -5^\circ C$), a solution of 10 mmole of imidates **1** in 20 ml of anhydrous THF was added dropwise. The mixture was stirred for 1 h at the same temperature, then 10 mmole of chlorophosphoramide dissolved in 15 ml of anhydrous ether was slowly added to the solution mixture.

Once addition is finished, the solution is stirred for 2 h at low temperature and 20 h at room temperature. The resulting salt was filtered off, and the solvent was evaporated under reduced pressure. The resulting oil was washed twice with 15 ml of petroleum ether and allowed to stay at room temperature for 2–3 days to crystallize, giving the imidates **2**.

N-*[1-(*N,N,N′,N′-*Tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-acetimidic Acid Ethyl Ester 2a*

Yield, 80%, m.p. 91°C. IR ($CHCl_3$): $\nu_{P=O} = 1251$, $\nu_{C=N} = 1639\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): 1.35 (t, C$\underline{H}_3$–CH_2, 3H), 2.25 (s, C$\underline{H}_3$–C=, 3H), 2.75 (d, 12H, C$\underline{H}_3$–N, $^3J_{P-H} = 12.5$ Hz), 4.40 (q, CH_3–C$\underline{H}_2$, 2H), 7.05–7.95 (mu, C=C$\underline{H}_{arom}$, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.28 ($\underline{C}H_3$–CH_2), 18.63 ($\underline{C}H_3$–C=), 36.62 ($\underline{C}H_3$–N), 36.68 ($\underline{C}H_3$–N), 63.10 (–$\underline{C}H_2$–O), 114.39 ($\underline{C}$=C)–143.30 ($\underline{C}$=C), 155.84 ($\underline{C}$=N), 168.32 (O–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 11.98.

N-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-propionimidic Acid Ethyl Ester 2b*

Yield, 89%. m.p. 127°C. IR ($CHCl_3$): $\nu_{P=O} = 1252$, $\nu_{C=N} = 1636\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): 1.2 (t, C$\underline{H}_3$–CH_2, 3H), 1.4 (t, C$\underline{H}_3$–CH_2, 3H), 2.55 (q, CH_3–C$\underline{H}_2$, 2H), 2.75 (d, 12H, C$\underline{H}_3$–N, $^3J_{P-H} = 12.9$ Hz), 4.35 (q, CH_3–C$\underline{H}_2$–O, 2H), 7.05–7.90 (mu, C=C$\underline{H}_{arom}$, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 10.87 ($\underline{C}H_3$–CH_2), 14.31 ($\underline{C}H_3$–CH_2), 25.77 (CH_3–$\underline{C}H_2$), 36.69 ($\underline{C}H_3$–N), 36.76 ($\underline{C}H_3$–N), 36.82 ($\underline{C}H_3$–N), 63.05

(CH_3—$\underline{C}H_2$—O), 114.38–143.46 ($\underline{C}$=C), 155.78 ($\underline{C}$=N), 171.68 (O—$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 11.97. MS (EI, 70 EV), *m/z* (%): 351 (66) [M^+], 322 (48) [$M^+ - Et$], 306 (16) [$M^+ - EtO$], 251 (26) [M^+-N=C(OEt)Et], 217 (59) [M^+ - $P(O)(NMe_2)_2$], 135 (100) [$P(O)(NMe_2)_2^+$].

N-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-benzimidic Acid Ethyl Ester 2c*

Yield, 73%. m.p. 138°C. IR (KBr disk): $\nu_{P=O} = 1261$, $\nu_{C=N} = 1629$ cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 1.51 (t, $C\underline{H}_3$—CH_2, 3H), 2.70 (d, $C\underline{H}_3$—N, 12H, $^3J_{P-H} = 12$ Hz), 4.55 (q, CH_3—$C\underline{H}_2$—O, 2H), 7.03–7.96 (mu, C=$C\underline{H}_{arom}$, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.28 ($\underline{C}H_3$—CH_2), 36.33 ($\underline{C}H_3$—N), 36.65 ($\underline{C}H_3$—N), 36.72 ($\underline{C}H_3$—N), 36.86 ($\underline{C}H_3$—N), 64.08 (CH_3—$\underline{C}H_2$—O), 114.00 ($\underline{C}$=C)–135.80 ($\underline{C}$=C), 155.74 ($\underline{C}$=N), 176.33 (O—$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 11.85.

Synthesis of bis[(N-1-benzimidazol-2-yl)-imidate)]-phosphoramides 3

To a stirred suspension of sodium hydride (15 mmole) in 15 ml of anhydrous THF, under an inert nitrogen atmosphere and cooled with an ice–salt bath ($\theta \sim -5$°C); a solution of 10 mmole of imidates **1** in 20 ml of anhydrous THF was added dropwise. The mixture was stirred for 1 h at the same temperature, then 10 mmole of dichlorophosphoramide dissolved in 15 ml of anhydrous ether was slowly added to the solution mixture.

Once addition is finished, the solution is stirred for 2 h at low temperature and 20 h at room temperature. The resulting salt was filtered off and the solvent was evaporated under reduced pressure. The resulting oil was washed twice with 15 ml of petroleum ether, and allowed to stay at room temperature for 2–3 days to crystallize, yielding imidates **3**.

N-*(1-{[2-(1-Ethoxy-ethylideneamino)-benzoimidazol-1-yl]-*N,N-*dimethylphosphamidoyl}-1*H-*benzoimidazol-2-yl)-acetimidic Acid Ethyl Ester 3a*

Yield, 85%. m.p. decomposes on heating. IR (KBr disk): $\nu_{P=O} = 1238$, $\nu_{C=N} = 1633$ cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.83 (t, $C\underline{H}_3$—CH_2, 3H), 1.27 (t, $C\underline{H}_3$—CH_2, 3H), 2.09 (s, $C\underline{H}_3$—C=, 3H), 2.17 (s, $C\underline{H}_3$—C=, 3H), 3.10 (d, 6H, $C\underline{H}_3$—N, $^3J_{P-H} = 13$ Hz), 3.85 (q, CH_3—$C\underline{H}_2$—O, 2H), 4.10 (q, CH_3—$C\underline{H}_2$—O, 2H), 7.09–7.91 (mu, C=$C\underline{H}_{arom}$, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): 13.64 ($\underline{C}H_3$—CH_2), 14.20 ($\underline{C}H_3$—CH_2), 18.31 (CH_3—$\underline{C}H_2$), 29.69 (CH_3—$\underline{C}H_2$), 36.72 ($\underline{C}H_3$—N), 36.80 ($\underline{C}H_3$—N), 60.38 (CH_3—$\underline{C}H_2$—O), 62.56 (CH_3—$\underline{C}H_2$—O), 113.01–143.29 ($\underline{C}$=C), 155.50

(C=N), 155.54 (C=N), 169.59 (O–C=N), 172.13 (O–C=N). ^{31}P NMR (121 MHz, DMSO-d_6): −5.46.

N-*(1-{[2-(1-Ethoxy-ethylideneamino)-benzoimidazol-1-yl]-*N,N-*dimethylphosphamidoyl}-1*H-*benzoimidazol-2-yl)-proponimidic Acid Ethyl Ester 3b*

Yield; 81%, m.p. decomposes on heating. IR (KBr disk): $\nu_{P=O}$ = 1233, $\nu_{C=N}$ = 1643 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.76 (t, CH_3–CH_2, 3H), 1.10 (t, CH_3–CH_2, 3H), 1.22 (mu, CH_3–CH_2, 6H), 2.30 (q, CH_3–CH_2, 2H), 2.51 (q, CH_3–CH_2, 2H), 3.05 (d, 6H, CH_3–N, $^3J_{P-H}$ = 13.6 Hz), 3.34 (q, CH_3–CH_2–O, 2H), 4.03 (q, CH_3–CH_2–O, 2H), 7.10–7.72 (mu, C=CH_{arom}, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): 8.94 (CH_3–CH_2), 10.31 (CH_3–CH_2), 13.41 (CH_3–CH_2), 14.07 (CH_3–CH_2), 24.77 (CH_3–CH_2), 26.81 (CH_3–CH_2), 34.05 (CH_3–N), 35.95 (CH_3–N), 59.64 (CH_3–CH_2–O), 61.83 (CH_3–CH_2–O), 111.12 (C=C)–146.70 (C=C), 151.30 (C=N), 154.43 (C=N), 170.78 (O–C=N), 173.29 (O–C=N). ^{31}P NMR (121 MHz, DMSO-d_6): -5.95. MS (CI, NH_3): *m/z* (%) = 525 (27) [M^+ + 2H], 524 (100) [M^+ + H], 523 (5) [M^+], 218 (35).

Synthesis of Amidines 4

To a solution of 2 mmole of imidates **2** in 15 ml of anhydrous THF 2 mmole of a primary amine was added, the solution was refluxed for 24 h. The solvent evaporated under reduced pressure. The resulting oil was washed twice with 10 ml of petroleum ether and allowed to stay at room temperature for 2–3 days, the product crystallized; the amidines **4** were filtered off.

N-*Benzyl-*N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-acetamidine 4a*

Yield, 95%, m.p. 185°C. IR ($CHCl_3$): $\nu_{P=O}$ = 1284; $\nu_{C=N}$ = 1615; ν_{N-H} = 3335 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 2.2 (s, CH_3–C, 3H), 2.75 (d, CH_3–N, 12H, $^3J_{P-H}$ = 13.3 Hz), 4.6 (d, Ph–CH_2, 2H), 7.2–8.1 (mu, C=CH_{arom}, 9H), 11.6 (br, N–H, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.25 (CH_3–C), 36.60 (CH_3–N), 36.66 (CH_3–N), 36.92 (CH_3–N), 36.99 (CH_3–N), 47.47 (Ph–CH_2), 114.80 (C=C)–142.38 (C=C), 158.15 (C=N), 163.46 (N–C=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.09. MS (CI, NH_3): *m/z* (%) = 400 (29) [M^+ + 2H], 399 (100) [M^+ + H], 398 (3) [M^+], 309 (3) [M^+ + H–Ph–CH_2], 265 (7) [M^+ + H–P(O)(NMe_2)$_2$].

N-*Sec-Butyl*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-acetamidine 4b*

Yield, 89%, m.p. 173°C. IR ($CHCl_3$): $\nu_{P=O} = 1286$; $\nu_{C=N} = 1616$, $\nu_{N-H} = 3337\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): 1.05 (t, C$\underline{H}_3$–CH_2, 3H), 1.35 (d, C$\underline{H}_3$–CH, 3H), 1.70 (mu, CH_3–C$\underline{H}$–CH_2, 2H), 2.30 (s, C$\underline{H}_3$–C, 3H), 2.75 (d, C$\underline{H}_3$–N, 12H, $^3J_{P-H} = 13.6$ Hz), 3.60 (mu, CH_3–C$\underline{H}$–CH_2, 1H), 7.10–8.01 (mu, C=C$\underline{H}_{arom}$, 4H), 11.20 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 10.28 ($\underline{C}H_3$–CH_2), 21.15 ($\underline{C}H_3$–C), 30.49 ($\underline{C}H_3$–$\underline{C}H_2$), 36.52 ($\underline{C}H_3$–N), 36.59 ($\underline{C}H_3$–N), 36.86 ($\underline{C}H_3$–N), 36.93 ($\underline{C}H_3$–N), 51.36 ($\underline{C}H_2$–N), 114.60 ($\underline{C}$=C)–142.51 ($\underline{C}$=C), 158.40 ($\underline{C}$=N), 162.02 (N–C=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.15.

N-*Benzyl*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-propionamidine 4c*

Yield; 92%, m.p. 189°C. IR ($CHCl_3$): $\nu_{P=O} = 1284$; $\nu_{C=N} = 1619$; $\nu_{N-H} = 3333$. ^1H NMR (300 MHz, $CDCl_3$): 1.2 (t, C$\underline{H}_3$–CH_2, 3H), 2.50 (q, CH_3–C$\underline{H}_2$, 2H), 2.80 (d, C$\underline{H}_3$–N, 12H, $^3J_{P-H} = 13.1$ Hz), 4.70 (d, Ph–C$\underline{H}_2$, 2H), 7.15–8.20 (mu, C=C$\underline{H}_{arom}$, 9H), 11.60 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 11.98 ($\underline{C}H_3$–CH_2), 27.20 (CH_3–$\underline{C}H_2$), 36.84 ($\underline{C}H_3$–CN), 36.91 ($\underline{C}H_3$–N), 44.74 ($\underline{C}H_2$–Ph), 114.96 ($\underline{C}$=C)–149.17 ($\underline{C}$=C), 158.30 ($\underline{C}$=N), 167.41 (N–C=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.29.

N-*(Pyridin-3-yl-methyl)*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-propionamidine 4d*

Yield, 90%, m.p. 170°C. IR ($CHCl_3$): $\nu_{P=O} = 1277$; $\nu_{C=N} = 1619$; $\nu_{N-H} = 3326\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): 1.30 (t, C$\underline{H}_3$–CH_2, 3H), 2.52 (q, CH_3–C$\underline{H}_2$, 2H), 2.80 (d, C$\underline{H}_3$–N, 12H, $^3J_{P-H} = 13.9$ Hz), 4.70 (d, Ph–C$\underline{H}_2$, 2H), 7.21–8.73 (mu, C=C$\underline{H}_{arom}$, 8H), 11.72 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.18 ($\underline{C}H_3$–CH_2), 27.42 (CH_3–$\underline{C}H_2$), 36.82 ($\underline{C}H_3$–N), 36.87 ($\underline{C}H_3$–N), 37.02 ($\underline{C}H_3$–N), 37.09 ($\underline{C}H_3$–N), 44.93 (π–$\underline{C}H_2$–), 115.14–149.35 ($\underline{C}$=C), 158.50 ($\underline{C}$=N), 167.62 (N–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.68.

N-*n-Butyl*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-propionamidine 4e*

Yield, 93%, m.p. 175°C. IR ($CHCl_3$): $\nu_{P=O} = 1282$, $\nu_{C=N} = 1617$; $\nu_{N-H} = 3330\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): 1.0 (t, C$\underline{H}_3$–CH_2, 3H), 1.30 (t, C$\underline{H}_3$–CH_2, 3H), 1.50 (mu, CH_2–C$\underline{H}_2$, 2H), 1.70 (mu, CH_2–C$\underline{H}_2$, 2H), 2.50 (q, CH_3–C$\underline{H}_2$, 2H), 2.80 (d, 12H, C$\underline{H}_3$–N, $^3J_{P-H} = 13.0$ Hz), 3.40 (q, CH_2–C$\underline{H}_2$, 2H), 7.15–8.05 (mu, C$\underline{H}_{arom}$, 4H), 11.15 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 11.97 ($\underline{C}H_3$–CH_2),

13.78 ($\underline{C}H_3$–CH_2–), 20.14 (CH_3–$\underline{C}H_2$–), 27.21 (CH_3–$\underline{C}H_2$–), 32.40 (CH_2–$\underline{C}H_2$–), 36.69 (N–$\underline{C}H_3$), 36.84 (N–$\underline{C}H_3$), 36.91 (N–$\underline{C}H_3$), 36.99 (N–$\underline{C}H_3$), 43.25(–$\underline{C}H_2$–N), 114.78–142.31 ($\underline{C}$=C), 158.80 ($\underline{C}$=N), 167.41 (N–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.37. MS (CI, NH_3): *m/z* (%) = 380 (20) [$M^+ + 2H$], 379 (100) [$M^+ + H$], 378 (3) [M^+], 306 (5) [$M^+ + H$-Bu], 245 (7) [$M^+ + H - P(O)(NMe_2)_2$].

N-*Phenyl*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-propionamidine 4f*

Yield, 75%, m.p. 141°C. IR ($CHCl_3$): $\nu_{P=O} = 1287$, $\nu_{C=N} = 1614$, $\nu_{N-H} = 3329\ cm^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): 1.20 (t, $C\underline{H}_3$–CH_2, 3H), 2.50 (q, CH_3–$C\underline{H}_2$, 2H), 2.75 (d, $C\underline{H}_3$–N, 12H, $^3J_{P-H} = 12.9$ Hz), 7.15–8.15 (mu, C=$C\underline{H}_{arom}$, 9H), 12.95 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.36 ($\underline{C}H_3$–CH_2), 27.19 (CH_3–$\underline{C}H_2$), 36.64 ($\underline{C}H_3$–N), 36.74 ($\underline{C}H_3$–N), 36.86 ($\underline{C}H_3$–N), 36.93 ($\underline{C}H_3$–N), 111.75 ($\underline{C}$=C)–142.08 ($\underline{C}$=C), 152.10 ($\underline{C}$=N), 166.29 (N–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.36. MS (CI, NH_3): *m/z* (%) = 400 (23) [$M^+ + 2H$], 399 (100) [$M^+ + H$], 398 (4) [M^+], 321 (4) [$M^+ + H$- Ph-], 265 (9) [$M^+ + H$–$P(O)(NMe_2)_2$].

N-*Benzyl*-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-benzamidine 4g*

Yield, 71%, m.p. 152°C. IR ($CHCl_3$): $\nu_{P=O} = 1287$, $\nu_{C=N} = 1615$, $\nu_{N-H} = 3332\ cm^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): 2.70 (d, $C\underline{H}_3$–N, 12H, $^3J_{P-H} = 13.1$ Hz), 4.55 (d, Ph–$C\underline{H}_2$, 2H); 7.05–8.20 (mu, C=$C\underline{H}_{arom}$, 14H), 12.80 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 36.52 ($\underline{C}H_3$–N), 36.61 ($\underline{C}H_3$–N), 36.73 ($\underline{C}H_3$–N), 36.85 ($\underline{C}H_3$–N), 48.81 ($\underline{C}H_2$–Ph), 111.71–138.31 ($\underline{C}$=C), 158.06 ($\underline{C}$=N), 164.60 (N–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.20.

N-Phenyl-N′-*[1-(*N,N,N′,N′-*tetramethylphosphamidoyl)-1*H-*benzoimidazol-2-yl]-benzamidine 4h*

Yield, 68%, m.p. 155°C. IR ($CHCl_3$): $\nu_{P=O} = 1280$, $\nu_{C=N} = 1616$, $\nu_{N-H} = 3325\ cm^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): 2.65 (d, $C\underline{H}_3$–N, 12H, $^3J_{P-H} = 12.8$ Hz), 7.05–8.20 (mu, $\underline{C}$=CH_{arom}, 14H), 13.15 (br, N–$\underline{H}$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 36.57 ($\underline{C}H_3$–N), 36.75 ($\underline{C}H_3$–N), 36.88 ($\underline{C}H_3$–N), 36.95 ($\underline{C}H_3$–N), 115.13($\underline{C}$=C)–142.05 ($\underline{C}$=C), 157.47 ($\underline{C}$=N), 160.77 (N–$\underline{C}$=N). ^{31}P NMR (121 MHz, $CDCl_3$): 12.50.

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