Novel Heterocyclic System – 2,4,1-Benzoxazaphosphinine: Convenient Substrate for Synthesis of Derivatives of 2,4-Diaminophenylphosphonic Acid

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Abstract: N-Acylanilides having electron-donating substituents attached at a proper position react with phosphorus (III) bromides forming the new heterocyclic system - 2,4,1-benzoxazaphosphinine. 1-Arylimino-2,4,1-benzoxazaphosphinines are hydrolyzed with cleavage of an oxazaphosphinine ring affording mixed amides of 2,4-diaminophenylphosphonic acid in high yield.

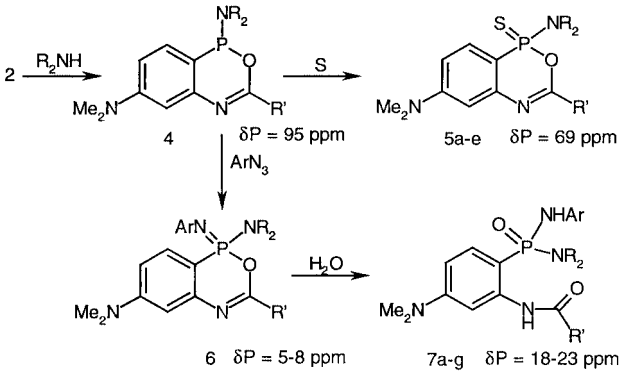
Key words: arylamides, phosphorus (III) halides, phosphorylation, heterocyclization, ring opening

Aminophosphinic and aminophosphonic acids and their derivatives in the past decade are probably the most investigated class of organophosphorus compounds. Overwhelming objects of study are the phospha analogues of natural amino acids, that is aminoalkyl type compounds. Aminoarylphosphinic and phosphonic acids and their derivatives are illustrated to a lesser degree, however, they have also found some application in view of their biological potency.[1-4]

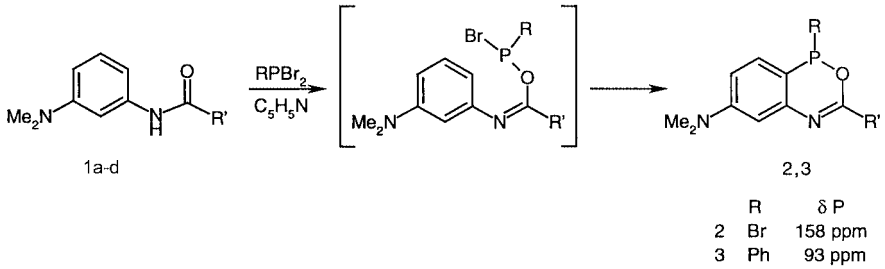
Though many methods of synthesis of aminoarylphosphonates are known, here we focus on a simple method that allows a wide range of substituents both in the amide substituents at the phosphorus, and in the acyl substituents at the 2-amino group of the benzene ring. The basis for this method is the non-catalyzed elecrophilic phosphorylation of N,N-dimethylaniline with phosphorus (III) halides.[5]

m-Acylaminodimethylanilines **1**[6] react with phosphorus (III) bromides forming the new phosphorus-containing fused heterocyclic system – 2,4,1-benzoxazaphosphinine **2, 3**. The first step, most plausibly, is the attack of the electrophilic reagent at the oxygen atom of the amide group[7] followed by heterocyclization at the C-nucleophilic centre[8] giving an energy favorable six-membered ring. The heterocyclization reaction in pyridine is complete at room temperature in 10 minutes.[9] After the reaction is complete the NMR ^{31}P spectrum exhibits one resonance peak. In the case of phosphorus tribromide the signal is at 158 ppm. Obtained in this way a solution of the benzoxazaphosphinine bromide **2** in pyridine can be utilized as a starting material to introduce new substituents on phosphorous.

Upon treatment with secondary amines benzoxazaphosphinine bromides **2** undergo a halogen substitution yielding amides **4** that can be oxidized e.g. with elemental sulfur or arylazides affording cyclic amides **5**[10] and **6** respectively. Thioamides **5** are stable to moisture in air, whereas iminoamides **6** are easily hydrolyzed.[11] In the presence of water the oxazaphosphine ring is opened resulting in high yields of mixed amides of 2,4-diaminophenylphosphonic acid **7**.[12]



Scheme 2



Scheme 1

Table 1 Yields and melting points of the 3-(dimethyamino)anilides **1a-d** and 1-amido-3-aryl(hetaryl)-6-(dimethylamino)-2,4,1λ^5-benzoxazaphosphinine-1-thioxides **5a-e**.

N	R'	R_2N	Yield (%) [a]	mp (°C) [b]
1a	4-ClC_6H_4-	-	**73**	**113-115**
1b		-	**88**	**135-136**
1c		-	**93**	**189**
1d		-	**68**	**136**
5a	4-ClC_6H_4-		**78**	**209**
5b		Et_2N	**76**	**145**
5c			**81**	**151**
5d		Et_2N	**79**	**167**
5e			**63**	**178**

[a] Yields refer to pure isolated products; [b] melting points are uncorrected.

Table 2 Yields and melting points of the 2-(acylamino)-4-(dimethylamino)phenylphosphonic acid amides **7a-g**.

7	R'	R_2N	Ar	Yield (%) [a]	mp (°C) [b]
a	4-ClC_6H_4-		4-$(O_2N)C_6H_4$-	**73**	**262**
b		Et_2N	3-$(CF_3)C_6H_4$-	**68**	**163**
c		Et_2N	4-$(CHF_2S)C_6H_4$-	**75**	**178**
d		Et_2N	2,4-$Br(CH_3)C_6H_3$-	**80**	**160-162**
e			4-$(O_2N)C_6H_4$-	**84**	**228**
f			3,4-$Cl(CH_3)C_6H_3$-	**71**	**203**
g			C_6H_5-	**74**	**177**

[a] Yields refer to pure isolated products; [b] melting points are uncorrected.

Besides the dimethylamino group other electron-donating groups can be utilized. Thus, as described, derivatives of 6-amino-1,2,3,3-tetramethyl-2,3-dihydro-5-indolylphosphonic acid **10** (Scheme 3) were synthesized in high yield.

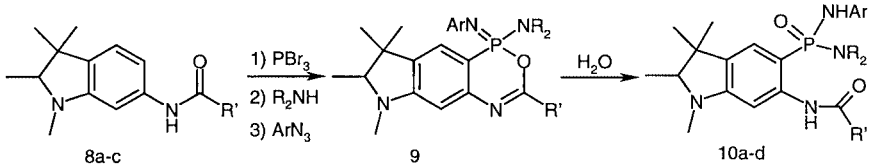
But activation of the benzene ring with alkoxy groups was effective only for 3,4,5-trimethoxyanilide **11** (Scheme 4), as a result compound **13** was obtained in low yield (16%).[13]

Table 3 Yields and melting points of the 6-(acylamino)-1,2,3,3-tetramethyl-2,3-dihydroindoles **8a-c** and 6-(acylamino)-1,2,3,3-tetramethyl-2,3-dihydro-5-indolylphosphonic acid amides **10a-d**.

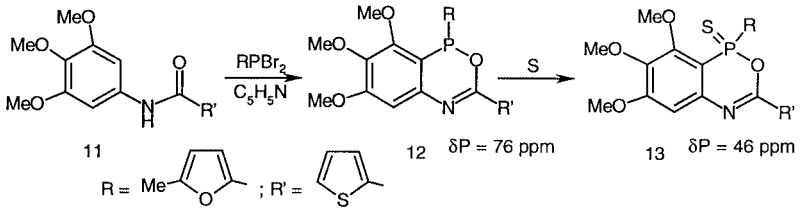
N	R'	R_2N	Ar	Yield (%) [a]	mp (°C) [b]
8a	3,4-$(CH_3O)_2C_6H_3$-	-	-	**92**	**168**
8b		-	-	**80**	**130**
8c		-	-	**89**	**190**
10a	3,4-$(CH_3O)_2C_6H_3$-		2-$(O_2N)C_6H_4$-	**77**	**128-129**
10b	3,4-$(CH_3O)_2C_6H_3$-		2-$(CF_3)C_6H_4$-	**78**	**166-167**
10c			3-$(CF_3)C_6H_4$-	**75**	**136-137**
10d			4-$(O_2N)C_6H_4$-	**82**	**176-177**

[a] Yields refer to pure isolated products; [b] melting points are uncorrected.

The structure of the new phosphorus (V) substances was confirmed by ^1H, ^{31}P and ^{13}C NMR spectroscopy. The absence of a signal for an amide proton[14] and a signal with a considerable coupling constant for C(8a) are the most convincing evidence for the formation of the oxazaphosphinine ring. For compound **5a** J_{CP} = 147 Hz.[15] The ^1H NMR spectra of aminoarylphosphonates **7**[16] and **10** are characterized by a doublet at δ = 6.3 – 6.6 with $^2J_{PNH}$ ~ 8.5 Hz and an amide signal at δ = 11 – 12.



Scheme 3



Scheme 4

Acknowledgement

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(9) Typical procedure: To a stirred solution 1.5 mmol of anilide **1** in 20 mL of dry pyridine 1.5 mmol phosphorus tribromide was added. After 10 min reaction mixture can be utilized for following transformations.
(10) Typical procedure: To a stirred solution **2** in pyridine[9] equimolar amounts of amine and elemental sulfur were added. After full dissolving of the sulfur pyridine was evaporated in vacuo. The residue was triturated with water and crystallized from 2-propyl alcohol.
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(12) Typical procedure: To a stirred solution **2** in pyridine[9] two-fold excess of amine and equimolar amount of arylazide were added. The mixture was maintained at 50 °C until the nitrogen evolution had stopped, and then pyridine was evaporated in vacuo. The residue was triturated with water and crystallized from 2-propyl alcohol.
(13) **13:** mp 164-166 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 2.3 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.42 (m, 1H, CH), 6.95 (d, 1H, ^3J = 5.7 Hz, CH), 7.22 (m, 1H, CH), 7.43 (s, 1H, CH), 7.76 (m, 1H, CH), 7.96 (d, 1H, ^3J = 3.8 Hz, CH).
(14) **5a:** ^{1}H NMR (300 MHz, $CDCl_3$): 3.07 (s, 6H, $N(CH_3)_2$), 3.28 (m, 4H, $N(CH_2)_2$), 3.58 (t, 4H, $O(CH_2)_2$), 6.7 (m, 2H, CH), 7.42 (d, 2H, ^3J = 8.5 Hz, CH), 7.6 (dd, 1H, $^3J_{PH}$ = 15.4Hz, ^3J = 8.5 Hz, CH), 8.15 (d, 2H, ^3J = 8.5 Hz, CH).
(15) **5a:** ^{13}C NMR (75 MHz, $CDCl_3$): 40 $N(CH_3)_2$, 45.1 NCH_2, 67.1 OCH_2, 104.1 ($^1J_{PC}$ = 147.2 Hz) C(8a), 109.4 ($^3J_{PC}$ = 9.1 Hz) C(7), 112.2 ($^3J_{PC}$ = 15.8) C(5), 128.7 °C', 129.6 ^{m}C', 130.5 ($^2J_{PC}$ = 11.8 Hz) C(8), 130.7 ($^3J_{PC}$ = 3.9 Hz) ^{ipso} C', 138.2 ^{p}C', 147 ($^4J_{PC}$ = 4.8 Hz) C(6), 151.8 ($^2J_{PC}$ = 12.1 Hz) C(4a), 154.1 ($^2J_{PC}$ = 2.8 Hz) C(3).
(16) **7a:** ^{1}H NMR (300 MHz, DMSO-d_6): 3.01 (s, 6H, $N(CH_3)_2$), 3.08 (m, 4H, $N(CH_2)_2$), 3.5 (m, 4H, $O(CH_2)_2$), 6.54 (d, 1H, $^2J_{PNH}$ = 8.7 Hz, PNH), 7.36 (m, 3H, CH), 7.67 (d, 2H, ^3J = 8.4 Hz, CH), 8.06 (d, 2H, ^3J = 8.4 Hz, CH), 8.14 (m, 3H, CH), 8.81(d, 1H, ^3J = 10.5 Hz, CH), 12.12 (s, 1H, NH).

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