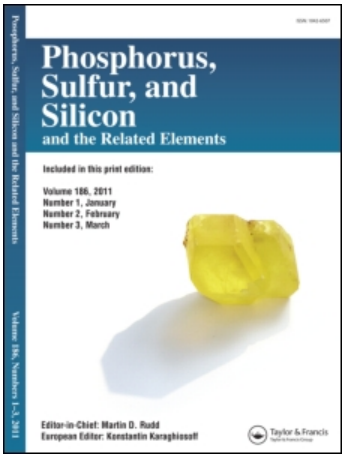

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Selective Monophosphorylation of Aliphatic Diamines

Marcos Costa de Souza[a]; William Pires de Macedo[a]; Thiago Silva Torres[a]; Leandro Ferreira Pedrosa[a]; Helmut G. Alt[b]

[a] Departamento de Química Orgânica, Universidade Federal Fluminense, Instituto de Química, Rio de Janeiro, Brazil [b] Universität Bayreuth, Laboratorium für Anorganische Chemie, Bayreuth, Germany

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Selective Monophosphorylation of Aliphatic Diamines

Marcos Costa de Souza
William Pires de Macedo
Thiago Silva Torres
Leandro Ferreira Pedrosa
Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Rio de Janeiro, Brazil

Helmut G. Alt
Universität Bayreuth, Laboratorium für Anorganische Chemie, Bayreuth, Germany

This article describes an improved method to synthesize phosphoramidic acid aminoalkyl esters from diamines by the adaptation of industrial patents. Four mono-phosphorylated products having amino sites were obtained in good a yield. Such compounds have potential coordination properties with transition metals and also potential biological activity.

Keywords Coordination chemistry; ligands; N-aminoalkyl phosphoramides; phosphoramidic acid; phosphorylation

INTRODUCTION

Esters of phosphoramidic acid [$H_2NP(O)(OH)_2$] have chelant properties with transition metals that make complexes with several applications, such as preventing corrosion of iron, steel, and ferrous alloys in oil wells and clarifying water containing suspended matter.[1–3]

The skeleton of phosphoramidic acid has also been found in many antiviral and antineoplastic agents associated with nucleoside units. As examples, the prodrugs Dextran-CM-EDA-P-araA **(1)** and polyglutamic

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Address correspondence to Marcos Costa de Souza, Universidade Federal Fluminense, Instituto de Química, Orgânica, Outeiro de São João Batista, s/n, Centro, Niterói, Rio de Janeiro, CEP 24020-150, Brazil. E-mail: gqomarc@vm.uff.br

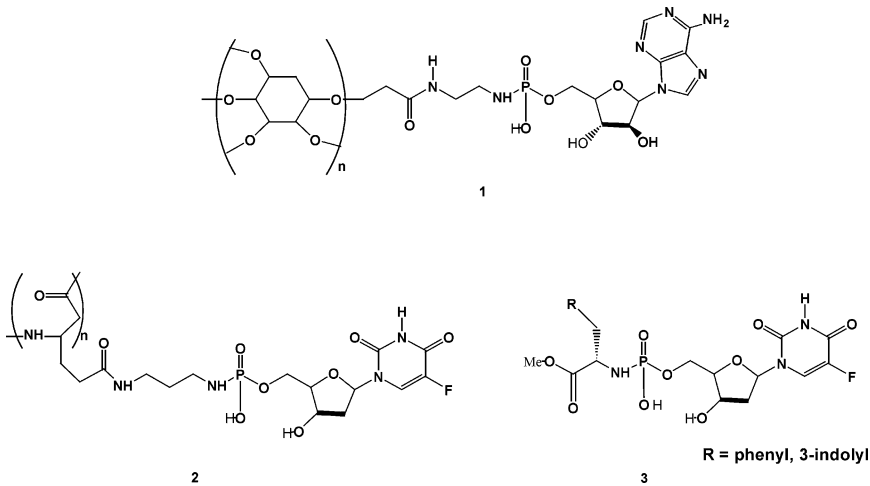


FIGURE 1 Examples of antiviral and antineoplastic agents derived from phosphoramidic acid.

acid-EDA-P-FUdR **(2)** were efficient inhibitors of viral replication and neoplastic cell proliferation in specific tests.[4] A series of phosphoramidate monoesters of 5-fluoro-2′-deoxyuridine (FUdR) **(3)** also showed inhibition growth of the human leukemia cell line CCRF-CEM in the presence of human prostatic acid phosphatase (hPAP)[5] (Figure 1).

The presence of a free nonprotonated -NH_2 group at the end of the alkyl chain in N-aminoalkyl derivatives of phosphoramidic acid **(4)** (Figure 2) affords many possibilities as building blocks in organic synthesis, such as the connection to heterocyclic systems and nucleoside analogues, or it even works as a potential electron-donating group to fix transition metals.

Conventional phosphorylation methods employ dialkyl phosphonate and two mole of the amine in a CCl_4 homogeneous medium.[6,7] From the two moles of amine used, one mole is inevitably lost as the corresponding hydrochloride unless it is substituted by one mole of a sufficiently strong base, e.g., NaOH or triethylamine. Alternatively,

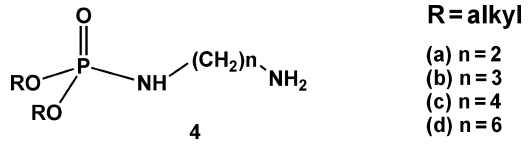


FIGURE 2 N-aminoalkyl derivatives of phosphoramidic acid.

Zhao's phosphorylation method, which employs an equimolecular mixture of dialkyl phosphonate, amine, and alkali in a biphasic H_2O/CCl_4 medium, has proven to be efficient.[8,9] Attempts to monophosphorylate diamines, however, result in the bis product preferentially, even when an equimolecular amount of amine is used. In the 1970s some industrial patents proposed a methodology in which diamines were phosphorylated once in a monophasic system using dialkyl phosphonate, carbon tetrachloride, or ethanol and diamine excess.[1–3] Nevertheless, reproduction of this methodology in our laboratory was unsuccessful, producing a non-resolvable mixture of bis-phosphorylated amine, monophosphorylated amine hydrochloride, and diamine hydrochloride.

In this article, a selective and reproducible method for the monophosphorylation of aliphatic diamines using diisopropyl phosphonate is described. Thus, the neutral ethylenediamine derivative (**4a; R = isopropyl**) was prepared as well as three new products of this series (**4b**, **4c** and **4d**) not found in the literature.

RESULTS AND DISCUSSION

More available ethylenediamine was firstly employed in our studies. Attempts to obtain the mono-phosphorylated product (**4a; R = isopropyl**) following the conventional biphasic methodology proposed by Zhao et al.[8,9] failed. Bis-phosphorylated diamine (**5a**) was obtained instead in a 47% yield (based on diamine), characterized by a melting point (78°C) and spectroscopic data that are in agreement with the literature[10] (Figure 3). Part of the unreacted diamine was recovered but the main fraction has gone with the washes with water. Similar results and yields were obtained with other diamines within this series.

Two different procedures describing the mono-phosphorylation of many diamines were found in industrial patents.[1–3] The main modification, comparing to Zhao's method, is the use of a solvent, such as ethanol, in place of an excess of carbon tetrachloride and the absence of alkali. Since HCl is given off in the reaction, in the case of monoamines, it is customary to employ 2 moles of the amine in order to consume it. In the case of polyamines, only one mole is employed since the product, being basic, will absorb HCl, as shown in Figure 4.

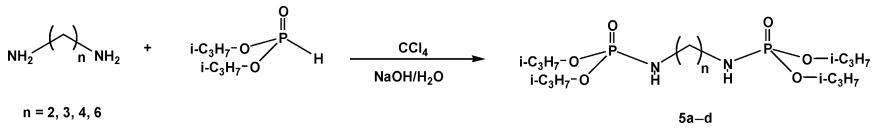
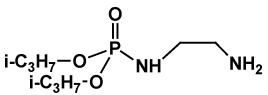
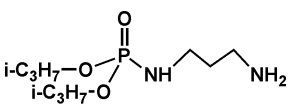
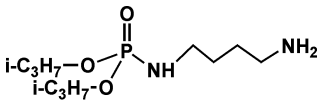
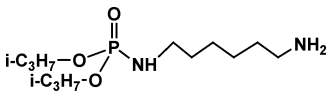


FIGURE 3 The phosphorylation of diamines using a biphasic system.

TABLE I Spectrometric Data of Diisopropyl N-Aminoalkyl Phosphoramidates 4a–d

Compound	IR (cm^{-1})[a]	MS m/z[b]	NMR (δ in ppm, J in Hz)[c]		
			^{31}P	^{1}H	^{13}C
 **4a**	989 ($\nu_{P\text{-}O}$) 1234 ($\nu_{P=O}$) 1640 (δ_{NH2}) 3321, 3345 (broad ν_{NH})	$C_8H_{22}N_2O_3P$ Calculated (M + 1) 225.13681 Found 225.13680	8.3	1.31, 1.32 (12H, 2d, CH_3, J_{HCCH} = 5.9) 2.15 (2H, s, NH_2 broad) 2.79 (2H, t, $\underline{CH_2}NH_2$, J_{HCCH} = 5.9) 2.96 (2H, m, $\underline{CH_2}NHP$) 3.38 (1H, dt, NH-P, J_{PNH} = 10.2, J_{HNCH} = 6.9) 4.65 (2H, dhep, HCO, J_{HCCH} = 5.9, J_{POCH} = 7.8)	24.0 (d, CH_3, J_{CCOP} = 4.6) 42.72 (d, CH_2CH_2NP, J_{CCNP} = 5.7) 43.84 (CH_2NP) 70.55 (d, CH, J_{COP} = 5.1)
 **4b**	980 ($\nu_{P\text{-}O}$) 1230 ($\nu_{P=O}$) 1645 (δ_{NH2}) 3240, 3340 (broad ν_{NH})	$C_9H_{23}N_2O_3P$ Calculated 238.14463 Found 238.14460	8.1	1.27, 1.30 (12H, 2d, CH_3, J_{HCCH} = 6.3) 1.60 (2H, quint, $CH_2\underline{CH_2}CH_2$, J_{HCCH} = 6.5) 1.76 (2H, s, NH_2, broad) 2.77 (2H, t, $\underline{CH_2}NH_2$, J_{HCCH} = 6.5) 3.00 (3H, m, $\underline{CH_2}NHP$, $CH_2\underline{NHP}$) 4.55 (2H, dhep, HCO, J_{HCCH} = 6.3, J_{POCH} = 7.5)	23.32 (d, CH_3, J_{CCOP} = 5.2) 34.18 (d, $CH_2\underline{CH_2}NP$, J_{CCNP} = 6,3) 38.80 (CH_2NP) 39.08 (CH_2NH_2) 69.98 (d, CH, J_{COP} = 6.0)

 **4c**	990 ($\nu_{P\text{-}O}$) 1230 ($\nu_{P=O}$) 1645 (δ_{NH2}) 3325, 3340 (broad ν_{NH})	$C_{10}H_{25}N_2O_3P$ Calculated 252.16028 Found 252.16030	8.0	1.31, 1.32 (12H, 2d, CH_3, J_{HCCH} = 6.0) 1.53 (4H, m, $\underline{CH_2}CH_2NP$, $\underline{CH_2}CH_2NH_2$) 2.02 (2H, broad s, NH_2) 2.72 (2H, t, $\underline{CH_2}NH_2$, J_{HCCH} = 6.6) 2.89 (3H, broad m, $\underline{CH_2}NHP$, $CH_2\underline{NHP}$) 4.58 (2H, dhep, HCO, J_{HCCH} = 5.9, J_{POCH} = 7.5)	23.39 (d, CH_3, J_{CCOP} = 5.1) 28.55 (d, $\underline{CH_2}CH_2NP$, J_{CCNP} = 6.5) 29.82 ($\underline{CH_2}CH_2NH_2$) 40.81 (CH_2NP) 41.10 (CH_2NH_2) 69.90 (d, CH, J_{COP} = 5.5)
 **4d**	980 ($\nu_{P\text{-}O}$) 1230 ($\nu_{P=O}$) 1650 (δ_{NH2}) 3225, 3340 (ν_{NH})	$C_{12}H_{29}N_2O_3P$ Calculated 280.19158 Found 280.19160	7.9	1.30, 1.32 (12H, 2d, CH_3, J_{HCCH} = 6.3) 1.36 [4H, m, $\underline{CH_2}(CH_2)_2NHP$, $CH_2(\underline{CH_2})_3NHP$] 1.49 (4H, m, $\underline{CH_2}CH_2NH_2$, CH_2CH_2NHP 2,87 (2H, broad m, CH_2NHP) 2.78 (1H, broad m, NHP) 2.71 (2H, t, $\underline{CH_2}NH_2$, J_{HCCH} = 7.2) 2.59 (2H, broad s, NH_2) 4.57 (2H, dhep, HCO, J_{HCCH} = 6.3, J_{POCH} = 7.5)	24.00 (d, CH_3, J_{CCOP} = 4.5) 26.67 and 26.69 [$\underline{CH_2}(CH_2)_3NH_2$ or $\underline{CH_2}(CH_2)_2NH_2$] 31.81 (d, $\underline{CH_2}CH_2NP$, J_{CCNP} = 6.2) 33,68 ($\underline{CH_2}CH_2NH_2$) 41.57 (CH_2NH_2) 42.17 (CH_2NP) 70.64 (d, CH, J_{COP} = 5.5)

[a] CH_2Cl_2 film/NaCl.
[b] EI-70eV, direct injection.
[c] $CDCl_3$/TMS or 85% H_3PO_4, 299.95 MHz (^1H), 75.42 MHz (^{13}C), 121.42 MHz (^{31}P).

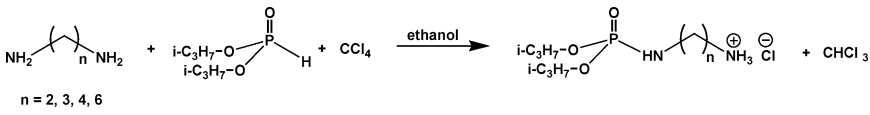
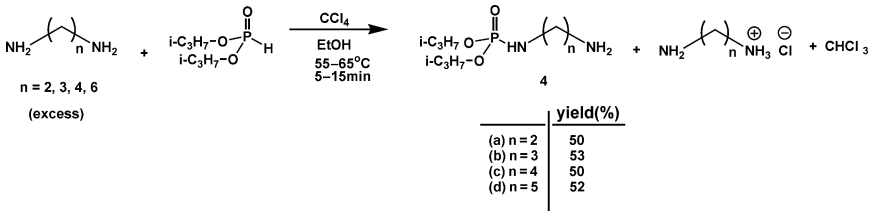


FIGURE 4 The phosphorylation of diamines using a monophasic system.

Using an excess of CCl_4, however, we obtained **5a** in a 40% yield and ethylenediamine hydrochloride as products. When ethanol was added, a trace of the desired mono-phosphorylated product (**4a**) was detected as its hydrochloride. Any attempt to isolate **4a** from the crude mass formed was unsuccessful. Alternatively, we employed the more reactive diisopropyl phosphorochloridate instead of diisopropyl phosphonate. Again, ethylenediamine hydrochloride and the bis-phosphorylated (**5a**) were the principal products, isolated in a 1:1 ratio. Considering the tendency to form bis-phosphorylated diamine, we tried in the sequence the use of excess of diamine. Among several experiments we found that a 2.5-fold excess must be employed in order to neutralize HCl and still keep a basic pH necessary to catalyze the reaction. Another point that was found to make a difference was the velocity by which the dialkyl phosphonate was dropped over the amine. The reaction is so exothermic that the temperature increases very fast, promoting bis-phosphorylation. Therefore, the addition of phosphonate should not exceed 10 min nor overtake the range 55–65°C. After the addition is complete, the mixture is stirred for an extra 5–15 min until no dialkyl phosphonate is detected by TLC. At this point, conventional methodology differs substantially because the procedure states that the reaction mixture must be under stirring for 2 h in most cases, inducing the course of the reaction to the bis product. Coupling these factors, we synthesized the neutral mono-phosphorylated product derived from ethylenediamine (**4a**) in a 50% yield. The final yield is moderate because of the number of washes with water in the workup needed to eliminate the diamine excess that impregnates the product. No considerable amount of bis-phosphorylated diamines was isolated



	yield(%)
(a) n = 2	50
(b) n = 3	53
(c) n = 4	50
(d) n = 5	52

FIGURE 5 Improved conditions for the mono-phosphorylation of diamines.

by using these improvements. The same methodology, when applied to 1,3-diaminopropane, 1,4-diaminobutane, and 1,6-diaminohexane, gave rise to the corresponding unpublished mono-phosphorylated products **4b**, **4c**, and **4d** in similar yields (Figure 5). This similarity has suggested to us that there should not exist a remarkable difference in the reactivity of diamines due to their chain length. The reaction is not limited to short-chain diamines but proceeds equally readily with 1,6-diaminohexane. Spectroscopic data are presented in Table I.

NH_2 stretching and NH_2 bending at 3300 cm^{-1} and 1640 cm^{-1} range are, respectively, diagnostic bands in the IR spectra for mono-phosphorylated diamines. Assignments of carbon and hydrogen by NMR were made with the aid of COSY and HETCOR experiments. For every compound (**4a**–**d**), NH and NH_2 hydrogen were assigned. The NH_2 signal was detected as a broad singlet in the range 1.76–2.59 ppm showing no coupling with the methylene group. On the other hand, NHP hydrogen showed coupling with phosphorus and the neighbor methylene group, giving rise to a doublet of a triplet around 3 ppm with coupling constants in the range 7 Hz (J_{HH}) and 10 Hz (J_{PH}). Curiously, we observed that in all cases phosphorus and carbon show coupling within the longer sequence PNCC, but no coupling was seen within the PNC sequence.

CONCLUSION

The mono-phosphorylation of aliphatic diamines was possible in a 50–53% yield of pure products after a delicate adaptation of conventional methods employing carbon tetrachloride and diisopropyl phosphonate as a phosphorylating agent. We found that at least a 2.5-fold excess of diamine must be used to neutralize HCl and still keep a basic pH necessary to catalyze the reaction. The addition of phosphonate to the amine should not exceed 10 min nor overtake the range 55–65°C; otherwise, bis-phosphorylation will occur preferentially. In this experiment, the terminal amino group in the alkyl chain is ready for complexation tests as well as to introduce the N-aminoalkyl phosphoramidate group in nucleoside substrates.

EXPERIMENTAL

General Remarks

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian UP-300 spectrometer at 299.95, 75.42, and 121.42 MHz, respectively, with TMS as an internal standard or 85% H_3PO_4 as an external standard. Signals

multiplicity was assigned as s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplet; and dhep, doublet of heptet. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer; high resolution mass spectra (EI-70eV) were recorded on a Varian MAT CH7 8500 direct inlet instrument; melting points are uncorrected. Solvents were fractionally distilled before use. Diisopropyl phosphonate was prepared as described in reference 11.

The General Procedure to Monophosphorylate Diamines (4a–d)

To a stirred solution containing 45 mmole of the appropriate diamine in ethanol (9 mL), 18 mmole of recently distilled diisopropyl phosphonate in carbon tetrachloride (4 mL) and ethanol (5 mL) were added. The temperature reached 55–65°C during the addition, which should not exceed 10 min. The mixture was stirred for an extra 5–15 min until no diisopropyl phosphonate was detected by TLC. The solution was evaporated under reduced pressure. Water (50 mL) was added to the residue, and the product was extracted twice with 20-mL portions of CH_2Cl_2; the extract was dried over $MgSO_4$ and evaporated giving an oily product of high purity. Additional washes with water can be performed if necessary.

(2-Aminoethyl) Phosphoramidic Acid Diisopropyl Ester (4a)

Pale yellow oil. Yield 2.02 g, 50%. Spectroscopic data are described in Table I.

(3-Aminopropyl) Phosphoramidic Acid Diisopropyl Ester (4b)

Colorless oil. Yield 2.27 g, 53%. Spectroscopic data are described in Table I.

(4-Aminobutyl) Phosphoramidic Acid Diisopropyl Ester (4c)

Colorless oil. Yield 2.27 g, 50%. Spectroscopic data are described in Table I.

(6-Aminohexyl) Phosphoramidic Acid Diisopropyl Ester (4d)

Colorless oil. Yield 2.62 g, 52%. Spectroscopic data are described in Table I.

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