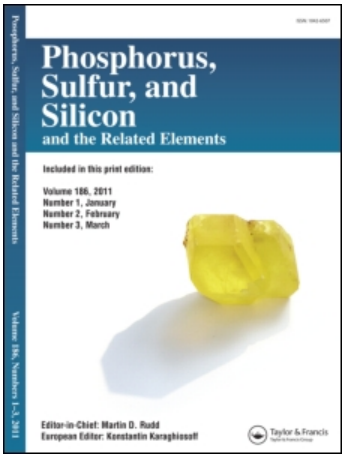

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ONE-POT SYNTHESIS OF N-ALKYL SUBSTITUTED PHOSPHORYL GUANIDINES

Marcos Costa de Souza, William Pires de Macedo,* Marcelo Campos M. da Silva,* Guilherme Costa de O. Ramos,* and Helmut G. Alt***
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This article describes an attractive and one-pot synthesis of the title compound by phosphorylation of just prepared N-substituted guanidines from cyanamide and the desired amine. The method allows a variety of N-substituents to hang on the final phosphoryl guanidine as a function of the wider availability of commercial simple amines.

Keywords: N-alkyl guanidines; phosphoramidic acid; phosphoryl guanidines

The well known system phosphoryl guanidine (**1**) has been investigated over the last 60 years, initially for its behavior as natural ligand in physiological medium. In this area, phosphoryl guanidines have proven to be efficient in the complexation[1] of ions such as Pb^{+2}, Ni^{+2}, Zn^{+2}, Cu^{+2}, Fe^{+3}, and Al^{+3}. Related studies showed that the P(O)N—C group serves as an oncolytic moiety against a sort of cancer as well as osteoporosis agent.[2] More specific application of phosphoryl guanidine derivatives is found in the new material field, giving rise to many industrial patents every year. (see Figure 1.)

Nevertheless, such studies are only related to a restrict set of N-substituted phosphoryl guanidines bearing few N-alkyl groups (R_2, R_3), which usually come from one of the two known methods to generate

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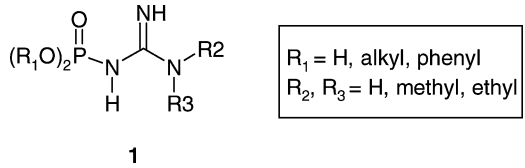
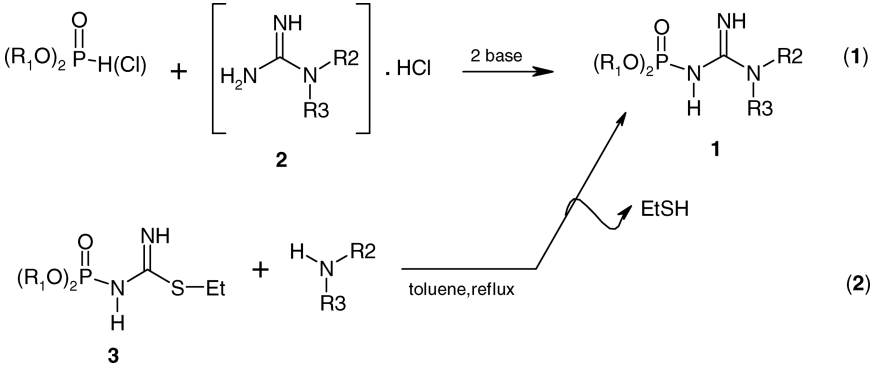


1

FIGURE 1 N-substituted phosphoryl guanidines.

1: the direct phosphorylation of scarcely available commercial N-substituted guanidines (**2**) (Eq. 1) or the addition-elimination reaction between amines and phosphoryl-S-ethyl isothioureas (**3**) (Eq. 2), sometimes disadvantageous because of the unpleasant mercaptan odor that impregnates the product.[3–7]

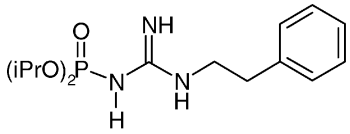


Herein we describe an attractive and one-pot synthesis of the title compound by phosphorylation of just prepared N-substituted guanidines from cyanamide and the desired amine. The method allows a variety of N-substituents to hang on the final phosphoryl guanidine as a function of the wider availability of commercial simple amines.

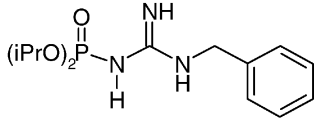
RESULTS AND DISCUSSION

Phosphorylation of amines easily can be accomplished by using the method of Zhao and Lin,[3] which consists on a two-phase reaction between dialkyl phosphonate and the amine in alkaline water-carbon tetrachloride medium. The same condition can be successfully employed for phosphorylation of commercial guanidines. There are only a few number of such commercial substituted guanidines, however, limiting the preparation of final phosphoryl guanidines bearing different substituents. In this paper we present preliminary results of an alternative

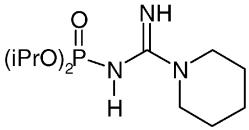
simple method to synthesize the N-alkyl substituted diisopropyl phosphoryl guanidines **1a–d** from simple aliphatic amines available in our laboratory.



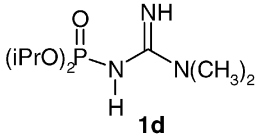
1a



1b



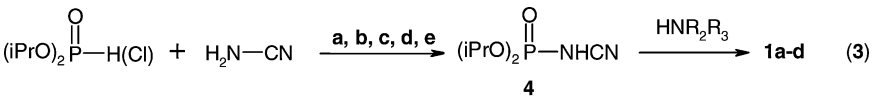
1c



1d

SCHEME 1 Phosphoryl guanidines prepared.

The first route we have investigated consists on the condensation of amines with diisopropyl cyanamidophosphonate (**4**). This was supposed to be a very versatile intermediate allowing a sort of aliphatic (and some aromatic) nucleophilic amines to react with, leading to the desired phosphoryl guanidine (Eq. 3)*. However, we were not able to prepare **4** even after changing the solvent, the base and the phosphorylating agent (entries a–e). Only polymerization products and unreacted cyanamide remained in the reaction bottle.

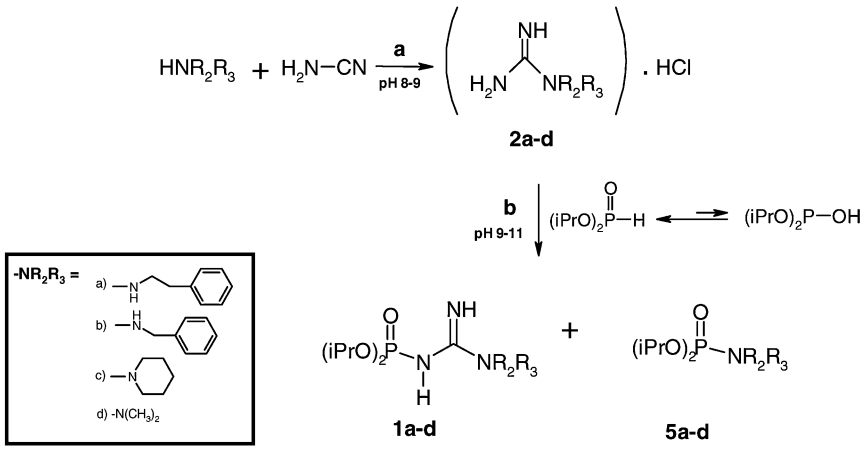


4

a) NEt_3/acetone; b) pyridine; c) pyridine/acetone; d) $NaOH/H_2O/CCl_4$; e) BuLi/THF.

In an alternative route we propose the synthesis of phosphoryl guanidines **1a–d** by direct phosphorylation of guanidine hydrochlorides using diisopropyl phosphonate in alkaline medium (Scheme 1). The guanidine hydrochlorides **2a–d** are prepared by condensing cyanamide with the desired amine in a buffered system (pH 8-9) consisting of amine/amine hydrochloride.

The whole process is strongly pH dependent. In the first step of the synthesis we found out that the best pH ranges between 8–9, so that the amine (HNR_2R_3) can act as a nucleophile toward the cyanamide carbon atom. In the next step phosphorylation must take place in alkaline basic medium in order to abstract the acidic hydrogen atom from



SCHEME 2 One-pot phosphorylation of guanidine hydrochlorides.

the diisopropyl phosphonate molecule and, at the same time, liberate the free guanidine from its salt form. Strong pH condition, however, decomposes the N-substituted guanidine into urea and the initial amine leading to simple phosphorylamine as the main product.

This methodology was preliminary tested with two primary amines (benzyl amine and 2-phenylethyl amine) and two secondary amines (dimethyl amine and piperidine). These amines provided the guanidine hydrochlorides **2a–d** as semi-solids which where employed directly in the phosphorylation step. Guanidines **2a** and **2b** were phosphorylated at pH 9 and 11, respectively, giving rise to phosphoryl guanidines **1a** and **1b** (Table I). Guanidine **2c** decomposes very easily at the pH range between 9-11 generating the phosphorylamine **5c** as the main product and a small and impure amount of phosphoryl guanidine **1c**. One reason for this behavior would be the sensitivity of N-heterocyclic guanidines under alkaline condition. Employing the N,N-acyclic dimethylguanidine **2d** in turn, the expected phosphoryl guanidine **1d** was obtained. Best result was reached at pH 11 showing that the corresponding guanidine resisted to strong alkaline medium.

Spectroscopic assignment of the products was carried out by infrared, mass, ^{31}P, ^{13}C, and ^{1}H-NMR techniques (Table II). Presence of C=N bond in both infrared and ^{13}C-NMR spectra as well as P=O bond indicated the formation of phosphoryl guanidines **1a**, **1b**, and **1d**. Very weak signals in the spectra showed that phosphoryl piperidine **5c** was preferentially formed instead of the corresponding phosphoryl guanidine

TABLE I Yield and Optimum pH in the Phosphorylation of the N-Substituted Guanidine Hydrochlorides **2a–d**

Product	Yield (%)	Optimum pH
1a	61	9
1b	31	11
1c	—	Not determined
1d	53	11

1c. Evidence for the formation of **1c**, however, was given by mass spectroscopy, showing the corresponding molecular pick and a fragmentation pattern similar to other guanidines.[7]

EXPERIMENTAL

^{1}H, ^{13}C, and ^{31}P-NMR spectra were recorded on a Varian UP-300 spectrometer (300 MHz) with TMS as internal standard or 85% H_3PO_4 as external standard; infrared spectra were recorded on a Perkin-Elmer spectrometer; mass spectra (EI-70 eV) were recorded on a VG Auto Spec instrument, GC column HP-5 (HP.ULTRA.2), ethyl acetate. Melting points are uncorrected. Solvents and amines were fractionally distilled before use. Diisopropyl phosphonate and diisopropyl chlorophosphonate were prepared as described in Lin et al.,[4] and McCombie et al.[8] The amine hydrochlorides were prepared by stirring stoichiometric amount of hydrochloric acid (37% aqueous solution) and the respective amine. After evaporation to dryness the salts were stored on a desiccator.

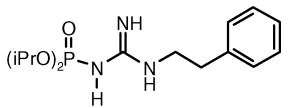
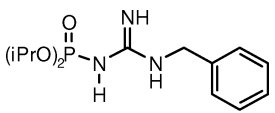
General Procedure to N-Substituted Guanidine Hydrochlorides 2a–d

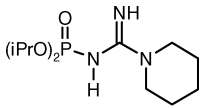
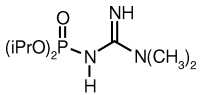
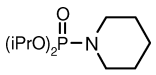
To a 1:1 mixture of cyanamide and the appropriate amine hydrochloride in water some drops of the corresponding amine is added until pH 8-9 is reached. The mixture is refluxed for 3.5 h keeping that pH by adding more amine if necessary. After cooling down to room temperature the mixture is acidified to pH 4 with hydrochloric acid. Water is removed under vacuum to give the guanidine salts as hygroscopic semi-solids which are ready to use in the following step.

General Procedure to N-Substituted Phosphoryl Guanidines 1a–d

To a stirred solution of crude guanidine hydrochloride (**2a–d**) and sodium hydroxide in water (15 ml) and ethanol (3 ml), recently distilled

TABLE II IR, MS, and NMR Data from **1a–d** and **5c**

Compound	IR (cm^{-1})[a]	MS m/z(%)[b,c]	NMR (δ in ppm, J in Hz)[d]		
			^{31}P	^{1}H	^{13}C
 **1a**	980 (ν_{P-O}) 1215 ($\nu_{P=O}$) 1560 (δ_{NH2}) 1618 ($\nu_{C=N}$) 3190, 3320, 3400 (broad ν_{NH})	327(65) $[M]^+$ 285(7) $[M\text{-}CH_3CH{=}CH_2]^+$ 243(3) $[285\text{-}CH_3CH{=}CH_2]^+$ 123(79) $[(HO)_2P(O)NH{-}C{\equiv}NH]^+$ 91(100) $[C_7H_7]^+$	−0.55	1.29, 1.31 (12H, 2d, CH_3, $J_{HCCH} = 6.2$) 2.50 [1H, broad m, $NH(CH_2)$] 2.80 (2H, m, CH_2—Ph) 3.14 (2H, m, CH_2—N) 3.44 (1H, broad m, NH=C) 4.53 (2H, dhep, HCO, $J_{HCCH} = 6.3$, $J_{POCH} = 7.8$) 5.90 (1H, broad s, NH—P) 7.26 (5H, m, Ph)	23.60, 23.71 (2d, CH_3, $J_{CCOP} = 4.0$) 37.68 (CH_2—Ph) 42.56 (CH_2—N) 70.56 (d, CH, $J_{COP} = 6.0$) 126.06–138.56 (Ph) 158.08 (d, C=N, $J_{CNP} = 8.1$)
 **1b**	980 (ν_{P-O}) 1210 ($\nu_{P=O}$) 1555 (δ_{NH2}) 1615 ($\nu_{C=N}$) 3200, 3390 (broad ν_{NH})	313(52) $[M]^+$ 271(14) $[M\text{-}CH_3CH{=}CH_2]^+$ 229(79) $[271\text{-}CH_3CH{=}CH_2]^+$ 123(23) $[(HO)_2P(O)NH{-}C{\equiv}NH]^+$ 91(100) $[C_7H_7]^+$	0.10	1.27, 1.32 (12H, 2d, CH_3, $J_{HCCH} = 6.3$) 2.87 [1H, broad m, $NH(CH_2)$] 4.07 (2H, m, CH_2) 4.60 (2H, dhep, HCO, $J_{HCCH} = 6.1$, $J_{POCH} = 7.5$) 6.12 (1H, broad s, NH=C) 6.54 (1H, broad s, NH—P) 7.30 (5H, m, Ph)	23.63 (d, CH_3, $J_{CCOP} = 5.0$) 45.26 (CH_2) 69.73 (d, CH, $J_{COP} = 4, 5$) 126.84–139.58 (Ph) 158.27 (d, C=N, $J_{CNP} = 8.5$)

 **1c**	—	291(10) $[M]^+$ 249(13) $[M\text{-}CH_3CH{=}CH_2]^+$ 207(9) $[249\text{-}CH_3CH{=}CH_2]^+$ 123(21) $[(HO)_2P(O)NH{-}C{\equiv}NH]^+$	—	—	—
 **1d**	980 (ν_{P-O}) 1240 ($\nu_{P=O}$) 1560 (δ_{NH_2}) 1645 ($\nu_{C=N}$) 3220, 3350 (ν_{NH})	251(70) $[M]^+$ 209(26) $[M\text{-}CH_3CH{=}CH_2]^+$ 167(87) $[209\text{-}CH_3CH{=}CH_2]^+$ 123(100) $[(HO)_2P(O)NH{-}C{\equiv}NH]^+$	2.33	1.30 (12H, d, CH_3, $J_{HCCH} = 6.0$) 2.98 [6H, s, $(CH_3)_2N$)] 4.52 (2H, dhep, HCO, $J_{HCCH} = 6.0$, $J_{POCH} = 8, 1$) 5.95 (2H, broad, NH)	23.71 (d, CH_3, $J_{CCOP} = 4.0$) 36.56, 36.81 $[N(CH_3)_2]$ 69.59 (d, CH, $J_{COP} = 6, 0$) 157.76 (d, C=N, $J_{CNP} = 9.5$)
 **5c**	975 (ν_{P-O}) 1240 ($\nu_{P=O}$)	249(34) $[M]^+$ 207(8) $[M\text{-}CH_3CH{=}CH_2]^+$ 165(45) $[207\text{-}CH_3CH{=}CH_2]^+$ 110 (22) $[(HO)_2P(O)NH{=}CH_2]^+$	−9.67	1.31, 1.29 (12H, 2d, CH_3, $J_{HCCH} = 5.7$) 1.53 [6H, m, $(C{-}CH_2{-}C)$] 3.06 (4H, m, $CH_2{-}N$) 4.53 (2H, dhep, HCO, $J_{HCCH} = 6.0$, $J_{POCH} = 7, 5$)	23.55, 23.60 (2d, CH_3, $J_{CCOP} = 4.0$) 24.34 ($CH_2{-}C{-}C{-}N$) 25.53 (d, $CH_2{-}C{-}N$, $J_{CCNP} = 5.5$) 45.27 (d, $CH_2{-}N$, $J_{CNP} = 2, 0$) 70.11 (d, CH, $J_{COP} = 6, 0$)

[a] CH_2Cl_2 film/NaCl.
[b] EI-70 eV.
[c] GC-MS column HP-5 (HP.ULTRA.2), ethyl acetate.
[d] $CDCl_3$/TMS or 85% H_3PO_4, 299.95 MHz (^1H), 75.42 MHz (^{13}C), 121.42 MHz (^{31}P).

diisopropyl phosphonate in carbon tetrachloride (15 ml) is added dropwise at 0°C. The mixture is then stirred at 65–75°C for 4.5 h keeping pH 9 or 11 by adding more sodium hydroxide if necessary. The two phases are decanted, the organic layer washed three times with water, dried with $MgSO_4$, and evaporated under reduced pressure to give the crude product.

1a. According to the general procedure, reaction of 4.48 g (0.022 mmol) of guanidine hydrochloride **2a**, 1.80 g (0.045 mmol) of sodium hydroxide (enough to keep pH 11), and 3.74 g (0.022 mmol) of diisopropyl phosphonate gave a yellow oil which was washed several times with brine to remove the persisting polar residues as showed by TLC. Such treatment gave a clear yellow oil in 61% yield.

1b. According to the general procedure, reaction of 4.30 g (0.030 mmol) of guanidine hydrochloride **2b**, 2.40 g (0.060 mmol) of sodium hydroxide (enough to keep pH 9), and 4.98 g (0.030 mmol) of diisopropyl phosphonate gave a yellow oil which was washed several times with brine to remove the persisting polar residues as showed by TLC. Such treatment gave a clear yellow oil in 31% yield.

1c. According to the general procedure, reaction of 3.27 g (0.020 mmol) of guanidine hydrochloride **2c**, 1.60 g (0.040 mmol) of sodium hydroxide (enough to keep pH 9, 10, and 11 in three experiences respectively), and 3.32 g (0.020 mmol) of diisopropyl phosphonate. Phosphoryl guanidine **5c** was obtained as the main product in all cases.

1d. According to the general procedure, reaction of 5.54 g (0.045 mmol) of guanidine hydrochloride **2d**, 3.60 g (0.090 mmol) of sodium hydroxide (enough to keep pH 11), and 7.48 g (0.045 mmol) of diisopropyl phosphonate gave a yellow oil which was boiled with active coal to generate a clear oil in 53% yield.

REFERENCES

[1] W. O. Lin, H. G. Alt, M. C. de Souza, J. B. N. da Costa, and C. N. Guimarães, *Phosphorus, Sulfur and Silicon*, **92,** 1 (1994).
[2] L. A. Cates and V. S. Li, *J. Pharm. Sci.*, **71**(3), 308 (1982).
[3] S. K. Xi, Y. F. Zhao, W. O. Lin, and M. C. de Souza, *Synth. Commun.*, **20**(21), 3295 (1990).
[4] W. O. Lin, M. C. de Souza, and J. B. N. da Costa, *Química Nova*, **18**(5), 431 (1995).
[5] Q. Wang, Y. Deng, W. Yu, et al., *Huaxue Shiji*, **19**(4), 230 (1997).
[6] M. C. de Souza, A. K. Ohara, D. R. Araripe, P. da C. V. Dias, and J. C. Kuwata, *Phosphorus, Sulfur and Silicon*, **148,** 143 (1999).
[7] W. O. Lin, H. G. Alt, M. C. de Souza, and L. de Amorim, *Phosphorus, Sulfur and Silicon*, **163,** 65 (2000).
[8] H. Mc Combie, B. G. Saunders, and G. J. Stacey, *J. Chem. Soc.*, **380** (1945).