Heteroatom Chemistry
Volume 7, Number 5, 1996

# Monophosphorylation of Ethylenediamine with Systems Generating Low-Coordination Phosphoryl Species

Gyongyi Szakal Quin* and Xiao-Ping Wu

*Department of Chemistry, Box 34510, University of Massachusetts, Amherst, MA 01003-4510*

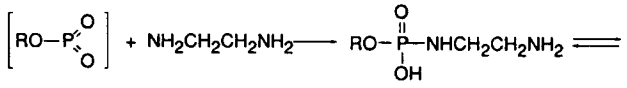
*Received 8 May 1996*

## ABSTRACT

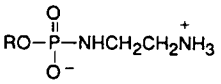
*Phenyldioxophosphorane was generated by thermal fragmentation of N-(1-adamantyl)phenylphosphonamidic acid in ethylenediamine to give a 61% yield of N-(2-aminoethyl)phenylphosphonamidic acid. The zwitterionic structure repressed reaction of the other amino group. Neopentyl metaphosphate and ethyl metaphosphate were generated in the presence of ethylenediamine by heating appropriate derivatives of the 2,3-oxaphosphabicyclo[2.2.2]octene system in toluene. Again, the metaphosphate phosphorylated only one amino group to give O-alkyl N-(2-aminoethyl)phosphoramidic acids, in zwitterionic form.* 

## *INTRODUCTION*

Earlier studies in this laboratory and elsewhere [1] on the generation of low-coordination phosphoryl compounds and their action as phosphorylating agents toward hydroxy groups have led us to recognize a feature of the use of such agents that offers a route to monophosphorylated derivatives of diamines. For example, the action of a nucleophile (Y–H) on a transient metaphosphate (**1**) leads to creation of a P–OH group; if the nucleophile is a diamine such as ethylenediamine, the acidic group in the product (**2**) could, in principle, proceed to protonate the second amino group, thereby protecting it from further attack by the metaphosphate.




**1** **2**




**3**

O-Alkyl derivatives of general structure **3** do not appear to be known, although some O-aryl derivatives [2] and N-(2-aminoethyl)phosphoramidic acid [3] itself have been reported. These phosphorylations were accomplished with aryl phosphorodichloridates or an aryl phosphate, respectively. An example of a phosphonate with a 2-aminoethylamino substituent was also prepared by the chloridate route; it was of biological interest in possessing some anticonvulsant activity [4]. In the latter study, the analogy to gamma-aminobutyric acid was pointed out. This activity added incentive to our exploration of the proposed new synthetic approach via metaphosphate chemistry.

Our methods also can produce the related transient dioxophosphorane structure (e.g., Ph–$PO_2$ [5]), which would provide N-(2-aminoethyl)phenylphosphonamidic acid (**4**) on reaction with ethyle-

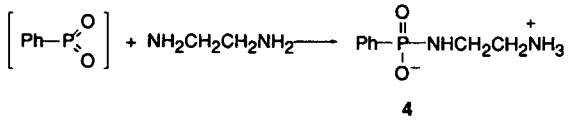
Dedicated to Professor Louis D. Quin on the occasion of his retirement from the University of Massachusetts at Amherst.

*To whom correspondence should be addressed.



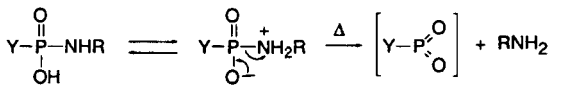
1042-7163/96/050295-04

nediamine, thus suggesting considerable breadth in the proposed new method. This phosphonamidic acid does not appear in the literature.

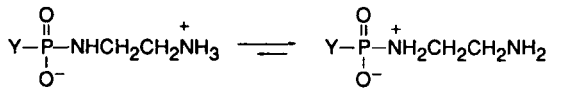


4

A further feature of interest in compounds 3 and 4 is a structural one, for they can be viewed also as monoalkyl esters of phosphoramidic acid and as a phosphonamidic acid, respectively; generally, such compounds are of low stability and are little studied. Their instability has, in fact, been exploited in recent work in this laboratory as a means of generating three-coordinate phosphoryl species [6].

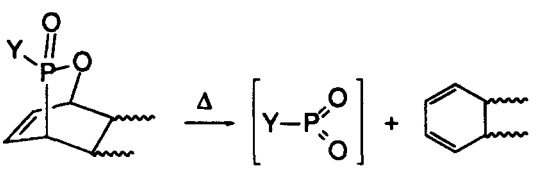


The zwitterionic character expected for compounds 3 on the basis of earlier observations [2] would appear to retard this mode of fragmentation; in this structure, the nitrogen attached to phosphorus is neutral and can only depart as a free amine if a proton transfer from the more basic terminal nitrogen takes place.



The most practical of the techniques devised in this laboratory for three-coordinate phosphoryl generation, in fact, depends on the thermal fragmentation of O-alkyl phosphoramidic or phosphonamidic acids when substituted on nitrogen by groups of high steric demand such as mesityl or l-adamantyl. With these groups, the reaction occurs by the desired elimination pathway, without complication from a bimolecular pathway [6]. The amidic acids are easily prepared by substitution reactions of $POCl_3$ or $PhPOCl_2$, respectively.

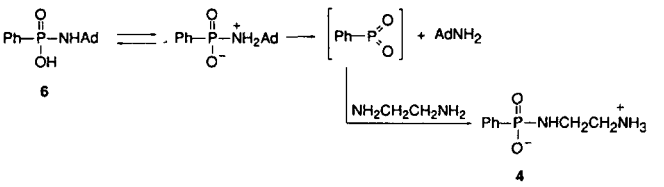
Our other method involves the thermal [7] or photochemical [8] fragmentation of derivatives of the 2,3-oxaphosphabicyclo[2.2.2]octene system. These reactions occur cleanly by unimolecular elimination of the phosphorus–oxygen bridge [9].



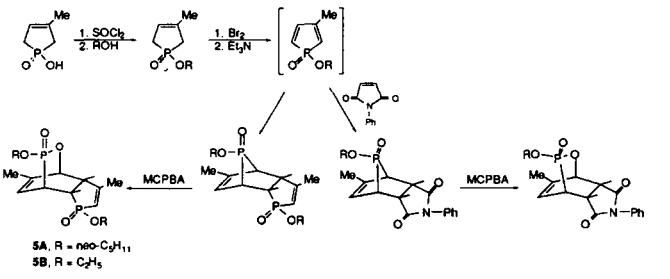
A disadvantage of the process is that several steps are required for the synthesis [7,10] of the starting material, as outlined in Scheme 1.

In this article, we report on a brief preliminary study to assess the possibility of synthesis of compounds of structure 3 and 4 by our methods of phosphorylation.

*Synthesis of N-(2-Aminoethyl)phenylphosphonamidic Acid.* This laboratory recently introduced the use of N-(1-adamantyl)phenylphosphonamidic acid (6) as a reagent for the generation of the highly reactive phenyldioxophosphorane [5]. Normally, reagent 6 is completely fragmented on being heated for brief periods in inert solvents; for example, in toluene, it has a half-life of 4.5 minutes at 64.5°C. However, when we attempted the fragmentation of 6 in toluene containing excess ethylenediamine at 100°C, little fragmentation occurred. The protective effect of salt formation on the phosphonamidic acid is therefore indicated. A solid that precipitated during the process appeared to be partly the ethylenediamine salt of 6($^{31}$P NMR $\delta$ 13.0 in $D_2O$) but gave a complicated $^1$H NMR spectrum. We then found that the desired reaction took place when it was conducted in ethylenediamine as solvent at 100°C. The reaction still was quite slow and required about 18 hours for completion. As before, material that precipitated appeared to be simply a salt of the starting material ($^{31}$P NMR $\delta$ 14.1 in $D_2O$); the main product was found in the solution, from which it was recovered by distillation of the excess diamine and trituration of the residue with acetone. The yield of 4 was 61%.



The solid had a $^{31}$P NMR shift of $\delta$ 17.5 ($D_2O$); a



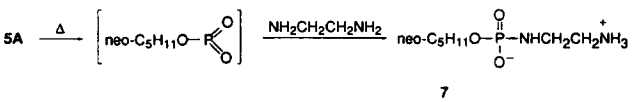
SCHEME 1

recrystallized sample gave an elemental analysis consistent with structure **4**, which was fully confirmed by the $^{13}C$ and $^{1}H$ NMR spectra. The former was especially indicative of the structure, in that it exhibited two different signals for the methylene carbons ($\delta$ 41.2 and 43.8). The downfield signal was split by $^{31}P$ coupling to a doublet with $J$ = 5.1 Hz. This coupling probably is for the carbon separated by three bonds from phosphorus, since this coupling is generally larger than two-bond coupling, but the assignment is tentative.

Since the starting phosphonamidic acid **6** is easily prepared in two steps from phenylphosphonic dichloride (displacement of Cl by adamantylamine, followed by basic hydrolysis and neutralization), the method presented here for the synthesis of the new compound **4** has practical value. The requirement for a large excess of ethylenediamine is not a detriment, since the excess is easily recovered by distillation. The use of polar solvents, rather than toluene, may have beneficial effects on the reaction; acetonitrile and tetrahydrofuran (THF) especially can be recommended in any further development of this phosphorylation technique.

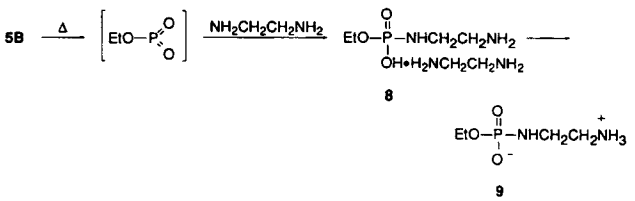
*Synthesis of O-Alkyl N-Substituted Phosphoramidic Acids.* The amidic acid fragmentation method that was successfully applied to the P-phenyl derivative **6** failed when used in the attempted synthesis of O-ethyl N-(2-aminoethyl)phosphoramidic acid. It was first noted that the fragmentation did not occur when conducted in toluene containing ethylenediamine, and with ethylenediamine as solvent, a different process involving loss of the ethyl group was encountered. This reaction has not been further studied. The synthesis of O-alkyl N-substituted phosphoramidic acids with the oxaphosphabicyclooctene fragmentation method was then explored. For this purpose, we employed the two compounds **5A** and **5B**, which are of a type we have found to be of value for small-scale testing of concepts of phosphorylation and in obtaining phosphorylated products in easily isolated form. These compounds serve as a source of neopentyl metaphosphate and ethyl metaphosphate, respectively.

Heating a mixture of **5A** and excess ethylenediamine in toluene at 110°C led to precipitation of a white solid. After 1.5 hours, all **5A** was consumed, as was determined by $^{31}P$ NMR spectroscopy. The precipitate had a shift of $\delta$ 12.0 ($D_2O$), as expected for an O-alkyl N-substituted phosphoramidic acid [6], and its water solubility and high melting point (269–270°C) indicated its zwitterionic character. The yield of crude product was 85.5%. The structure was confirmed as **7** by $^{13}C$ and $^{1}H$ NMR spectroscopy as well as by elemental analysis.



**7**

Similarly, compound **5B** was reacted with ethylenediamine, giving a precipitate with a $^{31}P$ NMR shift of $\delta$ 12.0. This product contained an additional mole of ethylenediamine, presumably as salt **8** according to the $^{13}C$ and $^{1}H$ NMR spectra. The amine was lost on recrystallization from methanol, giving the zwitterion **9**.



**8**

**9**

In neither case was there any indication of the formation of a diphosphorylated product, nor was any loss of the O-alkyl group detected.

## *CONCLUSIONS*

In this brief project, we have successfully shown that three-coordinate phosphoryl compounds can be used to perform monophosphorylation on ethylenediamine, leading to the synthesis of three simple but not previously described amidic acids. These compounds are quite stable, unlike structures that have alkyl rather than aminoalkyl N-substituents. Their stability is ascribed to the existence of the compounds in a zwitterionic form where the terminal nitrogen, rather than nitrogen attached to phosphorus, has the positive charge. This study has also revealed a new feature of the fragmentation chemistry of phosphonamidic and phosphoramidic acids, in that the presence of a base in the medium greatly retards the fragmentation. The base ethylenediamine removes a proton from the amidic acid, leaving an anion that is much more stable than the starting amidic acid. This renders the amidic acid fragmentation method of limited value for the phosphorylation of amines. To confirm this effect of an added base, an experiment was performed in which the fragmentation of O-ethyl N-mesityl phosphoramidic acid was attempted in the presence of triethylamine; as expected, no fragmentation was observed after 2 hours at 60°C in toluene; without $Et_3N$, the reaction was finished in 2 hours. This effect of base is entirely consistent with the mechanism pro-

posed for the fragmentation, which requires the presence of a proton on the nitrogen attached to phosphorus. It is possible that, in the formation of N-(2-aminoethyl)phenylphosphonamidic acid on prolonged heating of **6** in pure ethylenediamine, the mechanism no longer involves the normal elimination–addition but has shifted to direct displacement on phosphorus. No evidence bears on this point at this time. Regardless of mechanism, additional experimentation might show that other recoverable diamines can be monophosphorylated by this technique. Diamines higher than ethylenediamine failed to undergo useful phosphorylation when reacted with phosphorochloridates [2] and gave cyclic products, a problem that our monophosphorylation technique might circumvent by tying up the terminal amino group.

## *EXPERIMENTAL [11]*

*Synthesis of N-(2-Aminoethyl)phenylphosphonamidic acid* (**4**) *from Phosphonamidic Acid* **6**. A solution of 0.29 g (1.0 mmol) of N-(1-adamantyl)phenylphosphonamidic acid [5] (**6**; $^{31}$P NMR 20.3 in toluene) in 6 mL of anhydrous ethylenediamine was heated in a closed tube at 100°C for 18 hours. A white precipitate formed but gave a $^{31}$P NMR signal at $\delta$ 14.1 ($D_2O$) only for unreacted **6** as an ethylenediamine salt and was discarded. The filtrate was concentrated to dryness with a vacuum pump and the residual white solid (0.27 g) taken up in 30 mL of acetone. The insoluble material (**4**, 0.12 g, 61%) had $^{31}$P NMR ($D_2O$) $\delta$ 17.5; $^1$H NMR ($D_2O$) $\delta$ 3.0 and 3.1 (overlapping signals, -$CH_2CH_2$-), 7.5–7.9 (m, ArH); $^{13}$C NMR ($D_2O$) $\delta$ 41.2 (s, $C_2$ or $C_1$), 43.8 (d, $J_{PC}$ = 5.1 Hz, $C_1$ or $C_2$), 131–138 (Ar carbons). Anal. calcd for $C_8H_{13}N_2O_2P$: C, 47.97; H, 6.54; N, 13.99. Found: C, 47.41; H, 6.33; N, 13.67.

*Synthesis of O-Neopentyl N-(2-Aminoethyl)phosphoramidic Acid* (**7**) *with Bicyclic Compound* **5A**. A solution of **5A** [10] (351 mg, 0.84 mmol) and ethylenediamine (450 mg, 7.5 mmol) in 2 mL of dry toluene was heated at 110°C for 1.5 hours in a closed tube filled with nitrogen. Compound **7** precipitated as a white solid (151 mg, 85.5%). Recrystallization of this solid with water-acetone afforded plates with mp 269–270°C (dec); $^{31}$P NMR ($D_2O$) $\delta$ 12.0; $^{13}$C NMR ($D_2O$), $\delta$ 25.69 (s, $(\underline{C}H_3)_3C$); 31.26 (d, $J_{PC}$ = 7.9 Hz, $(CH_3)_3\underline{C}$), 38.64 (d, $J_{PC}$ = 5.4 Hz) and 41.1 (s) both -$CH_2$-$CH_2$, 74.89 (d, $J_{PC}$ = 5.9 Hz, $\underline{C}H_2CMe_3$); $^1$H NMR ($D_2O$) $\delta$ 0.73 (s, $C(\underline{C}H_3)_3$), 2.83–2.89 (m, -$CH_2$-$CH_2$), 3.27 (d, $^3J_{PH}$ = 4.9, 2H, -$\underline{C}H_2CMe_3$). Anal. calcd for $C_7H_{19}N_2O_3P$: C, 40.00; H, 9.05; N, 13.33. Found: C, 39.88; H, 8.89; N, 13.28.

*Synthesis of O-Ethyl N-(2-Aminoethyl)phosphoramidic Acid* (**9**) *with Bicyclic Compound* **5B**. A mixture of **5B** [7] (216 mg, 0.67 mmol) and ethylenediamine (360 mg, 6.0 mmol) in 1.5 mL of dry toluene was heated in a sealed tube filled with nitrogen at 110°C for 1.5 hours. The cooled mixture was filtered, and 190 mg of a yellowish solid **8** [$^1$H NMR ($D_2O$) $\delta$ 1.01 (t, $^3J_{HH}$ = 7.1 Hz, 3H, C–$CH_3$), 2.68 (s, 4H, $NH_2CH_2CH_2NH_2$), 2.60–2.90 (m, 4H, $NHCH_2CH_2NH_2$), 3.62 (quintet, $^3J_{PH}$ = $^3J_{HH}$ = 7.1 Hz, 2H, $OCH_2$)] was obtained. Recrystallization with methanol afforded granular crystals of **9**, $^{31}$P NMR ($D_2O$) $\delta$ 12.0; $^1$H NMR ($D_2O$) $\delta$ 1.05 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_3$), 2.80–3.00 (m, 4H, -$CH_2CH_2$-), 3.70 (quintet, $^3J_{PH}$ = $^3J_{HH}$ = 7.1 Hz, $OCH_2$); $^{13}$C NMR ($D_20$) $\delta$ 18.80 (d, $J_{PC}$ = 7.1 Hz, $CH_3$), 41.67 (d, $J_{PC}$ = 5.6 Hz) and 44.63 (s), both -$CH_2CH_2$-, 64.28 (d, $J_{PC}$ = 6.3 Hz, $OCH_2$).

## *ACKNOWLEDGMENT*

As members of Professor Louis D. Quin's research group, we would like to express our thanks to him for helping us learn the intricacies of phosphorus chemistry, while investigating a wide range of compounds in a logical scientific way.

## *REFERENCES*

[1] For a review, see: L. D. Quin, *Coordination Chem. Rev., 137,* 1994, 525.
[2] R. S. Edmundson, *J. Chem. Soc. (C), 2730,* 1969.
[3] J. Gloede, H. Gross, *J. Prakt. Chem., 312,* 1970, 326.
[4] L. A. Cates, V.-S. Li, C. C. Yakshe, M. O. Fadeyi, T. H. Andree, E. W. Karbon, S. J. Enna, *J. Med. Chem., 27,* 184, 654.
[5] G. S. Quin, S. Jankowski, L. D. Quin, *Phosphorus, Sulfur and Silicon,* in press.
[6] S. Jankowski, L. D. Quin, *J. Org. Chem., 59,* 1994, 4402.
[7] L. D. Quin, B. G. Marsi, *J. Am. Chem. Soc., 107,* 1983, 3389.
[8] L. D. Quin, B. Pete, J. Szewczyk, A. N. Hughes, *Tetrahedron Lett., 29,* 1988, 2627.
[9] S. Jankowski, L. D. Quin, *J. Am. Chem. Soc., 113,* 1991, 7011.
[10] L. D. Quin, X.-P. Wu, N. D. Sadanani, I. Lukes, A. S. Ionkin, R. O. Day, *J. Org. Chem., 59,* 1994, 120.
[11] Solvents were carefully dried by conventional methods, and glassware was flame-dried before use. All phosphorus starting materials were available from earlier studies, as referenced.