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ADDITION OF AMINE NUCLEOPHILES TO DIPHOSPHORYLALKYNES. THE CHEMISTRY OF THE DERIVED ENAMINES

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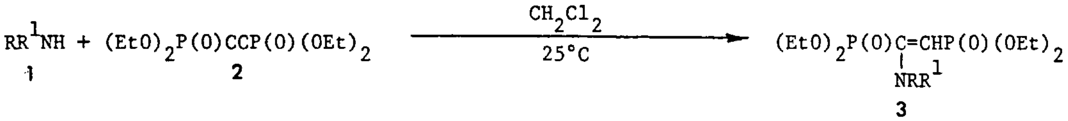
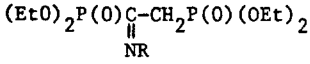
Abstract: Amine nucleophiles bearing at least one hydrogen substituent add across tetraethyl ethynyldiphosphonate to give enamine derivatives, one of which (derived from cyclohexylamine) has been evaluated as an imine anion precursor in alkylations and Wittig-Horner-Emmons types of reactions.

We would like to report the synthesis and characterization of several members of a novel class of enamines 3, and to elucidate the synthetic potential of some of such species. Reaction of various amine nucleophiles 1 with tetraethyl ethynyldiphosphonate 2[1,2], at room temperature in dichloromethane gave 3 in high yields (Table I).

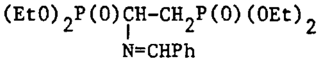


$$\underset{\mathbf{1}}{RR^1NH} + \underset{\mathbf{2}}{(EtO)_2P(O)CCP(O)(OEt)_2} \xrightarrow[25°C]{CH_2Cl_2} \underset{\mathbf{3}}{(EtO)_2P(O)\underset{NRR^1}{C}=CHP(O)(OEt)_2}$$



$$(EtO)_2P(O)\underset{NR}{\overset{\|}{C}}-CH_2P(O)(OEt)_2$$

4



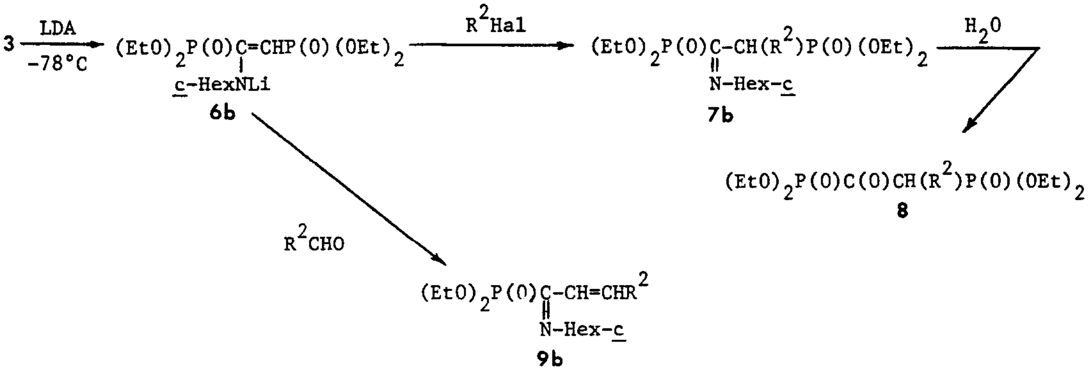
$$(EtO)_2P(O)\underset{N=CHPh}{CH}-CH_2P(O)(OEt)_2$$

5

Depending upon the nature of R and R^1, products 4 or 5 might be obtained ultimately. Thus with R^1=H and R=NH_2 or OH, the addition reaction was extremely rapid and 4 was obtained.

In the case of benzylamine (1, R^1=H, R=CH_2Ph), 3 is isolable, but very easily (trace of acid or heat) tautomerizes to 5.[3,4]

Species 3 (R^1=H, R=Me,c-Hex) may be utilized as imine anion precursors.[5] Thus treatment of 3 with LDA in THF at -78°C to give **6b**, followed by alkylation with methyl iodide gave **7b** (R^2=Me)[3] in 94% yield, which was hydrolyzed to 8 (71%, tautomeric mixture).[3] Similar chemistry was observed with allyl and benzyl bromide as alkylating agents in place of methyl iodide.[6]



Imine anion **6b** upon treatment with aldehydes gave high yields of 1-azadienes (**9b**)[7] in a Wittig-Horner-Emmons type of reaction.[8] The reaction failed when acetone, acetophenone and benzophenone were used as electrophiles, but cyclohexanone gave the corresponding 1-azadiene in 75% yield.

In summary, species 3 (R=H) are precursors to imine anions which can be alkylated or reacted with aldehydes and cyclohexanone. The products 7 and 9 are precursors to derivatives of α-aminoalkylphosphonic acids which have attracted some interest as biologically active compounds.[9] We are continuing our investigation of these and related species.

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References and Notes.

1. (a) Ionin, B.I.; Petrov, A.A. *J. Gen. Chem. USSR* **1965**, *35*, 1910. (b) Our yields of **2** are considerably higher than those reported by Ionin and Petrov, see: Kyba, E.P.; Rines, S.P.; Owens, P.W.; Chou, S.-S.P. *Tetrahedron Lett.* **1981**, *22*, 1875.
2. Although this communication deals only with species derived from **1**, other, more highly functionalized phosphorylalkynes behave analogously.
3. All spectroscopic and analytical properties were in accord with the assigned structures.
4. In the case of the methylamine adduct **3** (R^1 = H, R = Me), for example, the ^1H NMR spectrum featured a doublet of quartets at δ7.1 (N$\underline{H}$, $^3J_{P-H}$ = 33 Hz, $^3J_{H-H}$ = 5Hz) and a doublet at 3.0 ppm(N-C$\underline{H}_3$, $^3J_{H-H}$ = 5Hz); the former disappears and the latter collapses to a singlet upon addition of D_2O (the exchange is slow, *ca.* 15h).
5. Whitesell, J.K.; Whitesell, M.A. *Synthesis* **1983**, 0000.
6. Compounds prepared, yields (^{31}P NMR in $CDCl_3$): **7b** (R^2 = Me), 94%, two isomers, 4:1 ratio [major isomer, +26.7(d, J = 19 Hz), +1.7(d, J = 19 Hz); minor isomer, +25.0(d, J = 13 Hz), +5.3 ppm(d, J = 13 Hz)]; **7b**(R^2 = allyl), 90%; two isomers, 3:2 ratio [minor isomer, +27.7(d, J = 7 Hz), +0.1 ppm(d, J = 7Hz), major isomer, +25.2(d, J = 13 Hz), +1.6 ppm(d, J = 13 Hz)]; **7b** (R^2 = benzyl), 98%, two isomers, 2:3 ratio [major isomer, +27.3(d, J = 6 Hz), -0.3 ppm(d, J = 6 Hz); minor isomer, +25.0(d, J = 11 Hz), +1.7 ppm(d, J = 11 Hz)].
7. Compounds prepared, yields (^{31}P NMR in $CDCl_3$): **9b** (R^2 = *i*-Pr), 68% (+7.58 ppm); **9b** (R^2 = *t*-Bu), 94% (+7.56 ppm); **9b** (R^2 = Ph), 81% (+7.18 ppm).
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Table. Yields and ^{31}P NMR Data^{a} for the Production of Compounds **3** and **4**

	3a	**3b**	**3c**	**4d**^{b}	**3e**	**4f**^{c}
R,R^{1}	H,Me	H,c-Hex	H,Ch$_2$Ph	R=NH$_2$	(CH$_2$)$_4$	R=OH
Yield	93%	93%	100	100	100	85
^{31}P NMR: δ(ppm)	+16.7	+17.14	+16.4	+17.3	+16.7	+15.35
J_{AB}(ppm)	2.7	2.7	2.6	0.50	2.5	0.28
ν_{AB}(ppm)	11.7	11.3	11.3	12.7	8.6	13.4

[a] Spectra determined on _ca_. 0.1_M_ solutions in CDCl$_3$ at 32.2MHz and ambient temperature.

[b] Only the hydrazone tautomer observed.

[c] Only the oxime tautomer observed.

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