Organic Compounds of Phosphorus; XII[1]. Ammonium Acetate/Acetic Acid, A Reagent for the Direct Heterocyclization of Bis- and Tris[1-alkynyl]-phosphine Oxides

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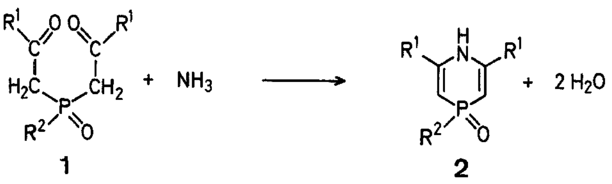
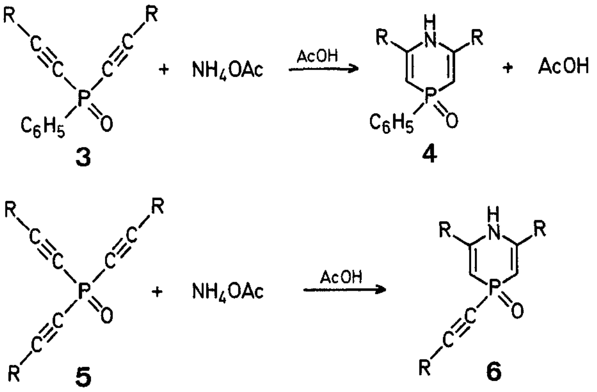
Bis[2-oxoalkyl]-phosphine oxides of the type **1** (R^1, $R^2 \neq H$) are starting materials for the synthesis of 2,4,6-trisubstituted 4-oxo-1,4-dihydro-P^V-1,4-azaphosphorins (**2**). The cyclocondensation of **1** with ammonia can be carried out using either fused ammonium carbonate[2,3] or ammonium acetate in acetic acid[4] as the source of ammonia.



The diketones **1** are obtained by direct or indirect hydration of tertiary bis[1-alkynyl]-phosphine oxides[2,3,5]. In the case of tris[1-alkynyl]-phosphine oxides, however, one alkynyl group is eliminated during hydration.

We report here a new method by which bis[1-alkynyl]-phenylphosphine oxides (**3**) and tris[1-alkynyl]-phosphine oxides (**5**) can be directly converted into 2,6-disubstituted 4-oxo-4-phenyl- (**4**) or 4-(1-alkynyl)-4-oxo-1,4-dihydro-P^V-1,4-azaphosphorins (**6**), respectively. It should be noted that the 1-alkynyl group is retained in the formation of **6**. The reaction is a [5+1]-cycloaddition, the source of ammonia being ammonium acetate in acetic acid.



The reaction medium consists of acetic acid containing 15–20% ammonium acetate hydrate. This solution is used in excess relative to **3** or **5**. With anhydrous ammonium acetate in acetic acid, the yields obtained are considerably lower.

In summary, our method has the following advantages:

- the ammonium acetate/acetic acid system serves as reagent and as solvent for both the starting materials **3** or **5** and the products **4** and **6**;
- the acid medium can protonate the O-atom and thus make the P-atom more positive and the triple bond more electrophilic; this should facilitate the attack of ammonia and the subsequent cyclization of the enamine or imine intermediate;
- ammonia is formed from the ammonium acetate in spite of an unfavorable equilibrium due to the presence of acetic acid.
- tris[1-alkynyl]-phosphine oxides (**5**) undergo the cyclization reaction with one 1-alkynyl group remaining unaffected.
- The yields of compounds **4** are good. Thus, compound **4b** is obtained in 83% yield whereas Aguiar et al.[2] reported an overall yield of 40% for their three-step synthesis of **4b** and we obtained **4b** in 51% by our previous three-step procedure[4,5].

The existence of a triple bond in compounds **6** seems to indicate that the heterocyclic ring stabilizes this acetylenic group since the third triple bond of Compounda **5** remains intact when compounds **6** are formed in spite of the presence of water and acetic acid. Polyphosphoric and sulfuric acids[5] react with phenylethynylphosphine oxide which suggests that in our reaction also direct addition of ammonia takes place. Direct addition of amines to mono- and bis-acetylenic phosphine oxides has been described[2,3,6-10]. The formation of heterocycles from certain phosphine oxides of the type **3** and ethanamine under conditions quite different from ours has previously been reported[11].

Table. 2,4,6-Trisubstituted 4-Oxo-1,4-dihydro-P^V-1,4-azaphosphorins (**4**, **6**)

Product	R	Yield [%]	m.p. (from solvent)	Molecular formula[a]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$)		
						$\delta_{P-CH=}$	J_{P-C-H}	$J_{NH-C=CH}$ [Hz]
4a	CH_3	68	334–336° (ethanol/water)	$C_{12}H_{14}NOP$ (219.2)	3280, 3180, 1610, 1135	5.10	6	—
4b	C_6H_5	83	314–315°[2,3,4] (ethanol/water)	$C_{22}H_{18}NOP$ (343.4)	3140, 1600, 1150	5.50	5.5	2
4c	t-C_4H_9	72	277–278°[2,3] (chloroform/cyclohexane)	$C_{18}H_{26}NOP$ (303.4)	3270, 3180, 1600, 1150	5.20	5	2
6a	CH_3	40	281–282° (chloroform)	$C_9H_{12}NOP$ (181.2)	3370, 3140, 2200, 1610	4.97	5	—
6b	C_6H_5	57	276–277° (chloroform/cyclohexane)	$C_{24}H_{18}NOP$ (367.4)	3130, 2180, 1600, 1140	5.70	4	2

[a] All products **4** and **6** gave satisfactory microanalyses: C, ±0.65; H, ±0.08; N, ±0.06; P, ±0.30.

The phosphine oxides **3** and **5** were prepared according to Ref.[6]; yield: 85–90%:

3a ($R = CH_3$); m.p. 90° (chloroform/hexane).
3b ($R = C_6H_5$); m.p. 150.5° (acetone).
3c ($R = t$-C_4H_9); oil; M.S.: $m/e = 286$ (M^+), 271, 244, 131.
5a ($R = CH_3$); m.p. 186° (chloroform/acetone).
5b ($R = C_6H_5$); m.p. 123–124° (benzene/hexane).

2,4,6-Trisubstituted 4-Oxo-1,4-dihydro-P^V-1,4-azaphosphorins (4, 6); General Procedure:

The bis- or tris[1-alkynyl]-phosphine oxide (**3** or **5**; 0.01 mol) is dissolved in glacial acetic acid (20 ml). Ammonium acetate hydrate (4–5 g) is added and the mixture is refluxed for 120–150 h. The acetic acid is then evaporated under reduced pressure and the residue treated with water (20–30 ml). The insoluble product is isolated by filtration or extracted with chloroform (and the extract evaporated). The product may be purified by recrystallization or chromatography over silica gel.

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