Oxo-phospholes from the Alkoxyphosphonium Ylides formed in the Reaction of Trialkyl Phosphites or Dialkyl Phosphonites with Dimethyl Acetylenedicarboxylate

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The cyclic ylides (3), formed by the reaction of trialkyl phosphites or dialkyl phosphonites with 2 mol equiv. of dimethyl acetylenedicarboxylate, undergo protonation and dealkylation in the presence of hydrogen bromide to give the 1-substituted 2,5-dihydrophosphole 1-oxides (4). The phospholes (4) undergo ready elimination of a molecule of alcohol on being heated to give the phosphole 1-oxides (5).

We have previously reported that the reaction between trimethyl phosphite and dimethyl acetylenedicarboxylate can be diverted from its normal reaction pathway (Scheme; R = Me, R' = OMe) to give the novel 4-co-ordinate phosphole (5; R' = OMe).[1] This was achieved by carrying out the reaction at
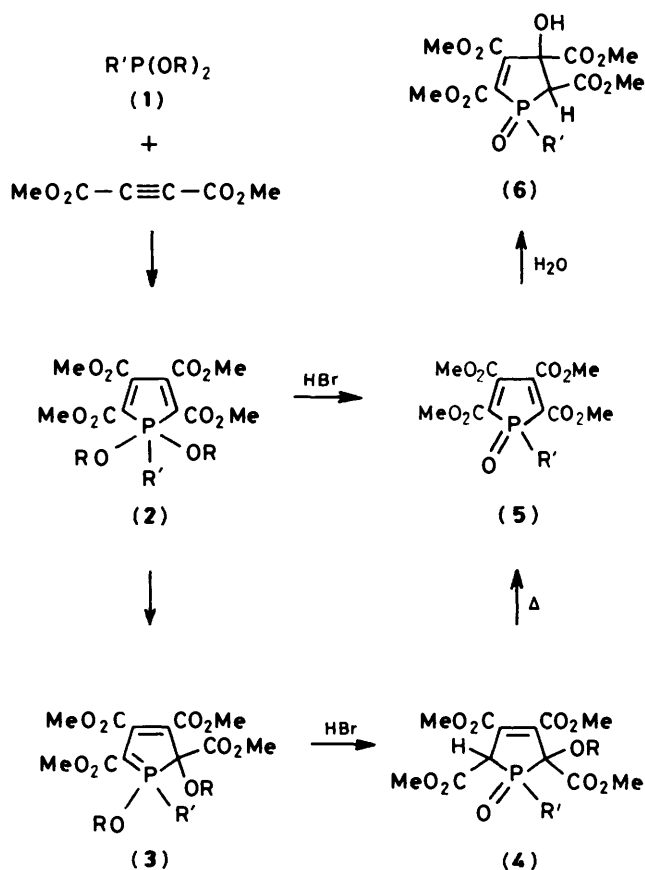
Scheme.

low temperature so that the 5-co-ordinate phosphole intermediate (2; R = Me, R' = OMe) could be trapped by the addition of hydrogen bromide before it could rearrange to the cyclic ylide (3; R = Me, R' = OMe). We have also shown[2] that it is possible to extend this approach to produce the phosphole

1-oxide (5; R' = Ph) by replacing the trialkyl phosphite by a dialkyl phenylphosphonite (1; R = Me or Et, R' = Ph). As expected, the intermediates (2; R' = Ar) were less stable than those arising from the trimethyl phosphite reaction and this made the trapping of the 5-co-ordinate phosphole intermediate (2; R = Me or Et, R' = Ph) more difficult to carry out. This resulted in a lower yield of the phosphole 1-oxide (5; R' = Ph) than has been obtained for (5; R' = OR). Attempts to use the same approach to prepare (5; R = Me), from dimethyl acetylenedicarboxylate and dimethyl methylphosphonite, were even less successful owing to the reduced stability of the 5-co-ordinate phosphole intermediate (2; R = R' = Me). Although it could be demonstrated that this intermediate could be converted to the desired phosphole 1-oxide (5; R' = Me) on being treated with anhydrous hydrogen bromide, it was not possible to generate this intermediate cleanly and in sufficient quantities to make the preparation of (5; R' = Me) by this route a practical proposition.

We now report an alternative, more convenient route for the production of both the phosphole 1-oxides (5; R' = OR) and those derived from the dialkyl phosphonites, namely (5; R' = alkyl and aryl), based on the corresponding cyclic ylides (3).

During our investigation of the reaction of dialkyl phosphonites with dimethyl acetylenedicarboxylate we noted that the intermediates (2; R = Et, R' = Me) and (2; R = Et, R' = Ph) rearranged to give the cyclic ylides (3; R = Et, R' = Me) and (3; R = Et, R' = Ph), respectively, rather than those in which the alkyl and aryl groups migrated. This is contrary to the conclusions drawn from a study of some tervalent phospholes[3] which suggested that the phenyl group had a much higher migratory aptitude than that of the alkoxy group. In the five-co-ordinate phosphole (2; R = Et or Me, R' = Ph) where there is a direct comparison of the migratory behaviour of a phenyl and an alkoxy group, this is clearly not the case.

Since the alkyl and aryl groups remained attached to the phosphorus atom after rearrangement we investigated whether these cyclic ylides might prove to be suitable precursors for the formation of the desired phosphole 1-oxides (5; R' = alkyl) and (5; R' = aryl). It was hoped that protonation and dealkylation of the cyclic ylides (3) would give the 2,5-dihydrophospholes (4) which could then, in theory, give the desired phosphole 1-oxides (5) by elimination of a molecule of alcohol.

The cyclic ylides (3; R = alkyl, R' = alkoxy), prepared by the reaction of trialkyl phosphites with a two molar equivalent of dimethyl acetylenedicarboxylate, were the first studied.

Table.

δ_C ^{a}	(5; R' = OPr^i)	(5; R' = Me)	(3; R = Et, R' = OEt)	(3; R = Pr^i, R' = OPr^i)	(3; R = R' = Me)
C-2	127.91(125)^b	132.21(87)^b	65.1(139)^{b,c}	66.52(139)^d	65.81(109)^d
C-3	143.88(28)	144.20(20)	159.37(38)	158.65(38)	160.88(26)
C-4			100.01(26)	101.13(25)	100.63(17)
C-5			82.46(114)	80.55(120)	83.53(86)
C=O	160.30(12)	160.60(12)	163.37(16)	164.10(17)	163.27(12)
	162.43(23)	162.15(18)	163.61(9)	164.09(11)	163.74(12)
			166.23(24)	166.69(25)	165.76(19)
			167.00	167.98(2)	166.86
OMe	53.04	53.36	50.68	50.39	50.47
	53.28	53.36	51.21	51.07	50.86
			52.45	52.27	52.02
			52.75	52.34	52.44
R'/R	24.04(4)	13.69(71)	15.54	24.15—23.47^e	6.56(86)
			15.99(7)	24.39(2)	53.85(8)
			15.99(7)		55.18(7)
	74.21(7)		62.49(7)	71.28(10)	
			68.06(9)	78.29(10)	
			69.15(9)	79.10(9)	
δ_P ^{f}					
	34.0^b	46.1^b	80.5^b	75.6^b	97.4^b

^{a} Shifts in p.p.m. from Me$_4$Si; J_{PC} in Hz in parentheses. ^{b} In CDCl$_3$ at 26 °C. ^{c} Obscured by overlapping resonances. ^{d} In CDCl$_3$ at 45 °C. ^{e} Complex. ^{f} Shifts in p.p.m. from 85% phosphoric acid; positive shifts to low field.

Bubbling hydrogen bromide through a solution of the ylide (3; R = Pr^i, R' = OPr^i) in toluene caused its signal at δ_P 76.5 p.p.m. to be replaced by a large signal at δ_P 44.8 p.p.m. together with a number of other smaller signals between δ_P 45.6 and 41.2 p.p.m. The proton-coupled ^{31}P n.m.r. spectrum of this material showed the major signal to be a doublet of doublets (J_{PH} 16 and 8 Hz), the larger coupling indicating the presence of a proton on the α-carbon and the smaller one indicating the presence of only one isopropoxy group on the phosphorus atom. This, therefore, clearly indicated that the cyclic ylide had not only been protonated but had also dealkylated to give the tetramethyl 1,2-di(isopropoxy)-1-oxo-2,5-dihydrophosphole-2,3,4,5-tetra-carboxylate (4; R = Pr^i, R' = OPr^i). Most of the remaining small signals in this region of the spectrum were attributed to other diastereoisomers of the dihydrophosphole (4; R = Pr^i, R' = OPr^i). Over a period of time these smaller signals became more intense at the expense of the major signal showing that equilibration of the diastereoisomers was occurring. The signals from these diastereoisomers also appeared as a doublet of doublets in the proton-coupled ^{31}P n.m.r. spectrum although the couplings were different from those observed for the signal at 44.8 p.p.m.

After a period of time a doublet began to appear in the proton-coupled ^{31}P n.m.r. spectrum of the reaction mixture at δ_P 32.4 p.p.m. (J_{PH} 9 Hz). This signal corresponded to the desired phosphole 1-oxide (5; R' = OPr^i) indicating that isopropyl alcohol was thus being eliminated spontaneously from the dihydrophosphole (4; R = Pr^i, R' = OPr^i). At room temperature the formation of the phosphole 1-oxide (5; R' = OPr^i) from the dihydrophosphole (4; R = Pr^i, R' = OPr^i) was relatively slow but this process could be accelerated by heating and by placing the dihydrophosphole under reduced pressure. At 50 °C and 16 mmHg the formation of the phosphole 1-oxide (5; R' = OPr^i) was complete after 30 min, and ^{31}P n.m.r. spectroscopy indicated that no other phosphorus-containing compounds had been produced.

The same procedure was applied to the synthesis of the corresponding methoxy- and ethoxy-substituted phospholes (5; R' = OMe and OEt). Although in these cases the yields were still good, they were lower than the excellent yield obtained for the isopropoxy-substituted phosphole (5; R' = OPr^i). The phosphole 1-oxides (5; R' = alkoxy) obtained in this way were identical to the samples previously prepared by trapping the phosphole intermediates (2; R = alkyl, R' = alkoxy) at low temperature in the manner previously reported.[1]

The cyclic ylides (3; R = alkyl, R' = alkyl or aryl), formed by the reaction of dialkyl phosphonites with dimethyl acetyl-enedicarboxylate, behaved in a similar way. Thus, for example, addition of hydrogen bromide to a cooled solution of the cyclic ylide (3, R = Et, R' = Ph) in toluene led to the formation of the dihydrophosphole (4; R = Et, R' = Ph). In this case, however, significant quantities of only two of the diastereoisomers, those giving δ_P values of 54.7 and 48.4 p.p.m. in [^{2}H]chloroform, were produced. These dihydrophosphole diastereoisomers eliminated alcohol less readily than those systems derived from the trialkyl phosphites so that even after 5 h at about 60 °C only about 30% of the dihydrophosphole (4; R = Et, R' = Ph) had been converted to the desired phosphole 1-oxide (5; R' = Ph). However, heating at 100 °C under reduced pressure for 1 h resulted in a complete conversion of (4; R = Et, R' = Ph) to the (5; R' = Ph). The identity of the product was confirmed by its ^{31}P n.m.r. spectrum (δ_P 38.7 p.p.m., t, J_{PH} 13 Hz) and its ^{13}C n.m.r. spectrum.[2] The latter showed the symmetrical nature of the product and the absence of ethyl groups, thus confirming the loss of ethanol. Although the phosphole 1-oxide (5; R' = Ph), produced in this way, contained no significant impurities initially, it did become hydrated on exposure to the air as previously reported.[2] Using the same approach (5; R' = Me), which we had not been able to prepare on a preparative scale via the intermediate (2; R = R' = Me),[2] was prepared from the corresponding ylide (3; R = R' = Me) in good yield. Interestingly, the phosphole 1-oxide (5; R' = Me) was found to be less susceptible to hydration than the corresponding phenyl-substituted system (5; R' = Ph). Thus, even after prolonged exposure to the atmosphere there was no sign of formation of the hydrated system (6; R' = Me). Moreover it was possible to purify a sample of some crude phosphole 1-oxide (5; R' = Me) by preparative t.l.c. (chromatotron system) on silica using ethyl

acetate as the eluant although the recovery from the plate was extremely low.

Further work is currently in progress to investigate whether other electrophilic acetylenes can be used in this type of synthesis.

Experimental

N.m.r. spectra were determined with a JEOL FX100 spectrometer. Detailed n.m.r. data are given in the table.

Tetramethyl 1,1,2-*Tri(isopropoxy)*-2H-*phosphole*-2,3,4,5-*tetracarboxylate* (3; R = Pr^i R' = OPr^i).—Tri-isopropyl phosphite (0.18 g) in dry toluene (5 cm^3) at −70 °C was rapidly added to a solution of dimethyl acetylenedicarboxylate (0.25 g) in dry toluene (5 cm^3) also at −70 °C. The two solutions were thoroughly mixed and then allowed to stand at −70 °C for 30 min before being allowed to warm to room temperature. The solvent was removed under reduced pressure and the residual oil was then heated at 50 °C at 0.1 mmHg to remove any other volatile components. On being cooled the resulting viscous oil gradually crystallised. The resulting solid was washed with dry diethyl ether and was then dried under reduced pressure to give the desired cyclic ylide (3; R = Pr^i, R' = OPr^i) (0.34 g, 79%), m.p. 109—111 °C (Found: C, 51.45; H, 6.9. $C_{21}H_{33}O_{11}P$ requires C, 51.2; H, 6.75%).

Tetramethyl 1,1,2-*Triethoxy*-2H-*phosphole*-2,3,4,5-*tetracarboxylate* (3; R = Et, R' = OEt).—The cyclic ylide (3; R = Et, R' = OEt) was prepared by the method previously described for (3; R = Pr^i, R' = OPr^i) and isolated as a white solid (4.95 g, 62%), m.p. 92—94 °C (Found: C, 47.85; H, 6.2. $C_{18}H_{27}O_{11}P$ requires C, 48.0; H, 6.05%).

Tetramethyl 1-*Isopropoxy*-1-*oxo*-1H-*phosphole*-2,3,4,5-*tetracarboxylate* (5; R' = OPr^i).—A solution of the cyclic ylide (3; R = Pr^i, R' = OPr^i) (1.7 g) in toluene (30 cm^3) was cooled in an ice bath and carefully treated with hydrogen bromide gas until the colour of the solution had changed from an orange-red to lime-green. ^{31}P N.m.r. spectroscopy confirmed that none of the cyclic ylide remained in the solution. The solvent was removed under reduced pressure and the residue was heated at 50 °C, initially at a pressure of 16 mmHg for *ca.* 30 min, and then at a lower pressure (0.01 mmHg) to remove any volatile contaminants. ^{31}P N.m.r. spectroscopy showed the product (1.17 g, 87%) to be the desired phosphole 1-oxide (5; R' = OPr^i), δ_P CDCl$_3$ 34.0 p.p.m., d, J_{PH} 9 Hz (Found: C, 46.1; H, 5.2. $C_{15}H_{19}O_{10}P$ requires C, 46.15; H, 4.9%).

Tetramethyl 1-*Ethoxy*-1-*oxo*-1H-*phosphole*-2,3,4,5-*tetracarboxylate* (5; R' = OEt).—A solution of the cyclic ylide (3; R = Et, R' = OEt) (4 g) in toluene (30 cm^3) was treated with hydrogen bromide gas in the manner previously described for (3; R = Pr^i, R' = OPr^i). This resulted in the formation of a number of diastereoisomers of (4; R = Et, R' = OEt) giving ^{31}P n.m.r. signals in the range δ_P 45.5—48.7 p.p.m. Equilibration between these diastereoisomers occurred with time leading to the signals at δ_P 48.7 and 47.15 p.p.m. becoming dominant. The solvent was removed under reduced pressure and the residue was heated at 50 °C under reduced pressure (0.01 mmHg) until the decomposition of the dihydrophosphole was complete. The resulting oil was triturated with ether to give the desired phosphole 1-oxide (5; R' = OEt), as a white solid (2.09 g, 63%), m.p. 133—135 °C, δ_P 35.3 p.p.m. (Found: C, 44.85; H, 4.5. Calc. for $C_{14}H_{17}O_{10}P$: C, 44.7; H, 4.5%).

Tetramethyl 1-*Methoxy*-1-*oxo*-1H-*phosphole*-2,3,4,5-*tetracarboxylate* (5; R' = OMe).—The phosphole 1-oxide (5; R' = OMe) was obtained from the cyclic ylide (3; R' = OMe)[1] by the method previously described for (5; R' = OEt). Slow addition of hexane to a solution of the crude phosphole 1-oxide in chloroform led to the precipitation of (5; R' = OMe) as a white solid (3.6 g, 59%), m.p. 110—113 °C (Found: C, 43.4; H, 4.2. Calc. for $C_{13}H_{15}O_{10}P$: C, 43.1; H, 4.2%).

Tetramethyl 1-*Oxo*-1-*phenyl*-1H-*phosphole*-2,3,4,5-*tetracarboxylate* (5; R' = Ph).—Diethyl phenylphosphonite (0.8 g) in dry toluene (10 cm^3) at −70 °C was rapidly added to a solution of dimethyl acetylenedicarboxylate (1.15 g) also in dry toluene (10 cm^3) at −70 °C. The resulting solution was shaken and then allowed to stand for 30 min at −70 °C. After this time the solution was allowed to warm to room temperature. ^{31}P N.m.r. spectroscopy confirmed the production of the cyclic ylide (3; R = Et, R' = Ph) (δ_P 83.7 p.p.m.). The solution was cooled in ice and treated carefully with anhydrous hydrogen bromide until the ^{31}P n.m.r. spectrum showed the absence of the cyclic ylide and the formation of two protonated intermediates [δ_P(CDCl$_3$) 54.7 and 48.4 p.p.m.]. The solvent was then removed and the residue heated under reduced pressure in a rotary evaporator (100 °C at 16 mmHg). After *ca.* 1.5 h the formation of the desired phosphole 1-oxide was complete (δ_P 38.7 p.p.m., t, 12 Hz). Its identity was confirmed by comparison with an authentic sample prepared by the low temperature trapping route.[2] The phosphole 1-oxide was isolated as the hydrated system (6; R' = Ph)[2] (1.5 g, 87%).

Tetramethyl 1,2-*Dimethoxy*-1-*methyl*-2H-*phosphole*-2,3,4,5-*tetracarboxylate* (3; R = R' = Me).—(*a*) Dimethyl acetylenedicarboxylate (1.31 g) in dry toluene (5 cm^3) at −70 °C was added quickly to a solution of dimethyl methylphosphonite (0.5 g) also in dry toluene (5 cm^3) at −70 °C. The mixture was shaken and then allowed to stand at −70 °C for 20 min before being allowed to warm to room temperature. ^{31}P N.m.r. spectroscopy showed the product to contain approximately 80% of the desired cyclic ylide (δ_P 97.5 p.p.m.). Addition of hexane to the reaction mixture caused the precipitation of a white solid which was filtered off. The solid was then dissolved in the minimum volume of chloroform and reprecipitated by the addition of either diethyl ether or hexane. The cyclic ylide (3; R = R' = Me) (1.27 g, 70%) was then filtered off and dried.

(*b*) To a solution of dimethyl acetylenedicarboxylate (0.75 g) in dry diethyl ether (5 cm^3), cooled in an ice bath, was slowly added, over a period of 15 min, a solution of dimethyl methylphosphonite (0.27 g) in dry diethyl ether (10 cm^3). After the addition had been completed the reaction mixture was allowed to warm to room temperature and the precipitation of the product was completed by the addition of hexane. The crude product was purified as previously described to give the cyclic ylide (3; R = R' = Me) (0.45 g, 45%). The cyclic ylide (3; R = R' = Me) slowly crystallised from ether–chloroform as a white solid, m.p. 138—139 °C (Found: C, 45.7; H, 5.35. $C_{15}H_{21}O_{10}P$ requires C, 45.9; H, 5.35%).

Tetramethyl 1-*Methyl*-1-*oxo*-1H-*phosphole*-2,3,4,5-*tetracarboxylate* (5; R' = Me).—Anhydrous hydrogen bromide was bubbled through a solution of the cyclic ylide (3; R = R' = Me) (0.2 g) dissolved in chloroform (2 cm^3) until ^{31}P n.m.r. spectroscopy indicated that no starting material remained. The chloroform and excess hydrogen bromide were quickly removed under reduced pressure and the resulting gummy solid was heated at 75 °C under reduced pressure (22 mmHg) for 30 min. ^{31}P N.m.r. spectroscopy indicated the resulting product to be desired phosphole 1-oxide (5; R' = Me) (δ_P 46.5 p.p.m., q, 15 Hz) in essentially quantitative yield. An analytically pure sample of the material was obtained by precipitating the phosphole 1-oxide from a chloroform solution by the addition of diethyl ether and hexane, m.p. 143—144 °C (Found: C, 44.95; H, 4.4. $C_{13}H_{15}O_9P$ requires C, 45.1; H, 4.35%).

References

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