An Original Approach to the Synthesis of Phosphorus-Carbon Heterocycles − The 3-Oxo-2,3-dihydro-1,3-oxaphospholes

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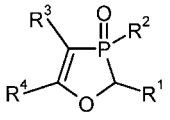
The synthesis of new highly functionalized phosphorus heterocycles, the 3-oxo-2,3-dihydro-1,3-oxaphospholes, was achieved by a cyclization reaction involving malonic enolates as 1,3-*O*,*C*-dinucleophiles and phosphorus compounds, such as (chloromethyl)phosphinic chlorides or alkyl (chloromethyl)phosphonochloridates, as 1,2-dielectrophiles. Owing to the structural restriction that results from the cyclic structure, the ^{1}H NMR spectra reveal extreme values of $^2J_{P,H}$ coupling constants that are sensitive to the HCPO dihedral angle.

Introduction

Heterocyclic compounds are generally known to have high potential as biologically active molecules. In the same way, acyclic phosphorus compounds[1] are very efficient pesticides[2] and drugs.[3] However, phosphorus heterocycles are still relatively unexplored, and few of these compounds, particularly with P−C bonds, have been synthesized and tested so far. In this paper, we report an original synthesis of 3-oxo-2,3-dihydro-1,3-oxaphospholes **1**, a representative of the 1,3-heterophosphole family.



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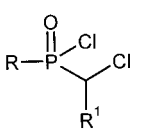
As has already been intimated, heterophospholes have scarcely been studied and previous investigations into the synthesis of 3-oxo-2,3-dihydro-1,3-oxaphospholes were often specific and quite limited.[4] Of the methods reported in the literature, Bovin and Tsvetkov[5] described the formation of benzoxaphospholes from *o*-[(chloromethyl)phosphinyl]phenols or *o*-[(chloromethyl)phosphonyl]phenols **2** in the presence of triethylamine in 78−93% yields (Scheme 1). The thermal rearrangement of 1,2,4-λ^3-diazaphospholes **3** in refluxing toluene also led to the formation of **1**.[6] Addition to the P=C double bond of benzoxaphosphole **4** allowed the synthesis of P^{III} heterocycles **1**.[7] Another method involves the acid-catalyzed or thermal rearrangements of the 3,5-dioxa-1-phosphabicyclo[2.2.1]-heptanes **5**.[8] Finally, a more general synthesis arises from the addition of (1-alkynyl)phosphinates **6** to aldehydes. The 1-(hydroxyalkyl)alkynylphosphinates that result from the Pudovik reaction of **6** then undergo an intramolecular 5-*endo*-*dig* cyclization to give the 1,3-oxaphospholes.[9]

Results and Discussion

The synthetic methodology developed here for the elaboration of 2,3-dihydro-1,3-oxaphospholes involves the formation of two of the carbon−heteroatom bonds of the heterocycle by the reaction of the enolate of ethyl or methyl malonate with 1,2-phosphorus dielectrophiles such as (chloromethyl)phosphinic chlorides and (chloromethyl)phosphonochloridates.

Synthesis of the Phosphorus Precursors

Prior to the synthesis of 2,3-dihydro-1,3-oxaphospholes **1**, reliable and general methods for the preparation of (chloromethyl)phosphinic chlorides **7** (R = alkyl, aryl) and (chloromethyl)phosphonochloridates **8** (R = OEt) were needed.



7a R = CH_2Cl, R^1 = H
7b R = Ph, R^1 = H
7c R = Ph, R^1 = Me

8a R = OEt, R^1 = H
8b R = OEt, R^1 = Me

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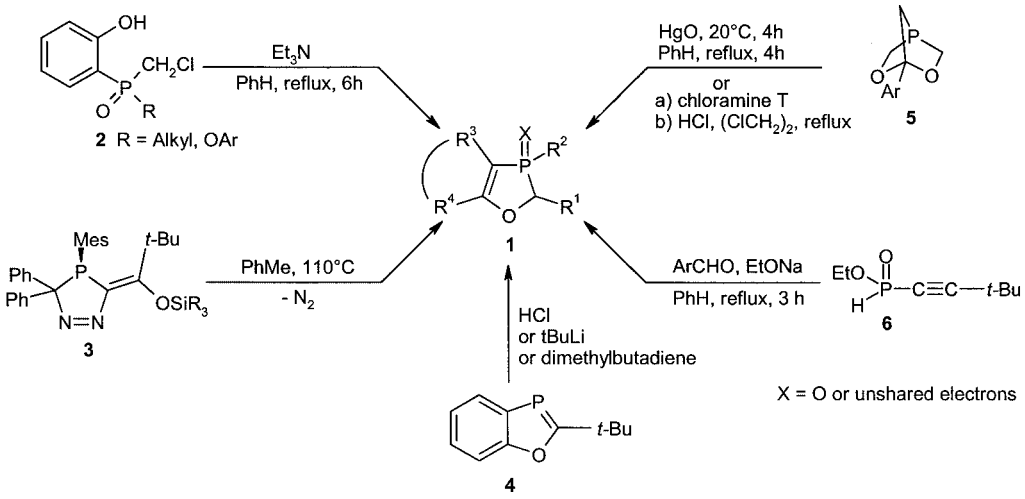
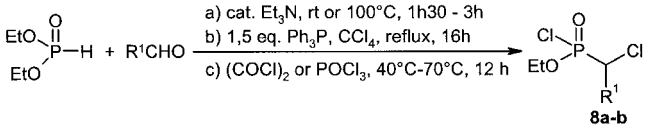


Scheme 1. Synthetic methods for the formation of 2,3-dihydro-1,3-oxaphospholes described in the literature

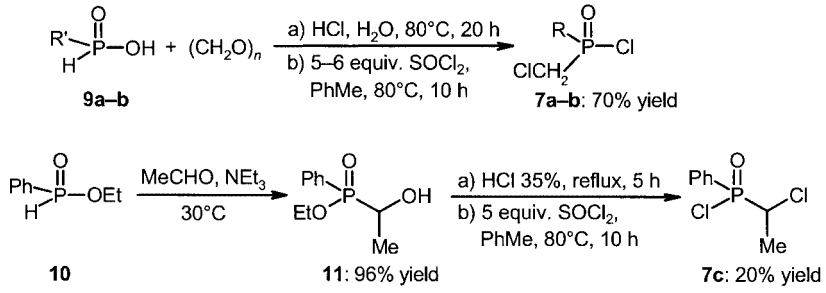
(Chloromethyl)phosphinic chlorides **7a**,**b** were prepared according to the literature in two steps from phosphinic acid (**9a**, R′ = H) or phenylphosphinic acid **9b** (R′ = Ph), respectively. The reaction of **9a**,**b** with paraformaldehyde in water or in a 50:50 mixture of water and ethanol, in the presence of hydrochloric acid, afforded good yields of the corresponding (hydroxymethyl)phosphinic acids.[10] Subsequent reaction with a large excess of thionyl chloride (6 and 5 equivalents, respectively) gave the expected (chloromethyl)phosphinic chlorides **7a**,**b** after distillation under reduced pressure (Scheme 2).[11]

The Pudovik reaction of hypophosphorus acid with acetaldehyde was not suitable using these conditions; the expected (1-hydroxyethyl)phenylphosphinic acid was formed in 94% yield, but only after three weeks at room temperature. The hydroxyalkylation of phosphinic acids is generally easy but limited by their low reactivity, particularly when high temperatures are not possible due to the use of low boiling aldehydes. To overcome this problem, activation of ester derivatives with triethylamine proved an excellent alternative by which to obtain (hydroxyalkyl)phosphinates in the shortest reaction time. In contrast with the previous experiment, ethyl 1-(hydroxyethyl)phenylphosphinate (**11**) was obtained in only 16 h at room temperature. The product was pure enough to be engaged in the next step without further purification. The deprotection of phosphinate **11** followed by reaction with thionyl chloride allowed us then to obtain the 1-(chloroethyl)phenylphosphinic chloride (**7c**) in 20% yield after distillation.

In contrast with the synthesis of the precursors **7a**−**c**, alkyl (chloroalkyl)phosphonochloridate formation is complicated by the presence of two alkoxy groups on the phosphorus atom. The first step involves the Pudovik reaction of diethyl phosphonate with paraformaldehyde or acetaldehyde using triethylamine as a catalyst (Scheme 3). The corresponding α-(hydroxyalkyl)phosphonates were obtained in good yields.[12] The second step is the Appel reaction, which leads to the substitution of the alcohol function by a chlorine atom under neutral conditions.[13] Finally, the third step involves the selective transformation of phosphonate to phosphonochloridate. The most suitable reagents listed in the literature for this transformation are oxalyl chloride and phosphorus oxychloride.[14]

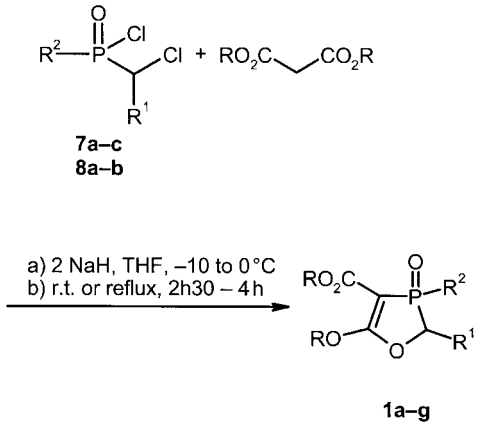


Scheme 3. Synthesis of ethyl (1-chloroalkyl)phosphonochloridates



Scheme 2. Synthesis of (1-chloroalkyl)phosphinic chlorides

These (α-chloroalkyl)phosphinic chlorides **7** and phosphonic chlorides **8** were used in the reactions with the malonic enolates. In practice, two equivalents of sodium hydride were used (Scheme 4). The formation of hydrogen gas in the initial reaction is consistent with the reaction of only one equivalent of sodium hydride with the malonic enolate. Slow addition of the phosphorus electrophile, **7** or **8**, at −10 °C resulted in further hydrogen evolution, in accordance with the reaction of the second equivalent of base. The expected 2,3-dihydro-1,3-oxaphospholes **1** were isolated in 23−70% yields (Table 1).



Scheme 4. Synthesis of 3-oxo-2,3-dihydro-1,3-oxaphospholes

Table 1. Isolated yields of 2,3-dihydro-1,3-oxaphospholes **1a**−**g**

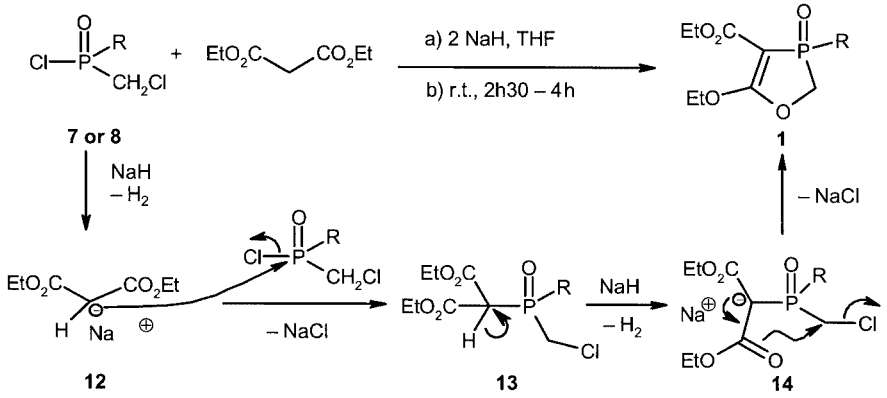
	R	R^1	R^2	Yield (%)
1a	Me	H	CH_2Cl	61
1b	Et	H	CH_2Cl	57
1c	Et	H	Ph	70
1d	Et	Me	Ph	23
1e	Et	H	OEt	33
1f	Et	Me	OEt	50
1g	menthyl	H	CH_2Cl	0

The reaction is a general one and we were able to isolate phosphorus heterocycles from several malonates, but not from dimenthyl malonate. In this case, the two menthyl groups probably have a greater steric hindrance than the methyl and ethyl groups, which suppresses the deprotonation reaction with sodium hydride, even in refluxing THF (no hydrogen gas was evolved).

From a mechanistic point of view, the heterocycles are likely to result from the attack of sodium malonate **12** on the more reactive P−Cl group by an S_NP process, leading to the *C*-phosphorylated malonate **13** (Scheme 5). According to the observations mentioned above, the second step is consistent with an acid-base reaction of the phosphinylated intermediate with the excess of sodium hydride. The resulting enolate **14** then reacts by an intramolecular S_N2 reaction, in which the oxygenated nucleophilic centre reacts with the α-chloroalkyl group leading to the five-membered ring in a 5-*endo-tet* process. The ease of the cyclization step depends on the nature of the electrophilic chloroalkyl group. With the primary PCH_2Cl group, cyclization occurs between 0 °C and room temperature. In contrast, with the secondary 1-chloroethyl group (**1d** and **1f**), it is necessary to reflux the reaction mixture in THF to obtain the 2,3-dihydro-1,3-oxaphospholes.

This mechanism is also supported by the isolation of the *P*-substituted malonate intermediate **13**. In a separate experiment, **13** was obtained as the major product (^{31}P NMR, δ = 40.63 ppm) in 93% yield: in practice, to avoid the formation of the enolate **14**, sodium malonate (1 equivalent) was added to a solution of bis(chloromethyl)phosphinic chloride (**7a**, 1 equivalent) in anhydrous THF at −20 °C. A first fraction of this solution was filtered off to give after concentration the expected compound **13** in 77% yield. The ^1H NMR spectrum of **13** exhibits a characteristic broad singlet at δ = 11.95 ppm, which corresponds to the highly acidic malonic proton.[15] Addition of one equivalent of sodium hydride to a second fraction leads to the expected oxaphosphole **1b** in 78% yield, as determined by ^{31}P NMR spectroscopy; the oxaphosphole **1b** was identified by the addition of a pure sample into the NMR tube.

The synthesis of 1,3-oxaphospholes can be compared with the reaction of malonates with chloracetyl chloride in



Scheme 5. Proposed mechanism for the formation of 2,3-dihydro-1,3-oxaphospholes **1**

the presence of base, which leads to 3-furanones.[16] Although, this reaction has received little attention in the literature, only five-membered rings were observed and no cyclopropanone derivatives, probably owing to the high strain of three-membered rings. However, with tetrahedral sp^3 dielectrophiles such as 1,2-dichloroethane, the main reaction is the formation of the cyclopropane rings.[17] In contrast, although phosphorus electrophiles are tetrahedral, they react like chloracetyl chloride to form five-membered rings in an alkylation-cyclization reaction.

NMR Characteristics of 2,3-Dihydro-1,3-oxaphospholes

The 2,3-dihydro-1,3-oxaphospholes exhibit an unusual ethylenic system; the $C^4=C^5$ double bond is strongly polarized due to the electron-withdrawing nature of the alkoxycarbonyl and phosphinyl groups and the presence of two electron-releasing oxygen atoms. Consequently, the chemical shifts of the C^4 and C^5 carbon atoms of the heterocycles **1** are at the extreme range of the chemical shifts found for sp^2 hybridized carbon atoms in C=C double bonds (Table 2).

Table 2. ^{13}C NMR chemical shifts for C^4 and C^5 of the oxaphospholes

	δ_{C4} (ppm)	δ_{C5} (ppm)
1a	71.7	174.9
1b	71.8	174.5
1c	75.7	174.9
1d	75.8	174.6
1e	74.7	173.9

According to the ^{13}C NMR spectra and to the RX structure of oxaphosphole **1a**,[18] the dialkoxymethylene phosphomalonate system is almost flat, strongly conjugated and can be considered as a new class of capto-dative ethylene group.[19] In terms of reactivity, such an olefinic bond is capable of enhanced Michael additions followed by an elimination process which could be interesting.[20]

The methylenic hydrogen atoms H_a and H_b in the PCH_2O linkage of 2,3-dihydro-1,3-oxaphospholes **1** show a second-order coupling pattern which can be readily interpreted as the AB part of an ABX spectrum. These two protons are diastereotopic and cannot rotate. Consequently, their $^2J_{P,H}$ coupling constants are very different. In comparison, the two $^2J_{P,H}$ coupling constants for the freely rotating PCH_2Cl group are almost identical, with values of 9.0 and 10.6 Hz, respectively, for compound **1a**.

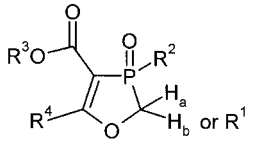
Actually, in such systems, $^2J_{P,H}$ coupling constants are very sensitive to the dihedral angles O=P−C−H; they are generally in the range of −16.5 to −13.5 Hz for the eclipsed conformation and increase to a range of −5 to 0 Hz for a 180° dihedral angle. The *trans* O=P−C−H conformation (120°) generally has $^2J_{P,H}$ values between −9 and −6 Hz.[21]

The ABX spectra of compounds **1a**−**f** have been simulated,[22] and the resulting chemical shifts and coupling constants are listed in Table 3. The signs of the $^2J_{P,H}$ and $^2J_{H,H}$ coupling constants have not been determined, and are given in accord with the geminal coupling of sp^3 hybridized systems reported in the literature.[23] According to the RX structure of oxaphosphole **1a**,[18] one proton is almost eclipsed by the phosphoryl bond and exhibits a dihedral angle of 7.5° (Figure 1); the *trans* proton has a dihedral angle of 112.2°. The $^2J_{P,H}$ coupling constants are, respectively, −9.6 Hz for the *cis* proton and +0.3 Hz for the *trans* one, in accord with the Karplus-type relationship.

The NMR characteristics of oxaphospholes **1** are homogeneous and their *cis* and *trans* $^2J_{P,H}$ coupling constants show similar trends. In compound **1c**, the *trans* proton is affected by the proximity of the phenyl ring and is shielded downfield of the *cis* proton. Moreover, in this case, the $^2J_{P,H}$ coupling constant for the *trans* proton decreases slightly from 0.3 Hz to −1.7 Hz.

Oxaphospholes **1d** and **1f** were both obtained as a mixture of two diastereoisomers due to the presence of two chiral atom in these molecules. However, the pattern

Table 3. Chemical shifts and coupling constants for the PCH_2O group in heterocycles **1**



	R^1	R^2	R^3	R^4	δ_A (ppm)	δ_B (ppm)	$^2J_{Ha,Hb}$ (Hz)	$^2J_{P,Ha}$ (Hz)	$^2J_{P,Hb}$ (Hz)
1a	H	CH_2Cl	Me	OMe	4.53	4.71	−14.1	−9.6	0.3
1b	H	CH_2Cl	Et	OEt	4.56	4.73	−13.9	−9.6	0.3
1c	H	Ph	Et	OEt	4.72	4.46	−13.8	−10.7	−1.7
1d[a,b]	Me	Ph	Et	OEt	4.62	–	–	−5.9	–
1f[a]	Me	OEt	Et	OEt	4.36	–	–	0.0	–
1f′[a]	Me	OEt	Et	OEt	4.49	–	–	−4.5	–

[a] Formally, we have an AM_3X spin system. For clarity $^3J_{AM}$ are omitted from Table 3. [b] Owing to the important superposition of some signals, the spectrum of **1d** was too complicated to attribute all the parameters completely.

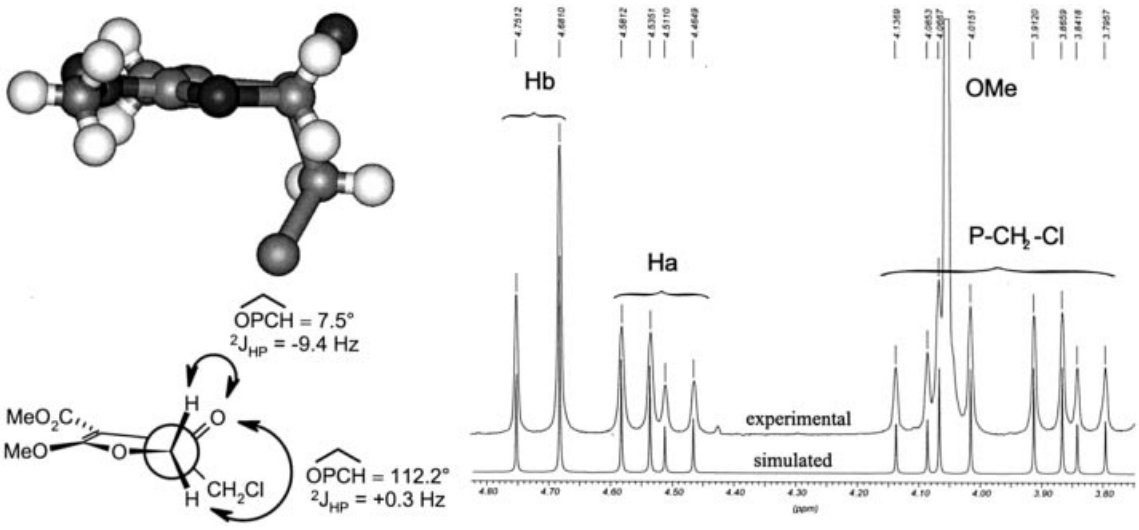


Figure 1. Conformation, dihedral angles and ^{1}H NMR spectrum of oxaphosphole **1a**

describing this system is the A part of an AM_3X spin system. The assignment for each diastereoisomer **1f** and **1f′** was corroborated experimentally by a COSY NMR experiment, in which each spin system was analysed. The $^2J_{P,H}$ coupling constants for the isomers of **1f** and **1f′** are 0.0 Hz and −4.5 Hz, respectively. The former is in perfect agreement with the previously determined $^2J_{P,H}$ coupling constant for the *trans* proton (relative to the phosphinyl group), but the latter, which should be attributed to the *cis* proton, is rather different to that of **1a** (−4.5 Hz compared to −9.6 Hz). This change could be attributed to a modification of the dihedral angle probably due to steric interactions between the *cis O*-ethyl and methyl groups.

Conclusion

A new and efficient method has been developed for the synthesis of 2,3-dihydro-1,3-oxaphospholes **1** from easily accessible and stable precursors by an original cyclization reaction involving a malonate and a (chloromethyl)phosphinic chloride or a (chloromethyl)phosphonochloridate in the presence of two equivalents of sodium hydride. In comparison to other existing methods, this process is straightforward, quite general, offers a simple access to these heterocycles and allows the control of substituents in positions 2 and 3 of the heterocycle.

Experimental Section

General Remarks: All reactions were carried out under nitrogen using Schlenk techniques. The solvents were dried by standard procedures, distilled and stored under nitrogen prior to use. All reactions were monitored by TLC (Merck, SIL G/UV254) or ^{31}P NMR spectroscopy. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker AC-200 or Avance-250 spectrometer and referenced to the solvent as internal standard. Chemical shifts are expressed in ppm and coupling constants in Hz.

General Procedure for the Preparation of 2,3-Dihydro-1,3-oxaphospholes (described for 1a): Dimethyl malonate (10.98 g, 83.2 mmol, 1 equiv.) in anhydrous THF (20 mL) was added dropwise to a suspension of 95% sodium hydride (4.19 g, 174.6 mmol, 2.1 equiv.) in anhydrous THF (200 mL) at −20 °C in a three-neck round-bottom flask equipped with a magnetic stirrer, a condenser and a dropping funnel. Then, after hydrogen gas had evolved, bis(chloromethyl)-phosphinic chloride (**7a**, 15.09 g, 83.2 mmol, 1 equiv.) in THF (20 mL) was added slowly to the flask at −20 °C and the temperature was not allowed to exceed 0 °C during this process. The reaction was hen stirred for 2 h at room temperature. The reaction mixture was concentrated using a rotary evaporator to remove THF, and water (100 mL) was added. The solution was extracted three times with chloroform (50 mL). The organic layers were dried over $MgSO_4$, and concentrated to afford a yellow oil which crystallized slowly. The resulting solid was filtered and washed with a minimum volume of acetone (or ether) to give pure oxaphosphole **1a** (12.16 g, 50.6 mmol) as a white solid in 61% yield.

Methyl 3-Chloromethyl-2,3-dihydro-5-methoxy-3-oxo-1,3-oxaphosphole-4-carboxylate (1a): M.p. 138−141 °C (dec.). ^{31}P NMR (81.0 MHz, $CDCl_3$): δ = 49.28 ppm. ^{1}H NMR (200.1 MHz, $CDCl_3$): δ = 4.71 (d, $^2J_{H,H}$ = −14.1 Hz, 1 H, PCH_2O), 4.53 (dd, $^2J_{H,H}$ = −14.1, $^2J_{P,H}$ = 9.6 Hz, 1 H, PCH_2O), 4.07 (dd, $^2J_{H,H}$ = −14.1, $^2J_{P,H}$ = 10.3 Hz, 1 H, PCH_2Cl), 4.05 (s, 3 H, CH_3), 3.86 (dd, $^2J_{H,H}$ = −14.1, $^2J_{P,H}$ = 9.2 Hz, 1 H, PCH_2Cl), 3.72 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 174.91 (d, $^2J_{P,C}$ = 33.1 Hz, =C), 162.90 (d, $^2J_{P,C}$ = 7.8 Hz, C=O), 71.71 (d, $^1J_{P,C}$ = 119.1 Hz, P-C), 66.87 (d, $^1J_{P,C}$ = 66.2 Hz, PCH_2O), 51.00 (s, CH_3), 57.25 (s, CH_3), 35.14 (d, $^1J_{P,C}$ = 84.1 Hz, PCH_2Cl) ppm. MS FAB$^+$ (NBA): *m*/*z* (%) = 241 (100) $[M + H]^+$, 209 (85) $[M - MeO^-]^+$. $C_7H_{10}ClO_5P$ (240.58): calcd. C 34.95, H 4.19; found C 34.89, H 4.22.

Ethyl 3-Chloromethyl-5-ethoxy-2,3-dihydro-3-oxo-1,3-oxaphosphole-4-carboxylate (1b): Oxaphosphole **1b** was prepared following the same procedure as described for **1a** and was isolated as a white solid in 57% yield (12.6 g) after recrystallization from diethyl ether.

M. p. 101−102 °C. ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 50.2 ppm. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 4.73 (d, $^2J_{H,H}$ = −13.9 Hz, 1 H, PCH_2O), 4.56 (m, $^2J_{H,H}$ = −13.9, $^2J_{P,H}$ = 9.6, $^2J_{H,H}$ = 0.6 Hz, 1 H, PCH_2O), 4.51 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2O), 4.33 (m, $^2J_{H,H}$ = −10.8, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2O), 4.20 (m, $^2J_{H,H}$ = −10.8, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2O), 4.14 (m, $^2J_{H,H}$ = −14.0, $^2J_{P,H}$ = 10.6, $^2J_{H,H}$ = 0.6 Hz, 1 H, PCH_2Cl), 3.89 (m, $^2J_{H,H}$ = −14.0, $^2J_{P,H}$ = 9.0 Hz, 1 H, PCH_2Cl), 1.48 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.33 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 174.5 (d, $^2J_{P,C}$ = 33.4 Hz, =C), 162.5 (d, $^2J_{P,C}$ = 7.8 Hz, C=O), 71.8 (d, $^1J_{P,C}$ = 120.2 Hz, P-C), 66.5 (d, $^1J_{P,C}$ = 66.3 Hz, PCH_2O), 67.2 (s, CH_2O), 59.8 (s, CH_2O), 34.9 (d, $^1J_{P,C}$ = 84.2 Hz, PCH_2Cl), 14.1 and 14.4 (2 s, 2 CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1720 ($\nu_{C=O}$), 1570 ($\nu_{C=C}$), 1230 ($\nu_{P=O}$), 1190 ($\nu_{P=O}$) cm^{-1}. MS FAB$^+$ (NBA): *m/z* (%) = 269 (45) $[M + H]^+$, 223 (100) $[M - EtO^-]^+$, 537 (12) $[2M + H]^+$: $C_9H_{14}ClO_5P$ (268.64): calcd. C 40.24, H 5.25, O 29.78; found C 40.04, H 5.27, O 29.97.

Ethyl 5-Ethoxy-2,3-dihydro-3-oxo-3-phenyl-1,3-oxaphosphole-4-carboxylate (1c): Oxaphosphole **1c** was prepared following the same procedure as that described for **1a** and was isolated as a white solid in 70% yield (4.78 g) after recrystallization from diethyl ether. M. p. 123−126 °C. ^{31}P NMR ($CDCl_3$, 81.017 MHz): δ = 38.34 (s) ppm. ^{1}H NMR ($CDCl_3$, 250.131 MHz): δ = 7.75−7.83 (m, 2 H, Ph), 7.48−7.56 (m, 3 H, Ph), 4.72 (dd, $^2J_{H,H}$ = −13.8, $^2J_{H,H}$ = 10.7 Hz, 1 H, PCH_2O), 4.55 (m, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.5 Hz, 1 H, CH_2O), 4.52 (m, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.5 Hz, 1 H, CH_2O), 4.46 (dd, $^2J_{H,H}$ = −13.8, $^2J_{P,H}$ = 1.7 Hz, 1 H, PCH_2O), 4.11 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.8 Hz, 1 H, CH_2O), 3.91 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.8 Hz, 1 H, CH_2O), 1.49 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 0.91 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50.327 MHz): δ = 174.86 (d, $^3J_{P,C}$ = 32.4 Hz, =C), 163.10 (d, $^2J_{P,C}$ = 7.4 Hz, C=O), 132.22 (d, $^4J_{P,C}$ = 2.9 Hz, ^{p}CH), 131.52 (d, $^2J_{P,C}$ = 10.8 Hz, ^{o}CH), 129.93 (d, one transition missing, ^{i}C), 128.58 (d, $^3J_{P,C}$ = 13.8 Hz, ^{m}CH), 75.68 (d, $^1J_{P,C}$ = 116.9 Hz, P-C), 71.46 (d, $^1J_{P,C}$ = 64.0 Hz, PCH_2O), 59.68 (s, CH_2O), 67.26 (s, CH_2O), 13.86 and 14.73 (2 s, 2 CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1698 ($\nu_{C=O}$), 1224 ($\nu_{P=O}$), 1208 ($\nu_{P=O}$) cm^{-1}. MS FAB$^+$ (GT): *m/z* 859 = 297 (36) $[M + H]^+$, 251 (100) $[M - EtO^-]^+$.

Ethyl 5-Ethoxy-2,3-dihydro-2-methyl-3-oxo-3-phenyl-1,3-oxaphosphole-4-carboxylate (1d): Oxaphosphole **1d** was prepared following the same procedure as that described for **1a**, except that the reaction mixture was heated for 1 hour in refluxing THF after addition of the (chloroethyl)phosphinic chloride was complete. Oxaphosphole **1d** was isolated as a pale yellow oil in 23% yield (1.42 g) after chromatography on silica (elution with EtOAc). ^{31}P NMR ($CDCl_3$, 81.01 MHz): δ = 37.77 ppm. ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ = 7.45−7.52 and 7.58−7.79 (2 m, 5 H, 5 CH aromatic), 4.62 (qd, $^3J_{H,H}$ = 7.2, $^2J_{P,H}$ = 5.9 Hz, 1 H, PCHO), 4.54 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.4 Hz, 1 H, CH_2O), 4.50 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.4 Hz, 1 H, CH_2O), 4.11 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.7 Hz, 1 H, CH_2O), 3.92 (qd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = −10.7 Hz, 1 H, CH_2O), 1.68 (dd, $^3J_{H,H}$ = 7.2, $^3J_{P,H}$ = 12.4 Hz, 3 H, CH_3), 1.49 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 0.93 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ = 174.58 (d, $^2J_{P,C}$ = 30.7 Hz, =C), 163.86 (d, $^2J_{P,C}$ = 6.2 Hz, C=O), 132.58 (d, $^4J_{P,C}$ = 2.9 Hz, ^{p}CH), 132.03 (d, $^2J_{P,C}$ = 10.6 Hz, ^{o}CH), 131.55 (d, $^1J_{P,C}$ = 118.0 Hz, ^{i}C), 128.97 (d, $^3J_{P,C}$ = 13.4 Hz, ^{m}CH), 79.44 (d, $^1J_{P,C}$ = 68.1 Hz, PCHO), 75.81 (d, $^1J_{P,C}$ = 114.2 Hz, P-C), 67.44 (s, CH_2O), 60.04 (s, CH_2O), 15.14 (s, CH_3), 14.40 (s, CH_3), 14.17 (d, $^2J_{P,C}$ = 1.4 Hz, CH_3) ppm. MS FAB$^+$ (Matrix GT): *m/z* (%) = 311 (21) $[M + H]^+$, 265 (100) $[M - EtO^-]^+$. HRMS FAB$^+$ (Matrix GT): calcd. for $C_{15}H_{20}O_5P$: 311.1048; found 311.0841 $[M + H]^+$.

Ethyl 3,5-Diethoxy-2,3-dihydro-3-oxo-1,3-oxaphosphole-4-carboxylate (1e): Oxaphosphole **1e** was prepared following the same procedure as that described for **1a** and was isolated as a white solid in 33% yield (0.94 g) after recrystallization from hexane. ^{31}P NMR ($CDCl_3$, 101.25 MHz): δ = 50.3 (s) ppm. ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ = 4.05−4.39 (m, 8 H, 4 CH_2), 1.39 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 173.9 (d, $^2J_{P,C}$ = 42.4 Hz, C=), 162.4 (d, $^2J_{P,C}$ = 6.3 Hz, C=O), 74.7 (d, $^1J_{P,C}$ = 194.6 Hz, P-C), 67.3 (d, $^1J_{P,C}$ = 95.0 Hz, PCH_2O), 66.3 (s, CH_2O), 62.7 (d, $^2J_{P,C}$ = 6.7 Hz, CH_2OP), 59.7 (s, CH_2O), 16.4 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 14.2 and 14.5 (2 s, 2 CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1713 ($\nu_{C=O}$), 1224 ($\nu_{P=O}$), 1206 ($\nu_{P=O}$) cm^{-1}. MS FAB$^+$ (GT): *m/z* (%) = 265 (45) $[M + H]^+$, 219 (100) $[M - EtO]^+$.

Ethyl 3,5-Diethoxy-2,3-dihydro-2-methyl-3-oxo-1,3-oxaphosphole-4-carboxylate (1f): Oxaphosphole **1f** was prepared following the same procedure as that described for **1a**, except that the reaction mixture was heated for 1 h in refluxing THF after addition of the (chloroethyl)phosphonochloridate was complete. Oxaphosphole **1f** was isolated as a pale yellow oil in 50% yield (3.33 g) after chromatography on silica (eluent EtOAc and gradient to EtOAc/EtOH, 98:2). ^{31}P NMR ($CDCl_3$, 81.051 MHz): δ = 49.90 and 50.39 (2 s) ppm. ^{1}H NMR ($CDCl_3$, 250.13 MHz): δ = 4.49 (qd, $^3J_{H,H}$ = 7.2, $^2J_{P,H}$ = 4.5 Hz, PCHO), 4.36 (q, $^3J_{H,H}$ = 7.2 Hz, PCHO), 4.00−4.28 (m, 6 H, 3 CH_2O), 1.52 (dd, $^3J_{H,H}$ = 7.2, $^3J_{P,H}$ = 13.1 Hz, CH_3) and 1.43 (dd, $^3J_{H,H}$ = 7.2, $^3J_{P,H}$ = 12.6 Hz, CH_3), 1.15−1.37 (m, 9 H, 3 CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 173.06 (d, $^2J_{P,C}$ = 40.9 Hz, C=), 172.97 (d, $^2J_{P,C}$ = 40.9 Hz, C=), 163.05 (d, $^2J_{P,C}$ = 5.9 Hz, C=O), 162.97 (d, $^2J_{P,C}$ = 5.6 Hz, C=O), 75.81 (d, $^1J_{P,C}$ = 98.3 Hz, PCH), 75.22 (d, $^1J_{P,C}$ = 99.7 Hz, PCH), 74.02 (d, $^1J_{P,C}$ = 147.0 Hz, P−C), 73.74 (d, $^1J_{P,C}$ = 144.4 Hz, P−C), 66.08 (s, CH_2), 62.85 (d, $^2J_{P,C}$ = 6.7 Hz, CH_2), 62.55 (d, $^2J_{P,C}$ = 6.7 Hz, CH_2), 59.72 (s, CH_2), 16.51 (d, $^3J_{P,C}$ = 5.9 Hz, CH_3), 14.66 (d, $^2J_{P,C}$ = 4.1 Hz, CH_3), 14.56 and 14.29 (2 s, 2 CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1716 ($\nu_{C=O}$), 1219 ($\nu_{P=O}$) cm^{-1}. MS FAB$^+$ (NBA): *m/z* (%) = 279 (31) $[M + H]^+$, 233 (100) $[M - EtO^-]^+$. HRMS (FAB$^+$, NBA): calcd. for $C_{11}H_{20}O_6P$ 279.0997; found 279.0995. $C_{11}H_{19}O_6P \cdot {}^{1/2}H_2O$ (287.25): calcd. C 46.00, H 7.02; found C 45.94, H 7.15.

Diethyl [Bis(chloromethyl)phosphoryl]malonate (13): Diethyl malonate (0.90 g, 5.5 mmol, 1 equiv.) in anhydrous THF (10 mL) was added dropwise to a suspension of 95% sodium hydride (0.13 g, 5.5 mmol, 1 equiv.) in anhydrous THF (30 mL) at −20 °C in a three-necked round-bottom flask equipped with a magnetic stirrer, a condenser and a dropping funnel. After the hydrogen gas had evolved, this solution was added dropwise using a cannula to a solution of bis(chloromethyl)phosphinic chloride (**7a**, 1.00 g, 5.5 mmol, 1 equiv.) in THF (20 mL) at −20 °C. The reaction was stirred for1 h at room temperature. The reaction mixture was then filtered to remove sodium chloride and the filtrate was then concentrated using a rotary evaporator to remove THF. Addition of dichloromethane (50 mL) followed by filtration to remove any impurities gave after concentration a yellowish solid (1.27 g, 4.2 mmol, 77%). ^{31}P NMR ($CDCl_3$, 81.051 MHz): δ = 39.60 (s) ppm. ^{1}H NMR ($CDCl_3$, 250.13 MHz): δ = 11.95 (br. s, 1 H, PCH), 4.21 (q, $^3J_{H,H}$ = 7.1 Hz, 4 H, 2 CH_2O), 3.76 (d, $^2J_{P,H}$ = 8.8 Hz, 4 H, 2 CH_2Cl), 1.29 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, 2 CH_3) ppm. MS FAB$^+$ (Matrix NBA): *m/z* = 305 $[M + H]^+$, 205 $[M + H - 2\,CH_2{=}CH_2 - CO_2]^+$.

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