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Reactions of β-alkoxyvinyl trihalogenomethyl ketones with triethyl phosphite

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Dedicated to Prof. Kenji Uneyama on the occasion of his winning of the ACS Award.

Abstract

The Perkow reaction of triethyl phosphite and β-alkoxyvinyl trihalogenomethyl ketones, which have common acyclic or cyclic structural fragment: –O–C=C–C(O)CX_2Cl, yielded dienyl phosphates: –O–C=C–C[OP(O)$(OEt)_2$]=CX_2 where X = F or Cl, whereas γ-bromo-β-methoxy-α,β-unsaturated trifluoromethyl ketone $CF_3C(O)CH{=}C(OMe)CH_2Br$ gave diene $CF_3C[OP(O)(OEt)_2]{=}CH{-}C(OMe){=}CH_2$.

Keywords: Triethyl phosphite; Trihalogenomethyl enones; Perkow reaction; Fluoro-containing phosphates; Fluoro-containing dienes

1. Introduction

It is well established that both the introduction of the fluorine atom or fluorinated groups [1] and phosphorous-containing fragments [2] into organic molecules can change their chemical and physical properties. The combination of two features in one molecule is useful methodology to search for new effective inhibitors of enzyme systems [3].

Chloro-containing vinyl phosphates were widely used at the second half of 20th century as powerful insecticides (DDVP, phosdrine, etc.) which are easy to synthesize by Perkow reaction – the interaction of trialkyl phosphites and α-halogeno carbonyl compounds [4]. However, until now Perkow reaction of fluorinated α-halogeno carbonyl compounds is not practically explored. Only three reports are available: the interaction of chlorodifluoromethyl ketones and di- or trialkyl phosphites gave difluoromethylene-containing vinyl phosphates which are of interest as pesticides [5] or intermediate compounds [6,7].

In our previous papers, we described the potential of β-alkoxyvinyl polyfluoroalkyl ketones **1** as useful synthons in fluoroorganic synthesis that was demonstrated by numerous examples of a synthesis of mostly trifluoromethyl-containing compounds such as heterocycles [8–11], aliphatic polyfunctional products [12–14] and also the enone was proposed as protective reagent in peptide synthesis [15]. At the same time it is known only a few examples of the reaction between β-alkoxyvinyl polyfluoroalkyl ketones and phosphites (Scheme 1): [1 + 4] cycloaddition of triethyl phosphite with (3*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one **1** [16]; an addition of diethyl phosphite to enone **1** with formation of the mixture of *E*- and *Z*-adducts [17]; and the reaction of tris(trimethylsilyl) phosphite with enone **1** which resulted in the mixture of 1,2- and 1,4-adducts [18].

Here, we report investigations on the reactivity of β-alkoxyvinyl chlorodifluoro-, trichloromethyl ketones with triethyl phosphite.

2. Results and discussion

2.1. Reaction of α-chloroenones 2, 6 and 8 with triethyl phosphite

The α- or γ-halogeno enones, which have common acyclic or cyclic structural fragment: –O–C=C–C(O)CX_2Cl where X = F or Cl were used in this work and were prepared by acylation reaction of correspondingly alkyl vinyl ethers [19,20]. In most cases the reaction of alkoxyenones **2** with triethyl phosphite occurs at soft conditions and corresponding dienyl phosphates **3**

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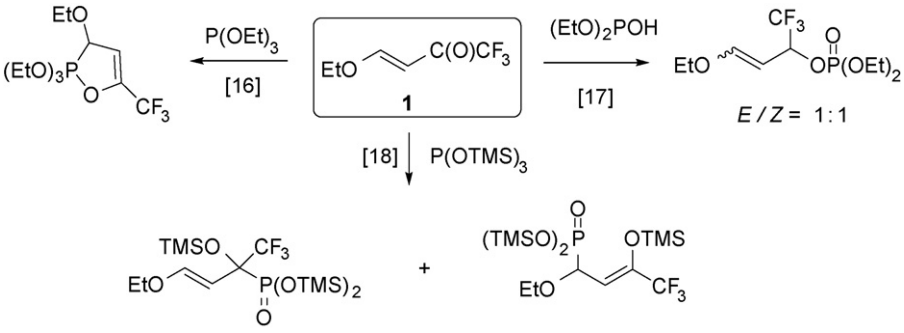


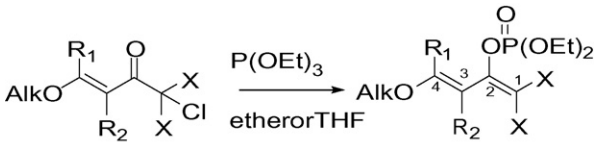
Scheme 1.

are formed in good yields (based on the ^{19}F and ^{31}P NMR spectra of the reaction mixtures) as a result of Perkow reaction (Scheme 2; Table 1, entries 1–6). The effectiveness of phosphorylation was monitored by TLC and/or ^{31}P and/or ^{19}F NMR spectroscopy, at that usually we observed the formation of only few phosphorus-containing unidentified by-products (with δ_P from 5 to −6 ppm) whose total percentage did not exceed 3–8%.

All structural and configurational assignments are based on the analysis of ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra. The diethyl phosphate group demonstrated a characteristic signal in the ^{31}P NMR spectra: multiplet at from 3 to −6 ppm for dienes **3**. Moreover, it was proved by ^{13}C NMR spectral data: doublet character of 2-C signal at about 109–118 ppm ($^{2}J_{CP}$ = 8–11 Hz) for dienes **3**, and ^{19}F NMR spectral data: two doublet of doublets (for **3b** at −93.12 and −104.53 ppm, $^{2}J_{FF}$ = 42.3, $^{4}J_{FP}$ = 6.0, $^{4}J_{FP}$ = 9.1 Hz) – ABX-system for fluoro-containing dienes **3a–c**. The alkyl vinyl ether double bond (C_3=C_4) in the dienes **3** has *E*-configuration as in the starting enones **2** since the observed olefinic coupling constant of 3-H and 4-H (about $^{3}J_{HH}$ = 13 Hz) for **3a**,**d** and a similarity of the corresponding chemical shifts of these protons for dienes **3**.

In order to decrease the reaction time we tried to increase the reaction temperature but it resulted in the formation of complex product mixtures. We found that the stability of dienyl phosphates **3** depended on the nature of substituents at the C=C double bonds. Thus, the compound **3a** (X = F) was not isolated in pure form and characterized only by NMR spectroscopy, whereas the product **3d** (X = Cl) was isolated by vacuum distillation. Bromo-substituted products **3b** and **3e** are the most thermally and hydrolytically stable among the dienyl phosphates synthesized. Methyl-substituted products **3c** and **3f** are very sensitive to moisture and we observed the formation of the mixture of corresponding ketones **4** and ketals **5** when allowed to stand in $CDCl_3$ solution at room temperature for several days (Scheme 3). This fact can be explained by hydrolysis of alkylvinyl ether fragment of dienes **3c**,**f** to ketones **4** with following addition of methanol to another molecule of dienes **3c**,**f** that results in the formation of ketals **5**. The structural assignments of compounds **4** and **5** are based on the analysis of ^{1}H, ^{31}P and/or ^{19}F NMR spectral data. Thus, the signals of olefinic hydrogen atom, methyl and methoxy groups of dienes **3c**,**f** disappeared and simultaneously the signals of methyl and methylene groups bonded to sp^2 and sp^3 hybridized carbon atoms grew for compounds **4** and **5**, correspondingly, in almost equal proportions.

Instead of above mentioned Perkow reaction of acyclic alkoxyenones **2**, the reaction of trichloromethyl-containing cyclic enones **6** with triethyl phosphite occurs only under reflux in benzene solution and corresponding dichlorodienyl phosphates **7** are formed in moderate yields (Scheme 4; Table 1, entries 7 and 8). Structural and configurational assignments for dienes **7** are based on the analysis of ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectral data which are very close to the data for chloro-containing compounds **3d–f** (see Section 4).



2 **3**

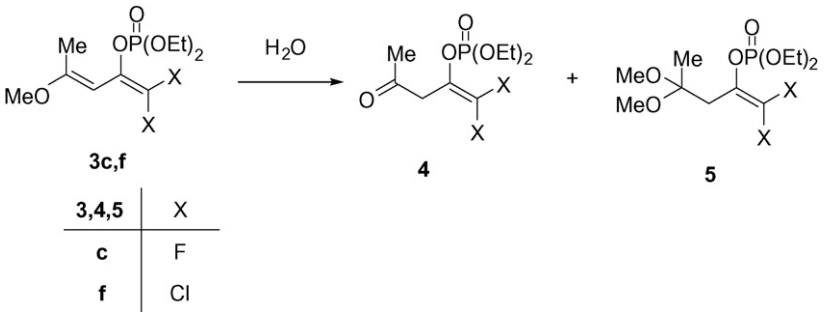
2, 3	X	Alk	R_1	R_2
a	F	Et	H	H
b	F	Et	H	Br
c	F	Me	Me	H
d	Cl	Et	H	H
e	Cl	Et	H	Br
f	Cl	Me	Me	H

Scheme 2.

Table 1
Conditions and yields for the reactions of **2**, **6** and **13** with triethyl phosphite

Entries	Compounds	Solvents	*T* (°C)	Time (days)	Yield[a] (%)
1	**2a**	Ether	20	2	–(62)
2	**2b**	Ether	20	4	82 (90)
3	**2c**	Ether	20	6	37 (70)
4	**2d**	Ether	20	6	65 (87)
5	**2e**	Ether	20	6	73 (92)
6	**2f**	THF	65	5	15 (23)
7	**6a**	Benzene	80	4	37 (65)
8	**6b**	Benzene	80	4	41 (65)
9	**13a**	Ether	20	5	42 (72)
10	**13b**	Ether	20	5	39 (64)
11	**13c**	Ether	20	5	35 (60)

[a] In parentheses the proportional contributions to crude reaction mixtures.



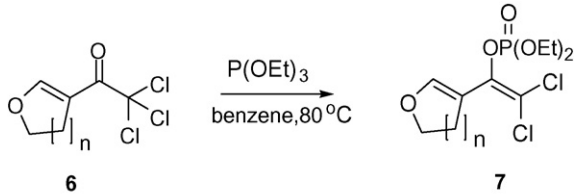
3c,f

4

5

3,4,5	X
c	F
f	Cl

Scheme 3.



6

7

6,7	n
a	1
b	2

Scheme 4.

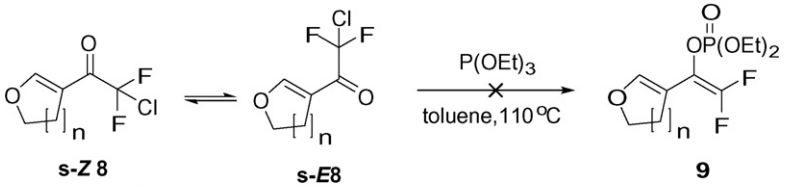
Unexpectedly, under refluxing of chlorodifluoromethyl-containing cyclic enones **8** with triethyl phosphite in toluene for a week we did not observe the formation of desired corresponding difluorodienyl phosphates **9** by the ^{19}F and ^{31}P NMR spectra of the reaction mixtures (Scheme 5).

The difference of the reaction ability between the cyclic enones **6** and **8** could be explained if we consider a possible Perkow-type reaction mechanism. Recently Polish scientists [21] supposed the mechanism of a reaction between γ-halogeno-α,β-unsaturated ketones and trialkyl phosphites which ran through initial formation of oxaphospholene intermediate. We believe that in our case a similar cyclic intermediate **10** is also formed primarily (Scheme 6). Then simultaneous dissociation of the phosphor–carbon bond and the elimination of chloride anion gives diene **11**. The following dealkylation results in dienyl phosphates **3** and **7**. One can see that [1 + 4] heterocycloaddition of triethyl phosphite to enones **2**, **6** or **8** is possible when the conjugated system is in s-*Z* conformation between C=C and C=O double bonds. From this point of view the absence of dienyl phosphates **9** in the reaction mixture can be explained by low stability of s-*Z*-**8**. We compared the stability of s-*Z* and s-*E* conformers of enones **6** and **8** on the basis of quantum chemical calculations *ab initio* (6–31**) and found that values of the total energy of s-*Z* and s-*E* conformers of enone **6a** are close, whereas s-*E* conformer of enone **8a** is more stable than s-*Z*-**8** with the difference in energy about 1 kcal/mol.

2.2. Reaction of γ-bromoenones *13* with triethylphosphite

As it was mentioned above W. Waszkuć and T. Janecki demonstrated that the structure of products (dienyl phosphates or phosphonates—results of Perkow or Arbuzov reactions, correspondingly) depends on the nature of γ-halogenoketones [21]. Recently, we published simple and useful synthetic route to γ-bromo-β-alkoxy-α,β-unsaturated ketones **13** by bromination enones **12** [22] (Scheme 7) and it was interesting to check on the regioselectivity of a phosphorylation of the enones **13b**,**c** bearing as γ-bromo- so α-chloro-substituents which both can be involved in Perkow reaction.

Instead of published results (the reaction temperature was 80–140 °C) [21] in our case the enones **13** react with triethyl phosphite at room temperature for several days in ether solution and corresponding dienyl phosphates **14** and **18** are formed in moderate yields (based on the ^{19}F and ^{31}P NMR spectra of the reaction mixtures) as a result of Perkow reaction (Schemes 8 and 11; Table 1, entries 9–11). In the case of the reaction between enone **13a** and triethyl phosphite the phosphate **14** was formed which structure is very similar to non-fluorinated



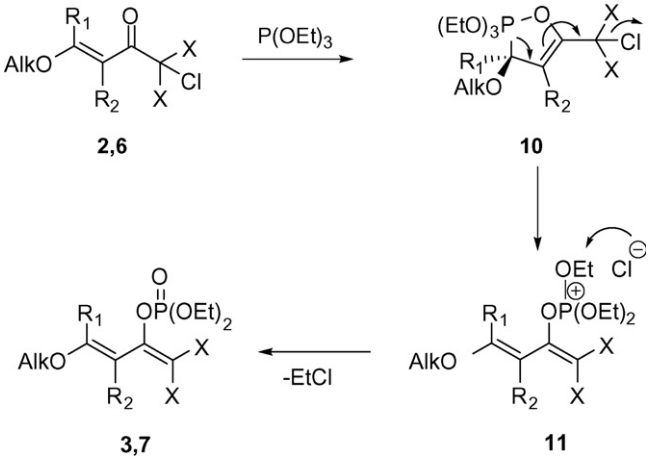
s-*Z* 8

s-*E*8

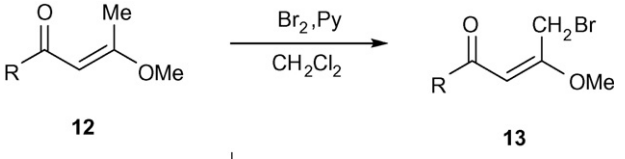
9

8,9	n
a	1
b	2

Scheme 5.

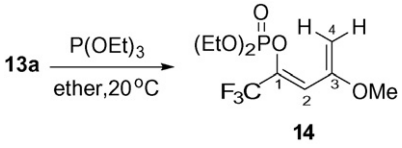


Scheme 6.



12,13	R
a	CF_3
b	$CClF_2$
c	CCl_3

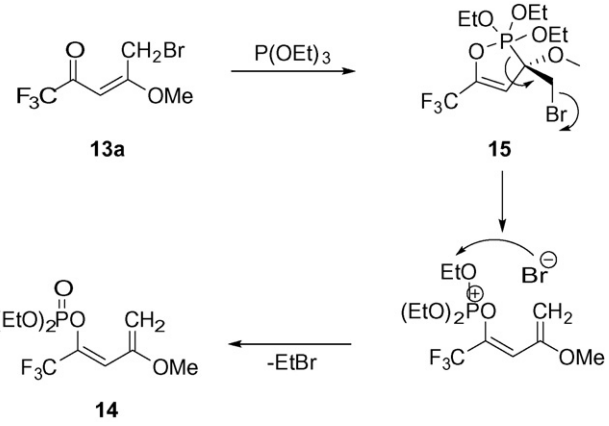
Scheme 7.



Scheme 8.

analogs: the chemical shift of the proton at the position 2 in the **14** (doublet at 6.08 ppm, $^4J_{HP}$ = 2.0 Hz) is similar to *Z*-isomer of non-fluorinated analog (doublet at 6.02 ppm, $^4J_{HP}$ = 1.0 Hz) [21]. The diethyl phosphate group demonstrates a characteristic signal in the ^{31}P NMR spectra as multiplet at about −3.09 ppm, and a characteristic signal of trifluoromethyl group bonded to C=C double bond is observed in the ^{19}F NMR spectra: singlet at −71.24 ppm. The terminal olefinic protons appeared in the ^{1}H NMR spectra as two broadened doublets at 4.43 and 4.49 ppm ($^2J_{HH}$ = 2.0 Hz).

The formation of new C=C double bond is fully stereoselective and leads to a single *Z*-stereoisomer of the



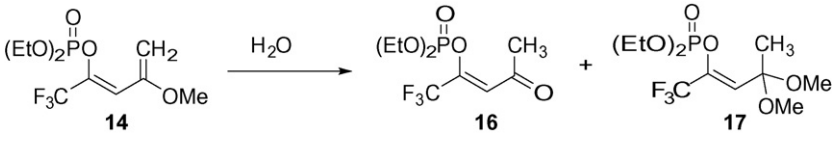
Scheme 9.

diene **14**. This assumption based on stereochemical evaluation of similar products of Perkow rearrangement and arose from proposed mechanism of the reaction which runs through initial formation of oxaphospholene intermediate [21]. We believe, in the case of vinylogous Perkow reaction between enone **13a** and triethyl phosphite the same cyclic intermediate **15** is formed primarily also (Scheme 9).

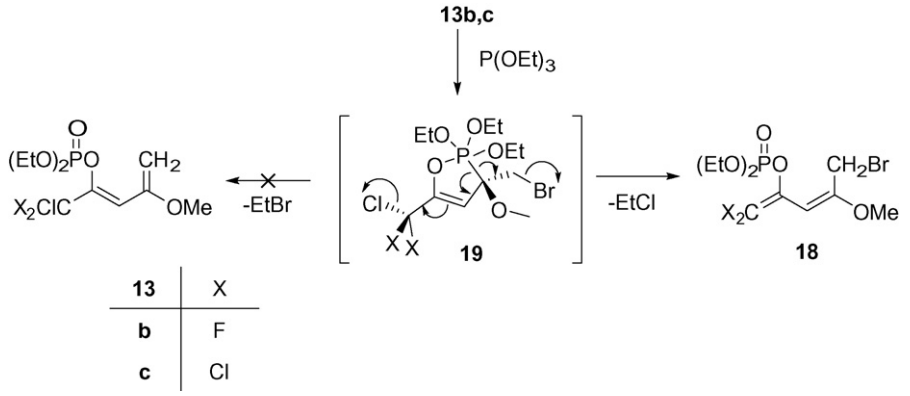
The hydrolytic stability of the diene **14** is similar to dienes **3c**,**f** and we observed the formation of the mixture of corresponding ketone **16** and ketal **17** when allowed to stand in $CDCl_3$ solution at room temperature for several days (Scheme 10). The changes in the ^{1}H, ^{19}F and ^{31}P NMR spectra of the hydrolyzed mixture are very similar to signal modifications at the transformation of diene **3c**,**f** to ketone **4** and ketal **5** (see above). At the same time the heating of the diene **14** in methanol gives the ketal **17** as almost a sole product.

Instead of the enone **13a**, γ-bromo-α,β-unsaturated halogeno ketones **13b** and **13c** react with triethyl phosphite in the manner of α-chloro ketones **2** and produce dienyl phosphates **18**, which structural is very similar to the one dienes **3c**,**f** (Scheme 11; Table 1, entries 10 and 11). Taking into account that bromide is a better leaving group than chloride, we can explain the fact of the diene **18** formation starting from structural consideration of the intermediate oxaphospholene **19**. We believe that the elimination of chloride ion from $CClX_2$ group, which is located in a plane of the oxaphospholene ring, is more energy preferable than the elimination of bromide ion from CH_2Br group, which is located out the plane of the heterocycle ring and the formation of conjugated diene system in the letter case should demand additional energy.

Structural and configurational assignments for dienes **18** are based on the analysis of ^{1}H, ^{31}P and/or ^{19}F NMR spectral data which are very close to the data for compounds **3c**,**f**: the main



Scheme 10.



Scheme 11.

difference is singlet of bromomethyl group shifted to low field instead of methyl one.

3. Conclusions

The phosphorylation of α-chloro-β-alkoxyvinyl trihalogenomethyl ketones **2**, **6** and **13b**,**c** with triethyl phosphite gave di(fluoro,chloro)methylene-containing dienyl phosphates **3**, **7** and **18** as the result of Perkow reaction, whereas γ-bromo-β-methoxy-α,β-unsaturated trifluoromethyl ketone **13a** gave diene **14** bearing trifluoromethyl group at C=C double bond. The mechanistic scheme was proposed to explain the formation of all products. The synthesized fluoro-containing compounds are of synthetic interest due to the formation of a variety of highly functionalized organophosphorus compounds such as 1,3-dienyl phosphates or keto- and ketal-vinyl phosphates in good to high yields.

4. Experimental

Unless specified, all reactions were carried out under an atmosphere of nitrogen or argon with rigid exclusion of moisture. The ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR-spectra were recorded on a Bruker DRX-500 instrument at 500, 125, 470 and 202 MHz, respectively. All spectra were recorded in $CDCl_3$. Chemical shifts (δ) are given in ppm relative to TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F) and 85% phosphoric acid (^{31}P). All solvents used were dried by distillation. Compounds **2a–f**, **6a**,**b**, **7a**,**b**, **12a–c** and **13a–c** were prepared according literature procedures [11,22]. $P(OEt)_3$ was commercially available from "Aldrich Chemical Company, Inc." Column chromatography was performed on silica gel 60 (Merck).

*4.1. Typical procedure for the synthesis of phosphates **3**, **7**, **14** and **18***

A solution of triethyl phosphite (5.5 mmol) in diethyl ether (10 mL) was added dropwise with stirring to a solution of **2**, **6** or **13** (5 mmol) in diethyl ether (10 mL) at −30 °C in the atmosphere of argon or nitrogen. After the addition had been finished, the temperature of the reaction mixture was arisen to RT. The end of the reaction was determined by TLC, ^{31}P and/or ^{19}F NMR spectra. Reaction mixture was washed with 5% solution $NaHCO_3$ (2 × 3 mL) and dried under $MgSO_4$. The solvent was removed in vacuum. Depends on a stability of the phosphate the product was purified by column chromatography (eluent ethyl acetate/hexane = 1:2) or distilled in vacuum. The reaction conditions and yields for the reactions of **2**, **6** and **13** with triethyl phosphite (see Table 1).

*4.1.1. (2E)-1-(Difluoromethylene)-3-ethoxyprop-2-enyl diethyl phosphate (**3a**)*

Light yellow oil. ^{1}H NMR: δ 1.27–1.40 (m, 9H, 3CH_3), 4.07–4.26 (m, 6H, 3OCH_2), 5,29 (dd, 1H, =C*H*–C, $^{3}J_{HH}$ = 12.7 Hz, $^{4}J_{HP}$ = 3.3 Hz), 6.78 (d, 1H, =C*H*–O, $^{3}J_{HH}$ = 12.7 Hz). ^{19}F NMR: δ −101.11 (d, 1F, $^{2}J_{FF}$ = 61.2 Hz), −113.46 (d, 1F, $^{2}J_{FF}$ = 61.2 Hz). ^{31}P NMR: δ 0.46 (m).

*4.1.2. (2Z)-2-Bromo-1-(difluoromethylene)-3-ethoxyprop-2-enyl diethyl phosphate (**3b**)*

Light yellow oil. ^{1}H NMR: δ 1.34 (m, 9H, 3CH_3), 4.07 (q, 2H, CH_2CH$_3$, $^{3}J_{HH}$ = 7.1 Hz), 4.18 (m, 4H, 2POCH_2), 6.92 (s, 1H, =C*H*). ^{13}C NMR δ: 15.27, 15.95 (d, $^{3}J_{CP}$ = 7.2), 64.77 (d, $^{2}J_{CP}$ = 6.9 Hz), 70.01, 85.63 (m), 110.21 (ddd, $^{2}J_{CP}$ = 7.6 Hz, $^{2}J_{CF}$ = 22.9 Hz, $^{2}J_{CF}$ = 44.3 Hz), 151.52 (dd $^{4}J_{CF} \approx {}^{4}J_{CF} \approx$ 2.4 Hz, 154.85 (ddd $^{3}J_{CP}$ = 9.2 Hz, $^{1}J_{CF}$ = 283.8 Hz, $^{1}J_{CF}$ = 296.8 Hz). ^{19}F NMR: δ −93.12 (dd, 1F, $^{2}J_{FF}$ = 42.3 Hz, $^{4}J_{FP}$ = 6.0 Hz), −104.53 (dd, 1F, $^{2}J_{FF}$ = 42.3 Hz, $^{4}J_{FP}$ = 9.1 Hz). ^{31}P NMR: δ 1.34 (m). Anal. Calcd for $C_{10}H_{16}BrF_2O_5P$: C, 32.9; H, 4.4. Found: C, 32.7; H, 4.6.

*4.1.3. (2E)-1-(Difluoromethylene)-3-methoxybut-2-enyl diethyl phosphate (**3c**)*

Light yellow oil. ^{1}H NMR: δ 1.29–1.35 (m, 6H, 2CH_3), 1.85 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 4.07–4.19 (m, 4H, 2POCH_2), 4.79 (br m, 1H, =C*H*). ^{19}F NMR: δ −99.85 (ddd, $^{2}J_{FF}$ = 56.8 Hz, $^{4}J_{FP} \approx {}^{4}J_{FH} \approx$ 5.5 Hz), −110.20 (dd, $^{2}J_{FF}$ = 56.8 Hz, $^{4}J_{FP}$ = 9.2 Hz). ^{31}P NMR: δ 0.60 (m).

*4.1.4. (2E)-1-(Dichloromethylene)-3-ethoxyprop-2-enyl diethyl phosphate (**3d**)*

Light yellow oil. bp 120–123 °C/1 mm. ^{1}H NMR: δ 1.28 (t, 3H, CH_3, $^{3}J_{HH}$ = 7.1 Hz), 1.32 (m, 6H, 2CH_3), 3.85 (q, 2H, OCH_2, $^{2}J_{HH}$ = 7.1 Hz), 4.20 (m, 4H, 2POCH_2), 5,73 (d, 1H,

=C*H*–C, $^3J_{HH}$ = 12.7 Hz), 7.05 (d, 1H, =C*H*–O, $^3J_{HH}$ = 12.7 Hz). ^{13}C NMR: δ 14.60, 16.07 (d, $^3J_{CP}$ = 6.9 Hz), 64.98 (d, $^2J_{CP}$ = 6.5 Hz), 66.57, 97.40, 109.18 (d, $^3J_{CP}$ = 9.1 Hz), 142.34 (d, $^2J_{CP}$ = 9.5 Hz), 153.40. ^{31}P NMR: δ −6.48 (m). Anal. Calcd for $C_{10}H_{17}Cl_2O_5P$: C, 37.6; H, 5.4. Found: C, 37.6; H, 5.6.

*4.1.5. (2Z)-2-Bromo-1-(dichloromethylene)-3-ethoxyprop-2-enyl diethyl phosphate (**3e**)*

Light yellow oil. ^{1}H NMR: δ 1.36 (m, 9H, 3C*H*$_3$), 4.09 (q, 2H, C*H*$_2$CH$_3$, $^3J_{HH}$ = 7.1 Hz), 4.22 (m, 4H, 2POC*H*$_2$), 6.97 (s 1H, =C*H*). ^{13}C NMR: δ 15.46, 16.00 (d, $^3J_{CP}$ = 7.8 Hz), 65.04 (d, $^2J_{CP}$ = 6.2 Hz), 70.15, 118.64 (d, $^2J_{CP}$ = 10.7 Hz), 140.53 (d, $^3J_{CP}$ = 7.6 Hz), 152.81. ^{31}P NMR: δ 2.59 (m). Anal. Calcd for $C_{10}H_{16}BrCl_2O_5P$: C, 30.2; H, 4.1. Found: C, 30.4; H, 4.2.

*4.1.6. (2E)-1-(Dichloromethylene)-3-methoxybut-2-enyl diethyl phosphate (**3f**)*

Light yellow oil. ^{1}H NMR: δ 1.32 (m, 6H, 2C*H*$_3$), 1.90 (s, 3H, C*H*$_3$), 3.59 (s, 3H, OC*H*$_3$), 4.16 (m, 4H, 2POC*H*$_2$), 5.01 (s, 1H, =C*H*). ^{31}P NMR: δ −1.89 (m).

*4.1.7. 2,2-Dichloro-1-(4,5-dihydrofuran-3-yl)vinyl diethyl phosphate (**7a**)*

Light yellow oil. ^{1}H NMR: δ 1.30 (t, 6H, 2C*H*$_3$, $^3J_{HH}$ = 7.0 Hz), 3.02 (m, 2H, C*H*$_2$), 4.16 (m, 4H, 2POC*H*$_2$), 4.42 (m, 2H, C*H*$_2$), 6.90 (s, 1H, =C*H*). ^{13}C NMR: δ 16.10 (d, $^3J_{CP}$ = 6.8 Hz), 30.84, 64.88 (d, $^2J_{CP}$ = 6.2 Hz), 71.95, 108.86 (d, $^3J_{CP}$ = 1.5 Hz), 110.82 (d, $^2J_{CP}$ = 9.2 Hz), 140.07 (d, $^3J_{CP}$ = 9.2 Hz), 151.18. ^{31}P NMR: δ −1.61 (m). Anal. Calcd for $C_{10}H_{15}Cl_2O_5P$: C, 37.9; H, 4.8. Found: C, 38.1; H, 5.0.

*4.1.8. 2,2-Dichloro-1-(3,4-dihydro-2H-pyran-5-yl)vinyl diethyl phosphate (**7b**)*

Light yellow oil. ^{1}H NMR δ: 1.24 (m, 6H, 2C*H*$_3$), 1.79 (m, 2H, C*H*$_2$), 2.12 (m, 2H, C*H*$_2$), 3.91 (m, 2H, C*H*$_2$), 4.08 (m, 4H, 2C*H*$_2$), 6.66 (s, 1H, =C*H*). ^{13}C NMR: δ 15.97 (d, $^3J_{CP}$ = 6.9 Hz), 21.24, 21.59, 64.49 (d, $^2J_{CP}$ = 6.1 Hz), 65.90, 105.23, 112.62 (d, $^2J_{CP}$ = 10.8 Hz), 144.13 (d, $^3J_{CP}$ = 6.2 Hz), 149.04. ^{31}P NMR: δ −2.11, (m). Anal. Calcd for $C_{11}H_{17}Cl_2O_5P$: C, 39.9; H, 5.2. Found: C, 39.7; H, 5.0.

*4.1.9. Diethyl (1Z)-3-methoxy-1-(trifluoromethyl)buta-1,3-dienyl phosphate (**14**)*

Light yellow oil. ^{1}H NMR: δ 1.31–1.39 (m, 6H, 2C*H*$_3$), 3.61 (s, 3H, OC*H*$_3$), 4.14–4.24 (m, 4H, 2POC*H*$_2$), 4.43 (d, 1H, =C*H*H, $^2J_{HH}$ = 2.0 Hz), 4.49 (d, 1H, =CH*H*, $^2J_{HH}$ = 2.0 Hz), 6.08 (d, 1H, =CH, $^4J_{HP}$ = 2.0 Hz). ^{19}F NMR: δ −71.24 (s). ^{31}P NMR: δ −3.09 (m).

*4.1.10. (2E)-4-Bromo-1-(difluoromethylene)-3-methoxybut-2-enyl diethyl phosphate (**18b**)*

Light yellow oil. ^{1}H NMR: δ 1.31–1.37 (m, 6H, 2C*H*$_3$), 3.67 (s, 3H, OC*H*$_3$), 4.03 (s, 2H, C*H*$_2$Br), 4.14–4.24 (m, 4H, 2POC*H*$_2$), 5.03 (br s, 1H, =C*H*). ^{19}F NMR: δ −96.36 (ddd, $^2J_{FF}$ = 51.6 Hz, $^4J_{FP} \approx {}^4J_{FH} \approx$ 4.7 Hz), −106.55 (dd, $^2J_{FF}$ = 51.6 Hz, $^4J_{FP}$ = 9.2 Hz). ^{31}P NMR: δ 0.51 (m).

*4.1.11. (2E)-4-Bromo-1-(dichloromethylene)-3-methoxybut-2-enyl diethyl phosphate (**18c**)*

Light yellow oil. ^{1}H NMR: δ 1.32–137 (m, 6H, 2C*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 4.03 (s, 2H, C*H*$_2$Br), 4.15–4.23 (m, 4H, 2POC*H*$_2$), 5.25 (d, 1H, =C*H*, $^3J_{HP}$ = 2.0 Hz). ^{31}P NMR: δ −1.92 (m).

*4.2. Typical procedure for the hydrolysis of phosphates **3c,f** and **14***

A solution of the phosphate (0.5 mmol) in $CDCl_3$ (1 mL) was standing in NMR tube at room temperature for 1–2 week and the hydrolysis was monitored by ^{1}H, ^{31}P and/or ^{19}F NMR spectroscopy.

*4.2.1. 2,2-Difluoro-1-(2-oxopropyl)vinyl diethyl phosphate (**4c**)*

^{1}H NMR: δ 1.29–1.35 (m, 6H, 2C*H*$_3$), 2.21 (s, 3H, C*H*$_3$), 3.41 (s, 2H, C*H*$_2$), 4.07–4.19 (m, 4H, 2POC*H*$_2$). ^{19}F NMR: δ −98.30 (dm, $^2J_{FF}$ = 60.5 Hz), −111.95 (dm, $^2J_{FF}$ = 60.5 Hz). ^{31}P NMR: δ 0.18 (m).

*4.2.2. 1-(2,2-Dimethoxypropyl)-2,2-difluorovinyl diethyl phosphate (**5c**)*

^{1}H NMR: δ 1.29–1.35 (m, 9H, 3C*H*$_3$), 2.60 (s, 2H, C*H*$_2$), 3.17 (s, 6H, 2OC*H*$_3$), 4.07–4.19 (m, 4H, 2POC*H*$_2$). ^{19}F NMR: δ −98.60 (dm, $^2J_{FF}$ = 60.5 Hz), −112.60 (dm, $^2J_{FF}$ = 60.5 Hz). ^{31}P NMR: δ −0.10 (m).

*4.2.3. 2,2-Dichloro-1-(2-oxopropyl)vinyl diethyl phosphate (**4f**)*

^{1}H NMR: δ 1.32 (m, 6H, 2C*H*$_3$), 2.22 (s, 3H, C*H*$_3$), 3.76 (s, 2H, C*H*$_2$), 4.16 (m, 4H, 2POC*H*$_2$). ^{31}P NMR: δ −2.72 (m).

*4.2.4. 2,2-Dichloro-1-(2,2-dimethoxypropyl)vinyl diethyl phosphate (**5f**)*

^{1}H NMR: δ 1.32 (m, 6H, 2C*H*$_3$), 1.36 (s, 3H, C*H*$_3$), 2.95 (s, 2H, C*H*$_2$), 3.19 (s, 6H, 2OC*H*$_3$), 4.16 (m 4H, 2POC*H*$_2$). ^{31}P NMR: δ −2.93 (m).

*4.2.5. Diethyl (1Z)-3-oxo-1-(trifluoromethyl)but-1-enyl phosphate (**16**)*

^{1}H NMR: δ 1.31–1.39 (m, 6H, 2C*H*$_3$), 2.37 (s, 3H, C*H*$_3$), 4.14–4.24 (m, 4H, 2POC*H*$_2$), 6.32 (d, 1H, =C*H*, $^3J_{HP}$ = 2.0 Hz). ^{19}F NMR: δ −70.98 (s). ^{31}P NMR: δ −3.16 (m).

*4.2.6. (1Z)-3,3-Dimethoxy-1-(trifluoromethyl)but-1-enyl diethyl phosphate (**17**)*

^{1}H NMR: δ, 1.31–1.39 (m, 6H, 2C*H*$_3$), 1.55 (s, 3H, C*H*$_3$), 3.19 (s, 6H, 2OC*H*$_3$), 4.14–4.24 (m, 4H, 2POC*H*$_2$), 5.77 (d, =C*H*, $^3J_{HP}$ = 2.0 Hz). ^{19}F NMR: δ −70.87 (s). ^{31}P NMR: δ −3.25 (m).

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