ISSN 1070-3632, Russian Journal of General Chemistry, 2011, Vol. 81, No. 2, pp. 307–314. © Pleiades Publishing, Ltd., 2011.
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Pyridinium Perchlorate: A New Catalyst for the Reaction of Trialkyl Phosphites with the C=X Electrophiles

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Received August 26, 2010

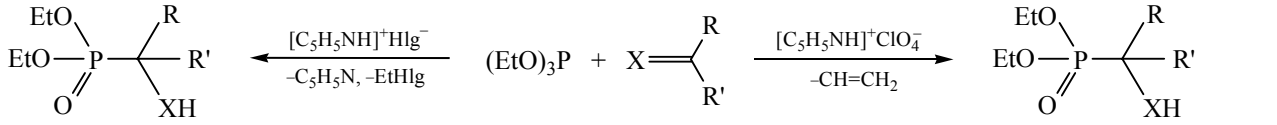
Abstract—Pyridinium perchlorate is an effective catalyst for the reaction of trialkyl phosphites with various C=X electrophiles: aldehydes, ketones, ketophosphonates, imines, isocyanates, isothiocyanates, and activated alkenes. The reaction leads to the formation of α-substituted phosphonates in a high yield. Advantages of the new catalyst are its high activity, availability, high product yields, and mild reaction conditions.

DOI: 10.1134/S107036321102006X

The synthesis of functionalized phosphonates has attracted much attention because of their high biological activity [1–3]. They act as mimetics of peptides, haptens of catalytic antibodies, antibiotics and pharmaceuticals, herbicides and enzyme inhibitors [4]. There are two main methods of synthesis of α-functionalized phosphonates: the reaction of dialkyl phosphites with unsaturated C=X electrophiles in the presence of Brønsted bases or Lewis acids (Abramov reaction [5, 6], Kabachnik–Fields reaction [7, 8], the Pudovik reaction [9, 10] etc.), and the reaction of trialkyl phosphites with aldehydes or imines in the presence of Lewis acids [7, 11]. However, despite the potential usefulness of these methods, they have several disadvantages, such as, for example, low activity compared to dialkyl phosphites toward ketones and ketimines. The reactions are accompanied by the formation of impurities appearing under the influence of alkaline catalysts (phosphate–phosphonate rearrangement [11], retro-Abramov reaction [12], and others). In addition, Lewis acids used as catalysts are sensitive to moisture and require very careful handling.

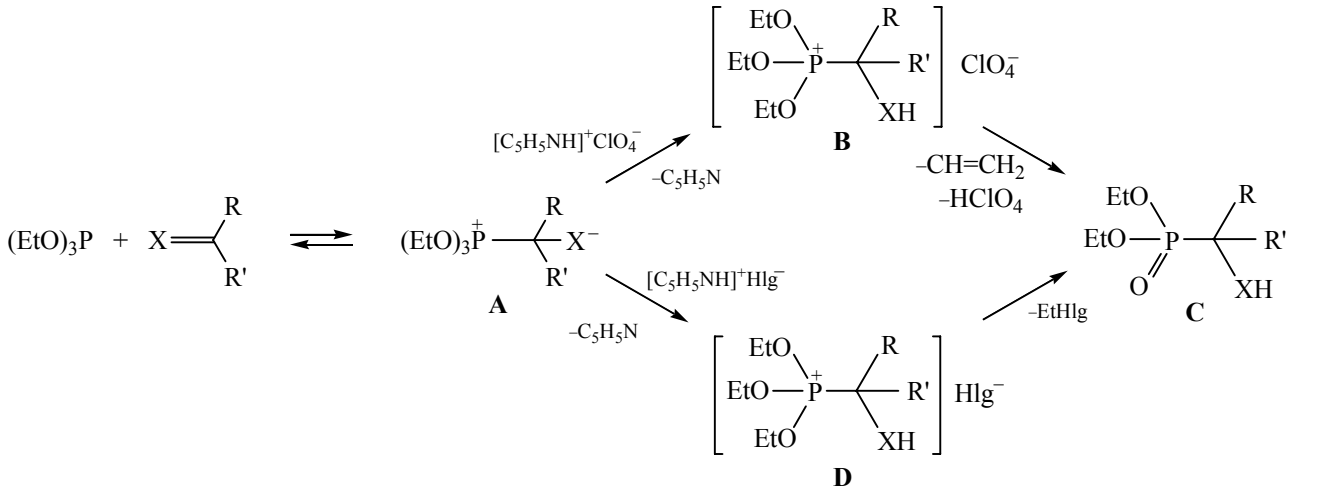
In this article we offer pyridinium perchlorate as a new effective catalyst for the phosphonylation of the C=X electrophiles (X = O, C, N, CR_2) with trialkyl phosphites. This probably is the first time that ammonium or pyridinium salts are used as catalysts of the reaction of trialkyl phosphites with electrophiles [13, 14].

We recently reported that pyridinium halides ($[C_5H_5NH]^+Hlg^-$, where Hlg = Cl, Br, I) activate the reaction of trialkyl phosphites with C=X electrophiles [15]. The pyridinium perchlorate reminds pyridinium halides by its action. The difference lies in the fact that pyridinium halides act as reagents and are consumed in the reaction with the formation of pyridine and alkyl halide, while pyridinium perchlorate is a catalyst rather than a reagent. It initiates the reaction of trialkyl phosphite with C=X electrophile, but it is not consumed in the reaction: The pyridinium perchlorate can be isolated from the reaction mixture in the same amount as introduced, and can be reused. No reduction of the catalyst activity was observed.



The scheme below underlain by the general theoretical concepts on the mechanism of the reaction of trialkyl phosphites with C=X electrophiles [1, 8], suggests the following reasons of the catalytic effect of pyridinium perchlorate. The nucleophilic attack of triethyl phosphite on the electron-deficient carbon

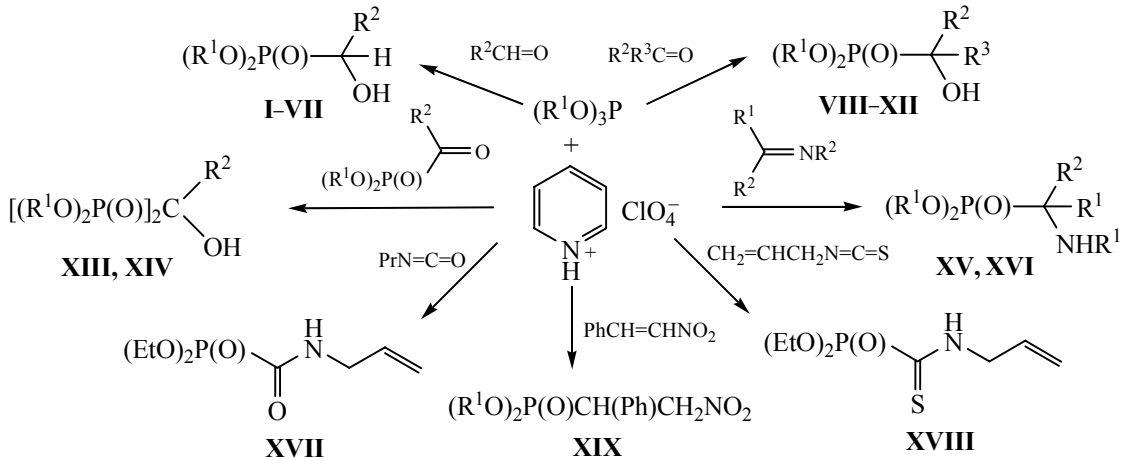
atom of the C=X group leads to the formation of betaine **A**, which reacts with the pyridinium perchlorate and is transformed into alkoxyphosphonium perchlorate **B** and pyridine. The salt **B** is unstable and decomposes with the formation of phosphonate **C**, alkene, and perchloric acid, which reacts with the pyridine formed in the previous stage, regenerating the catalyst. In contrast, the quasiphosphonium intermediate **D** formed from pyridinium halide decomposes liberating the alkyl halide.



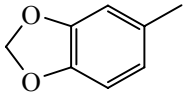
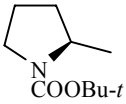
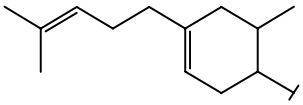
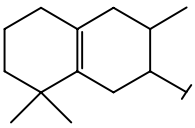
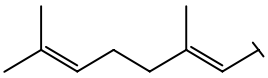
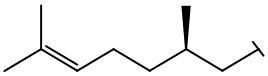
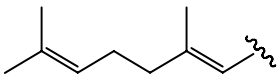
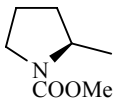
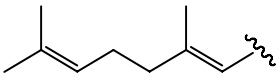
The pyridinium perchlorate initiates the reaction with alkyl electrophiles C=X more actively than pyridinium halides. The use of pyridinium perchlorate instead of halides increases the reaction rate and the yield of the reaction products. In all cases with pyridinium perchlorate as a catalyst the reaction proceeded smoothly without solvent or in a methylene chloride solution at room temperature with the formation of α-substituted phosphonates without unwanted impurities (see the table) [14].

$[C_5H_5NH]^+X^-$	X = Cl	X = Br	X = I	X = ClO_4
Reaction duration, h	12	12	6	5
Temperature, °C	35	35	25	25
Yield of **XI**, %	55	70	85	92

The pyridinium perchlorate can be easily prepared by the reaction of pyridine with perchloric acid in aqueous solution. The salt is poorly soluble in water and precipitated in a high yield as a crystalline substance. After filtering and drying in a vacuum desiccator, the pyridinium perchlorate is ready for use. Below are presented typical examples of the synthesis, demonstrating the high efficiency of pyridinium perchlorate as a catalyst for the reaction of trialkyl phosphites with the C=X electrophiles. This very active catalyst allows phosphonylation of some low-active electrophiles, which are difficult to turn into phosphonates by the other methods. The results are presented in the table.



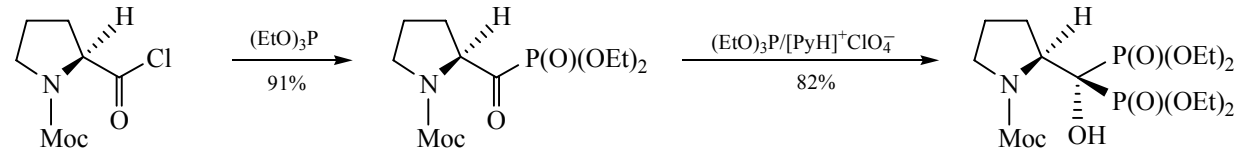
Products yield and the conditions of reaction $(R^1O)_3P + R^2R^3C{=}X + [C_5H_5NH]^+ ClO_4^- \rightarrow (R^1O)2P(O)C(XH)R^2R^3$

Comp. no.	R^1	R^2	R^3	X	*T*, °C	Duration, h	Yield, %
I	Me		H	O	0–20	2	89
II	Et		H	O	0–20	2	88
III	Me		H	O	0–20	2	85
IV	Et		H	O	0–20	4	90
V	Et		H	O	0–20	4	90
VI	Et		H	O	0–20	2	90
VII	Et		H	O	0–20	2	90
VIII	Et	3-$F_3CC_6H_4$	Me	O	25	6	80
IX	Et	4-*t*-BuC_6H_4	Me	O	25	12	70
X	Et	3,4-$(MeO)_2C_6H_3$	Et	O	50	12	80
XI	Et	$-(CH_2)_5-$	O	25	4	85	
XII	Et	$-CH_2CH_2OCMe_2CH_2-$	O	25	4	85	
XIII	Et		$(EtO)_2P(O)$	O	25	10	70
XIV	Et		$(EtO)_2P(O)$	O	25	6	75
XV	Et		H	PhN	30	12	60
XVI	Me	Ph	H	BnN	28	12	71
XVII	Et	Ph	H	$CHNO_2$	0–20	6	65
XVIII	Et	PrN=C		O	0–20	2	90
XIX	Et	$CH_2{=}CHCH_2N{=}C$		S	0–20	2	80

Several aldehydes, including aromatic, aliphatic, and unsaturated aldehydes, readily react with trialkyl phosphites in the presence of pyridinium perchlorate with the formation of α-hydroxyphosphonates **I–VII** in high yields. The reaction is exothermic and therefore it is carried out at cooling below 0°C. No formation of unwanted by-products was observed. Only a small admixture of dialkyl phosphite was formed in case of the penetration of moisture from the environment into the reaction mixture, but the dialkyl phospite admixture can be easily removed by heating (70–100°C) in a vacuum that allows the preparation of spectroscopically pure hydroxyphosphonates **I–VII** even without additional treatment.

The pyridinium perchlorate initiates the reaction of triethyl phosphite with ketones. This reaction usually gives low yields of hydroxyphosphonate at the use of dialkiphosphites because of their low reactivity. Due to the high activity of the catalyst, the reaction of trialkyl phosphites with ketones in the presence of pyridinium perchlorate in most cases proceeds under mild conditions leading to the formation of the hydroxyphosphonates **VIII–XII** in a good yield.

In the presence of pyridinium perchlorate, ketophosphonates react with trialkylalkyl phosphites in methylene chloride at room temperature or at cooling to 0°C, to form 1-hydroxy-1,1-bisphosphonates (**XIII, XIV**) [15, 16]. The reaction completes in a few hours giving hydroxy-bisphosphonates **XIII** and **XIV** in a high yield. These compounds being the derivatives of terpenes and amino acids are of interest as potential biologically active substances. Chiral bisphosphonate (*S*)-**XIV** was obtained from the *N*-Moc-L-proline acid chloride **XX** [17]. *N*-Moc-L-prolinoyl chloride **XX** reacts readily with triethyl phosphite to form the chiral ketophosphonate (*S*)-**XXI**, which was purified by vacuum distillation and then transformed in a good yield into the bisphosphonate (*S*)-**XIV** by the reaction with triethylphosphite in the presence of pyridinium perchlorate.



(*S*)-(–)-**XX** Moc-MeOCO (*S*)-(–)-**XXI** (*S*)-(–)-**XIV**

The reaction of $(EtO)_3P/[PyH]^+ClO_4^-$ with imines leads to the formation of aminophosphonates (**XV, XVI**) under mild conditions (see the table) [18]. The reaction proceeds at 0°C, that is, easier than the Kabachnik–Fields reaction described in literature between the benzylbenzaldimine and diethyl phosphite requiring the heating at 140°C over several hours. Triethyl phosphite in the presence of pyridinium perchlorate phosphonylates also ketimines that is difficult to reach by other methods (see the table) [19].

Pyridinium perchlorate initiates the reaction of nitrostyrene with trialkyl phospites in a methylene chloride solution at 0°C with the formation of β-nitro-α-phenylethylphosphonate **XVII** in a good yield [20]

Triethyl phosphite in the presence of $[PyH]^+ClO_4^-$ phosphonylates isocyanates and isothiocyanates at 0°C in a methylene chloride solution, turning them into carbamoylphosphonates **XVIII** or thiocarbamoylphosphonates **XIX** in high yields.

Thus pyridinium perchlorate is a new effective catalyst for the reaction of trialkyl phosphites with the C=X electrophiles. The use of pyridinium perchlorate allows the phosphonylation of aldehydes, ketones, aldimines and ketimines, ketophosphonates, and some of alkenes with the formation of functionalized phosphonates. Pyridinium perchlorate is stable, convenient in handling, can be easily separated by filtration and is suitable for reuse as a catalyst. The advantages of the developed procedure is the preparative simplicity, a wide range of substrates used and high yields of products. In many cases, pyridinium perchlorate allows the preparation of functionalized phosphonates, which are difficult or even impossible to obtain by known methods.

EXPERIMENTAL

Melting points are uncorrected. The NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 (^{1}H) and 126.16 (^{31}P) MHz with internal TMS

(^{1}H) and 85% H_3PO_4 in D_2O (^{31}P) as references. All chemical shifts are expressed in δ scale (ppm). The IR spectra were taken from KBr pellets or solutions in CCl_4 on a Vertex 70 IR Fourier spectrophotometer.

Thin layer chromatography was performed on aluminum plates with silica gel (0.25-mm layer) with the spots detection under UV irradiation. The column chromatography was carried out on Merck 60 silica gel. In reactions anhydrous solvents were used: THF was freshly distilled over sodium in the presence of benzophenone, methylene chloride was distilled over P_4O_{10}. Reagents were purchased from Merck and used without special purification.

Pyridinium perchlorate. To 0.1 mol of pyridine in 100 ml of water at stirring and cooling to 0°C was added 0.1 mol of 10% perchloric acid solution in water. The mixture was stirred for 15–20 min at this temperature, then the formed white crystalline product was filtered off or the reaction mixture was kept in a refrigerator for 2 h for complete separation of pyridinium perchlorate from the reaction mixture and the formation of the best crystals, then filtered, and the solid was washed on the filter with a small amount of water cooled to 0°C. The product was dried first in a vacuum of 0.05 mm Hg, and then overnight in a vacuum desiccator over phosphorus pentoxide. Yield 85–90%, mp > 250 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.5–8.5 m (C_6H_5N). Found, %: Cl 19.4. $C_5H_6ClNO_4$. Calculated, %: Cl 19.77

Addition of trialkyl phosphites to aldehydes in the absence of solvent (general procrdure). The pyridinium perchlorate (~0.005 mol) was added to a mixture of aldehyde (0.01 mol) and trialkyl phosphite (0.01 mol) at cooling to 0°C, the reaction mixture was stirred for the time specified in the table. Then the reaction mixture was extracted with methylene chloride or diethyl ether and filtered. As a result, ~0.0049 moles of the used catalyst was separated. The solvent was evaporated in a vacuum of 10 mm Hg and then if necessary the residue was maintained in a vacuum of 0.05 mm Hg at 70–100°C, the product obtained was used without additional treatment or either distilled in a vacuum, or crystallized, or subjected to chromatography on a silica gel column.

Addition of trialkyl phosphites to aldehydes in a solvent (general procrdure). The pyridinium perchlorate (~0.005 mol) was added to a solution of C=X compounds (0.01 mol) and trialkyl phosphite (0.01 mol) at cooling to 0°C, the reaction mixture was stirred for the time and at the temperature specified in the table. The mixture was then filtered, diluted with diethyl ether, and filtered again to separate ~0.0049 mol of pyridinium perchlorate. The solvent was evaporated and the residue was purified either by distillation in a vacuum, or crystallized, or subjected to chromatography on a silica gel column.

Reuse of the catalyst. The pyridinium perchlorate used in the previous experiment and isolated was washed with diethyl ether and dried in a vacuum. Then the regenerated pyridinium perchlorate (~0.005 mol) was added to the mixture of triethyl phosphite (0.01 mol) and piperonal (0.01 mol) at cooling to 0°C, and the reaction mixture was stirred for 2 h at room temperature. The catalyst was separated (~0.0049–0.005 mol), the residue was distilled in a vacuum. The resulting diethyl (1,3-benzodioxol-5-yl)-hydroxymethylphosphonate was isolated in 85% yield, bp 160°C (0.05 mm Hg), mp 83°C. Colorless crystalline substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.14–1.27 m, (6H, CH_3), 3.94–4.08 m (4H, OCH_2), 5.00 d (*J* = 11.0, 1H, PCH), 7.25–7.4 m (3H, C_6H_3). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 21.69. Found, %: P 10.59. $C_{12}H_{17}O_6P$. Calculated, %: P 10.75.

Similarly, the reaction of triethyl phosphite with cyclohexanone catalyzed by the regenerated pyridinium perchlorate gave diethyl 1-hydroxycyclohexylphosphonate (**XI**). 85% yield, bp 120°C (0.08 mm Hg), mp 61–63°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.3 m (6H, *J* = 7.2, CH_3), 1.52 m (2H, CH_2), 1.66 m (4H, CH_2), 1.87 m (4H, CH_2), 3.6 m (1H, OH), 4.16 d.q (4H, *J* = 7, *J* = 8, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.45 d (*J* = 6.25), 20.20 d (*J* = 11.5), 25.37, 31.51 d (*J* = 2.5, CH_2), 62.51 q (*J* = 7.5, OCH_2), 70.95 q (*J* = 147.5, PC). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.9 [15].

Dimethyl (1,3-benzodioxol-5-yl)hydroxymethylphosphonate (I). Colorless crystalline substance, mp 91°C ($CHCl_3$ / hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.7 d (*J* = 15, CH_3O), 5.36 d (*J* = 10, HCH), 5.91 s (3H, CH_2O_2), 7.2–7.4 m (5H, C_6H_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 53.0 d (*J* = 28), 70.1 d (165), 101.1, 107.9 d (*J* = 21), 120, 130, 147.48, 147.68. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 28.1. Found, %: C 46.34, H 5.21. $C_{10}H_{13}O_6P$. Calculated, %: C 46.16, H 5.04.

Diethyl *N*-*tert*-butoxycarbonyl-3-amino-1-hydroxypropilphosphonate (II). Colorless oil, bp 160°C (0.008 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm

(*J*, Hz): 1.34 t (6H, *J* = 7 CH_3), with 1.44 [9H, $(CH_3)_3C$], 1.89 m (2H, CH_2), 3.23 m (1H, NCH_2), 3.46 m (1H, NCH_2), 3.96 m (1H, PCH), 4.18 m (OCH_2), 5.1 br (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16. 4, 28.5, 33.0, 35.0, 62.05 d (*J* = 8), 64 d (*J* = 160). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 25.7. Found, %: N 4.55, P 9.81. $C_{12}H_{26}NO_6P$. Calculated, %: N 4.50, P 9.95.

Diethyl (*S,R*)-2-*N*-Boc-pyrrolidinehydroxymethylphosphonate (III). To 0.01 mol of trimethyl phosphite at –10°C was added 10 mmol of *N*-Boc-prolinal and 6 mmol of pyridinium perchlorate. The reaction mixture was stirred for 5 h at –10°C, 2 h at 0°C, and 1 h at room temperature, then diluted with diethyl ether and filtered, the residue was evaporated. The product yield 95%, a mixture of (*S,R*)- and (*S,S*)-diastereoisomers in the ratio 4:1. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.9 and 26.3. The product was purified by chromatography on silica gel column (EtOAc–hexane, 1:3) and then repeatedly recrystallized from the mixture of hexane and chloroform with cooling to –20°C, and then from hexane. (*S,R*)-diastereomer **III** was obtained, mp 79°C, $[\alpha]_D$ –60° (*c* 2, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.42 s [9H, $(CH_3)_3C$], 1.8–2.3 m (4H, CH_2) 3.2 m (1H, PCH), 3.7–3.8 m (2H, CH_2N), 3.7 d (6H, *J* = 10, CH_3O), 4.1 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 24.5, 28.5, 28.8, 47.5, 53.0 d (*J* = 6.9), 59.0, 73.5 d (*J* = 158.8), 81.5, 159. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.9 [15,16].

Diethyl hydroxy[6-methyl-4-(4-methylpentene-3-enyl)cyclohexyl-3-en-1-yl]methylphosphonate (IV). Yield 80%. The product was purified by chromatography on a silica gel column (EtOAc–hexane, 1:3). Colorless oil, bp 180°C (0.08 mm Hg). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 d (3H, *J* = 6, CH_3), 1.33 m (6H, *J* = 7, CH_3 CH_2), 1.6 s (3H, CH_3), 1.87 s (3H, CH_3), 1.91–2.22 m (10H, CH_2 + CH), 3.51 br (OH), 4.17 m (5H, *J* = 7, *J* = 8, OCH_2 + PCH), 6.28 s (1H, CH=C), 5.32 m (2H , CH=C). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.87, 16.28, 17.3, 25.4, 25.78, 27.01, 27.08, 29.96, 32.15, 33.69 d (*J* = 150), 42.8, 61.81 d (*J* = 6), 120.6, 123.9, 130.8, 135.59. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.6 [15].

Diethyl hydroxy(3,8,8-trimethyl-1,2,3,4,5,6,7,8-octahydronaphth-2-yl)methylphosphonate (V). Yield 80%. Colorless crystals, bp190°C (0.1 mm Hg), mp 107–110°C (hexane). ^1H NMR spectrum (500 MHz, $CDCl_3$): 0,957 d (3H, *J* = 6, CH_3 C), 0.975 s (6H, *m*-CH_3), 1.34 m (6H, *J* = 7, CH_3CH_2O), 1.43 m (2H, CH_2), 1.6 m (4H, CH_2), 1.8 m (2H, CH_2), 1.9 m (1H, CH), 2.0 m (1H, CH) , 2.19 m (2H, CH_2) 2.91 br (1H, OH), 4.2 m (5H, CH_2O + PCH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.4, 19.27, 19.99, 24.87, 27.02, 27.07, 28.01, 28.97, 32.89, 33.73, 39.5, 48.9, 62.17 d (*J* = 6), 62.17, 70.88 d (*J* = 160), 127.2, 133.61. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 25.63 [15].

Diethyl (2*E*)-1-hydroxy-3,7-dimethyl-2,6-octadienylphosphonate (VI). Yield 80%, bp 135°C (0.08 mm Hg). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 m (3H, J_{HH} = 7, CH_3), 1.29 m (3H, J_{HH} = 7, CH_3), 1.61 s (3H, CH_3), 1.69 s (3H, CH_3), 2.1 br (4H, CH_2), 4.12 m (4H, OCH_2) 4.52 d.d (1H, J_{HH} = 9, J_{HP} = 9) 5.12 br (1H, CH=C), 5.36 br (1H, CH=C). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.4, 17.0, 17.6, 25.60, 07.26, 37.90, 37.9, 61.7, 61.8, 65.1, 66.1, 119.1, 124.0, 131.7, 138.8. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 24.19 [15].

Diethyl (S_P/R, R/R_P)-(6*E*)-1-hydroxy-3,7-dimethyl-2,6-octenylphosphonate (VII). Yield 80%, bp 145–150 on C (0.08 mm Hg.). A mixture of (S_P/R, R/R_P)-diastereoisomers. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 d, (3H, *J* = 7, CH_3), 1.29 m (3H, *J* = 7, CH_3), 1.30 m (3H, *J* = 7, CH_3), 1.58 s (3H, CH_3) 1.65 s (3H, CH_3), 1.83 m (2H, CH_2), 1.96 m (2H, CH_2), 3.82 m (1H, CH), 4.09 m (4H, OCH_2), 5.07 m (1H, *J* = 7, CH=C), 5.7 br (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): (S_P/R), 16.45, 16.49, 17.06, 20.25, 25.19, 25.52, 25.65, 28.30 d (*J* = 12), 35.75, 38.11, 62.51 d (*J* = 7.5), 62.64 d (*J* = 6), 65.59 d (*J* = 158), 124.70, 131.09. (R_P/R), 16.45, 16.49, 18.35, 20.25, 25.19, 25.52, 25.65, 29.0 d (*J* = 12), 37.80, 38.56, 62.51 d (*J* = 7.5), 62.64 d (*J* = 6), 66.06 d (*J* = 157), 124.72, 131.13. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.50, 26.54. Found, %: P 10.69. $C_{14}H_{29}O_4P$. Calculated, %: P 10.59.

Diethyl 1-hydroxy-1-(3-trifluoromethylphenyl)-ethylphosphonate (VIII). Yield 80%. The product was purified by crystallization from hexane. Colorless crystals, mp 125–128°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.24 m (6H, *J* = 7, CH_3), 1.83 d (3H, *J* = 15.6, CH_3CP), 4.04 m (2H, OCH_2), 4.12 m (2H, OCH_2), 4.66 br (1H, NH), 7.44–7.9 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.17, 26.33, 63.5 d (*J* = 94), 73.5 d (*J* = 161), 127 q (*J* = 271), 123.1, 123.88, 128.16, 130.01, 130.27, 143.00. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –57.67. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 25.3 d (*J* = 8). Found, %: C 47.55, H 5.50, P 9.65. $C_{13}H_{18}F_3O_4P$. Calculated, %: C 47.86, H 5.56, P 9.49.

Diethyl 1-hydroxy-1-(4-*tert*-butylphenyl)ethylphosphonate (IX). Yield 80%. Colorless crystals, mp 84–86°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15 m (3H, CH_3) 1.17 m (3H, CH_3), 1.24 s [9H, $(CH_3)_3C$)], 1.8 d (*J* = 14.5, CH_3), 3.93 m (2H, OCH_2), 4.07 m (2H, OCH_2), 7.3–7.5 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.35, 25.83, 31.34, 34.44, 63.26 d (*J* = 16), 73.4 d (*J* = 158), 124.9, 125.55 d (*J* = 4), 137.88, 150.24. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.0. Found, %: C 61.01, H 8.75, P 9.65. $C_{16}H_{27}O_4P$. Calculated, %: C 61.13, H 8.66, P 9.85.

Diethyl [1-(3,4-dimethoxyphenyl)-1-hydroxypropyl]phosphonate (X). The product was purified by column chromatography on silica gel (EtOAc–hexane 1:3). Colorless oil, R_f 0.33, yield 60%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.77 t (3H, *J* = 7.2, CH_3), 1.15 t (3H, *J* = 7, C*H*$_3$CH$_2$O), 1.27 t (3H, *J* = 7, C*H*$_3$CH$_2$O), 2.13 d.q (1H, PCC*H*, *J* = 7, *J* = 8), 2.24 d.q (1H, PCC*H*, *J* = 7, *J* = 8), 3.87 s, 3.89 s (3H, CH_3O), 4.1 m (4H, CH_2O), 6.9–7.5 m (3H, C_6H_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 9.09, 16.45, 27.82, 55.97, 62.35, 71.93, 72.94, 114.35, 116.59, 123.85, 125.3, 150.31, 151.02. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 24.3. Found, % 54.16, H 7.54. $C_{15}H_{25}O_6P$. Calculated, %: C 54.21, H 7.58.

Diethyl 1-hydroxycyclohexylphosphonate (XI). Yield 80%, bp 120°C (0.1 mm Hg), mp 71–73°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.3 t (6H, *J* = 7.2, CH_3 CH_2), 1.52 m (2H, CH_2) 1.66 m (4H, CH_2), 1.87 m (4H, CH_2), 3.6 br (1H, OH), 4.16 d.q (4H, *J* = 7, *J* = 8, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.45 d (*J* = 6.25), 20.22 d (*J* = 11.5), 25.37, 31.5 d (*J* = 2.5), 62.5 d (*J* = 7.5) , 70.95 d (*J* = 147.5). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.93 [15].

Diethyl hydroxy-4-(tetrahydro-2,2-dimethyl-2*H*-pyran-4-yl)phosphonate (XII). Yield 80%, bp 130–135°C (0.08 mm Hg), mp 72–75°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 s [3H, $(CH_3)_2C$], 1.43 s [3H, $(CH_3)_2C$], 1.64–19 m (4H, CH_2), 3.65 m (2H, CH_2O), 3.95 br (1H, OH), 3.65 m (1H, CH_2), 4.05 m (1H, CH_2), 4.15 d.q (4H, *J* = 7, *J* = 8, CH_3CH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.45, 24.29, 31,909, 32.61, 39.87, 56.1 d (*J* = 12.5), 62.8 d (*J* = 8.5), 63.0 d (*J* = 7.5), 70 d (*J* = 183.5), 70.57. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23.6. Found, %: P 11.63. $C_{11}H_{23}O_5P$. Calculated, %: P 11.63.

Tetraethyl (*E*)-1-hydroxy-3,7-dimethylocta-2,6-diene-1,1-diyldiphosphonate (XIII). The product was purified by chromatography on silica gel column (EtOAc–hexane, 50:50). Yield 65%, oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27 t (6H, *J* = 7, CH_3) 1.28 t (6H, *J* = 7, CH_3), 1.6 s (3H, CH_3), 1.63 s (3H, CH_3), 1.8 d (3H, J_{HH} = 8, CH_3), 2.0 m (4H, CH_2), 4.21 m (8H, OCH_2), 4.8 m (1H, CH=), 5.1 m (1H, J_{HH} = 7, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.21, 16.41, 17.59, 17.81, 25.61, 26.87, 36.9, 60.93, 64.53, 67.83, 71.13, 115.5, 124.03, 131.67, 139.77. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23.3. Found, %: C 50.45, H 8.41, P 14.40. $C_{18}H_{36}O_7P_2$. Calculated, %: C 50.70, H 8.51, P 14.53.

Bis(dietoxyphosphinyl)hydroxymethyl-*N*-(methoxycarbonyl)-1-pyrrolidine (XIV). R_f 0.15 (EtAc : MeOH : C_6H_{12} = 1:1:1). $[\alpha]_D^{20}$ –59° (*c* 3.5, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.37 m (12H, CH_3), 1.68 m, 1.91 m (2H, CH_2), 2.37 m, 2.65 m (2H, CH_2), 3.39 m (2H, CH_2N), 3.75 s (3H, CH_3O), 4.3 m (8H, OCH_2), 4.4 m (1H, CHN). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.3, 23.63, 29.50, 47.69, 53.18, 63.07, 63.23 s, 63.29, 63.50, 64.05 t, *J* = 62 (CHN), 79.3 t (*J* = 153), 159.4. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 21.72, 21.57, 20.94, 20.80 (rotamers and magnetic nonequivalence). MS APCI, *m/z*: 432.3 (*M* + 1). Calculated: *M* 431.3.

Diethyl 1-(benzylamine)benzylphosphonate (XV). Yield 70%, bp 150°C (0.02 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20 d (3H, *J* = 7, CH_3), 1.30 d (3H, *J* = 7, CH_3), 5.2 d (1H, *J* = 24, PCH), 6.8–7.28 m (5H), 7.3 d (2H, *J* = 8.5), 7.5 d (*J* = 8.5, 2H). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 24 [18].

Diethyl (2*E*)-1-anilino-3,7-dimethylocta-2,6-dienylphosphonate (XVI). The product was purified by chromatography on a silica gel column. Oil. Yield 50%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27–1.17 m (6H, CH_3), 1.49 s (3H, CH_3), 1.54 s (3H, CH_3), 1.61 s (3H, CH_3), 1.72–1.71 m (2H), 2.06–1.97 m (2H), 4.15–3.97 m (4H, CH_2), 4.38 d.d (1H, $^1J_{PH}$ 20.7, $^3J_{CH}$ 9.4, PCH), 4.95–5.12m (2H, C=CH), 7.13–6.54 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.4, 16.5, 17.1, 17.7, 25.6, 26.2, 39.6, 50.6 d (*J* = 158.5), 62.8 d (*J* = 7.3), 63.1 d (*J* = 6.6), 113.9, 118.4, 119.9, 123.6 , 129.1, 131.8, 141.6, 146.8. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 28.4 [19].

Diethyl (2-nitro-1-phenyl)ethylphosphonate (XVII). Yield 70%, mp. 65°C (hexane). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.2, 37.46, 37.94, 61.74, 78.35, 127.3, 128, 128.9, 133.7. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 28.0 [20].

Diethyl (propylamino)carbonylphosphonate (XVIII). Yield 90%, colorless oil, bp100–110°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 t (3H, *J* = 7.5, CH_3), 1.3 t (6H, *J* = 7, CH_3CH_2O), 1.51 m (2H, $CH_3CH_2CH_2$), 3.2 q (4H, *J* = 7, NCH_2), 4.15 m (4H, CH_2O): 7.34 m (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 11.2 d (*J* = 8), 16.15 d (*J* = 15), 22.6, 40.98, 64.15 d (*J* = 8), 165 d (*J* = 221). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: –0.71 [15.21].

Diethyl (allylamino)tiocarbonylphosphonate (XIX). Yellowish liquid. Yield 80%, bp 120°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 t (6H, CH_3CH_2), 4.08–4.3 m (6H, OCH_2 + NCH_2), 5.27 d.d (1H, *J* = 6, *J* = 1, C=CH_2), 5.31 d.d (1H, *J* = 12.5, *J* = 1, C=CH_2), d.d.t 5.91 (1H, *J* = 17, *J* = 10.2, *J* = 6, CH_2CH=C), 9.27 br (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.24 d (*J* = 10), 42.4 d (*J* = 9), 63 d (*J* = 6), 119, 130.7, 193 d (*J* = 155). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: –1.7 [15].

Diethyl *N*-(methoxycarbonyl)-1-pyrrolidinoketophosphonate (XXI). To 0.02 mol of *N*-Moc-*L*-proline (**XX**) [17] was added 0.04 mol of triethyl phosphite at –20°C. Then the temperature of the reaction mixture was raised to 20°C, the mixture was stirred for 2 h and then distilled in a vacuum. Yield 85%, bp 140°C (0.08 mm Hg). Colorless liquid, $[\alpha]_D^{20}$ –44 (*c* 2, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.37 m (6H), 1.9 m (2H), 2.2 m (2H), 2.2 (m, 2H), 3.59 s, 3.71 s (3H, CH_2), 4.24 m (3H, OCH_2), 4.81 m, 4.87 m (1H, CHN). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 17.8, 28.89, 29.31, 29.53, 30.63, 46.39, 46.90, 52.21, 52.27, 63.30, 63.35, 63.55, 63.61, 154.25, 155.04, 208.8 d (*J* = 157.5), 208.6 d (*J* = 160). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: –2.98 and –2.78 (rotamers). Found, %: N 4.61, P 10.67. $C_{11}H_{20}NO_6P$. Calculated, %: N 4.78, P 10.56.

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