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Convenient synthesis of α-perfluoroaryl and α-perfluorohetaryl substituted α-aminomethanephosphonates

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ABSTRACT

Potassium salt of diethyl (diphenylmethyleneamino)methanephosphonate reacts with pentafluoropyridine, octafluorotoluene, diethoxymethylpentafluorobenzene, or octafluoronaphthalene to afford, on product hydrolysis, the corresponding α-perfluoro(het)aryl substituted derivatives in high yield and regioselectivity. The method provides a new prospective route to fluorinated α-aminophosphonates. In the case of *N*-benzylidenepentafluoroaniline the outcome of the reaction is different and results in the formation of diethyl (pentafluorophenyl)amidophosphate.

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1. Introduction

Schiff bases derived from phosphoglycine esters are among its most popular synthetic equivalents that played an important role in the development of the chemistry of α-aminophosphonic acids [1]. They were introduced into the synthetic practice about thirty years ago and nowadays undergo a kind of the Renaissance, turning out to be convenient reactants for both the classical organic synthesis and its modern directions, in particular, catalytic and stereoselective methods [2–5]. This class of compounds and, first of all, diethyl (diphenylmethyleneamino)methanephosphonate (**1**), was very actively applied in the reactions of alkylation [6] and palladium-catalyzed allylation [2,3,6b,7], in the Michael [4,6b,8] and Mannich [5] condensations, and finally, in sulfenylation [9]. However, the possibility of using phosphoglycine Schiff bases in the reactions of nucleophilic aromatic substitution has not been demonstrated so far. Moreover, examples of the reactions of nucleophilic aromatic substitution of α-phosphoryl-stabilized carbanions with activated substrates described in the literature are rare as a whole [10] and not always successful [11]. Meanwhile, in the case of success, this reaction could form a basis for a new strategy for the synthesis of potent bioactive α-aminophosphonates containing in the α-position various aromatic or heteroaromatic substituents (including polyfluorinated ones), which are not always accessible in terms of traditional synthetic approaches (for instance, by the Kabachnik–Fields reaction [12]).

Examples of described fluorine containing α-aminophosphonates are not numerous [13]; however, interest in them is permanently increasing [14], because it is known that the introduction of the fluorine atom (bioisosteric analog of hydrogen and isoelectronic analog of hydroxyl group) into a molecule very substantially changes such its properties as lipophilicity and capability of hydrogen bonding, affects the metabolic degradation of biologically active compounds, and finally, makes it possible to use the ^{19}F NMR method for studying metabolism of these substances.

Herein we would like to report our results on the synthesis of α-perfluoroaryl- and α-perfluorohetaryl substituted α-aminomethanephosphonic esters, interesting objects of medicinal chemistry and valuable intermediate reagents, by the nucleophilic aromatic substitution reaction of perfluoroarenes with Schiff base **1**.

2. Results and discussion

Schiff base **1** was synthesized from accessible reagents via Scheme 1, being a compilation of the known literature procedures [6a,b,15]. A small modification (the use of diethyl aminomethanephosphonate instead of the corresponding hydrochloride as in the literature prototype [6a]) offers more simple work up and substantially enhances the yield of Schiff base **1**.

The first problem we faced was the choice of an adequate metallating agent. A whole range of bases was used in the literature [2–9] for azomethine **1** (p*K*a = 23.0 (DMSO) [9]). A specific feature of the reactions of CH-acids with perhaloaromatic

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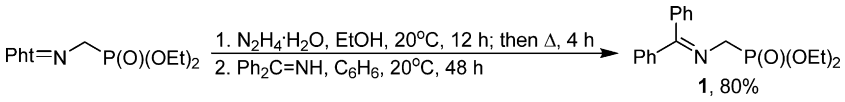


Scheme 1. Synthesis of diethyl (diphenylmethyleneamino)methanephosphonate (**1**).

compounds is that the acidity of the product formed is considerably higher than that of the initial substrate due to the electron-withdrawing influence of the α-Ar_F substituent. So, to gain the quantitative conversion at least two equivalents of the base should be used and the base should not be nucleophilic, i.e. it should not react with perhaloarenes. This excludes the application not only *n*-butyl- and phenyllithium but also potassium *tert*-butylate and lithium diisopropylamide which rather easily react with perfluoroaromatic compounds to form the di- and trisubstituted derivatives [16]. Taking into account these circumstances, the choice was made in favor of alkaline metal hydrides, since it is known that nucleophilic substitution in perfluoroarenes under the action of hydride ion hardly occurs even at elevated temperatures [17].

It turned out that sodium hydride almost does not react with Schiff base **1** in dimethoxyethane: no hydrogen evolution was visually observed, the solution gained only weak yellow color, probably due to the formation of the anion of the substrate in trace amounts, and only the signal of the initial reactant was detected by $^{31}P\{^1H\}$ NMR spectroscopy. Perhaps, sodium salt of Schiff base **1** is poorly soluble in DME, which results in blocking of the hydride surface. The metallation of Schiff base **1** by sodium hydride in such a well solvating solvent as DMF was spectrally detected by the appearance in the $^{31}P\{^1H\}$ NMR spectrum of the signal at δ_P = 30.80 ppm corresponding to the anion formed; however, in this case, the degree of metallation did not exceed 43%.

Schiff base **1** is metallated completely within 30 min by potassium hydride in THF at 0 °C: hydrogen is vigorously evolved, an intensive orange color appears, and the single signal at δ_P 35.20 ppm corresponding to the anion appears in the $^{31}P\{^1H\}$ NMR spectrum instead of the signal of the initial compound at δ_P = 15.95 ppm (Scheme 2).

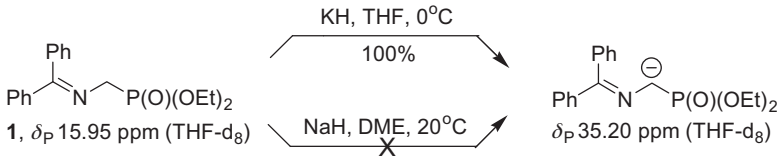
The reaction of Schiff base **1** with pentafluoropyridine in the presence of 3 equiv. of potassium hydride at 0 °C occurs quantitatively and affords (after acidification of the reaction mixture) diethyl (diphenylmethyleneamino)(2,3,5,6-tetrafluoropyridin-4-yl)methanephosphonate (**2a**) as the single product isolated in 70% yield (Table 1, Entry 1) (note, that the yield of the desirable product **2a** did not exceed 25% when potassium *tert*-butylate was used as a base in the same reaction). It turned out that product **2a** is rather strong CH-acid: the anion formed in the reaction is not protonated even with water, and acetic acid (4 equiv.) was used for neutralization. Both anion **1** and anion **2a** are very readily oxidized with air oxygen and, hence, all manipulations, including the neutralization stage, were carried out using a vacuum experimental technique. In our hands, when the reactions were performed under dry argon using Schlenk techniques the yields were two times lower.

The composition of product **2a** was confirmed by elemental analysis data, and its structure was determined by IR and $^{31}P\{^1H\}$, ^{19}F, ^1H, and $^{13}C\{^1H\}$ spectroscopy. The IR spectrum confirms completely the retention of the diethoxyphosphoryl moiety in the product: the very intense band of P=O stretching vibrations lies at 1261 cm^{-1}, two intense bands at 1043 and 1018 cm^{-1} correspond to O–C vibrations, and a medium-intensity bands of vibrations ν(C–C) and ν(P–O) appear at 980 and 779 cm^{-1}, respectively [18]. In the ^{31}P NMR spectrum, the resonance of phosphorus undergoes an upfield shift by $\Delta\delta_P$ = 6.84 ppm relatively to the signal of the initial Schiff base **1**. In the ^1H NMR spectrum, the doublet of the methine proton with the characteristic spin-spin coupling constant $^2J_{P,H}$ = 18.8 Hz lies at δ_H = 5.53 ppm. The ethoxy groups, which were equivalent in Schiff base **1**, become diastereotopic in **2a** and appear as two sets of signals in the both ^1H and $^{13}C\{^1H\}$ spectra. The signal of the α-carbon atom with $^1J_{P,C}$ = 161.2 Hz is characteristic in the carbon spectrum. An analysis of the $^{13}C\{^1H\}$ NMR spectrum unambiguously suggests that the substitution in pentafluoropyridine occurred in position (4): the characteristic [19] spin–spin coupling constants with the fluorine nucleus $^1J_{F,C}$ = 263.0 and 246.2 Hz are observed only for two signals of the quaternary carbon atoms of the aromatic ring.

The reaction of Schiff base **1** with octafluorotoluene is also regiospecific affording diethyl (diphenylmethyleneamino)(2,3,5,6-tetrafluoro-4-trifluoromethylphenyl)methanephosphonate (**2b**) as the single product isolated in 71% yield (Table 1, Entry 2).

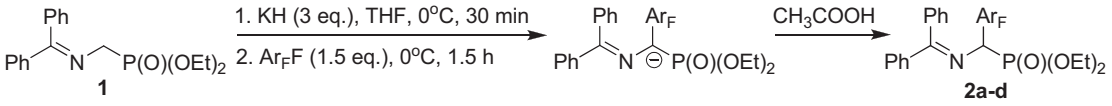
Schiff base **1** reacts with diethoxymethylpentafluorobenzene with a lower selectivity: the ^{31}P NMR spectrum of the reaction mixture (after neutralization) reveals three signals with characteristic splitting on fluorine nuclei at δ_P = 18.54, 18.81, and 18.92 ppm with the ratio of integral intensities 88:8:4. They possibly correspond to three regioisomers of the product. The individual major isomer, diethyl (diphenylmethyleneamino)(4-diethoxymethyl-2,3,5,6-tetrafluorophenyl)methanephosphonate (**2c**), was isolated in 71% by crystallization from petroleum ether and was completely characterized. *para*-Substitution in the fluorinated aromatic ring is unambiguously proved by the date of $^{13}C\{^1H\}$ spectroscopy: two and only two signals of quaternary carbons at δ_C = 144.37 and 144.83 ppm with the characteristic constants $^1J_{F,C}$ = 251.2 and 255.4 Hz, respectively, are observed in a low field.

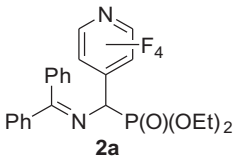
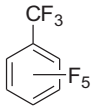
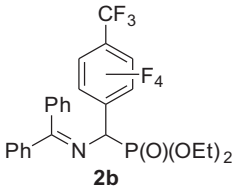
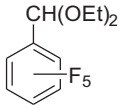
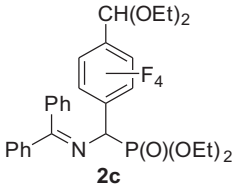
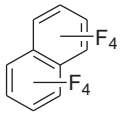
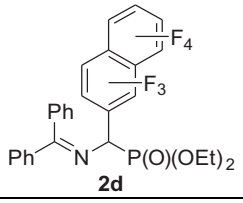
The reaction of Schiff base **1** with octafluoronaphthalene results in the predominant formation of diethyl (diphenylmethyleneamino)(1,3,4,5,6,7,8-heptafluoro-2-naphthyl)methanephosphonate (**2d**) isolated in 75% yield. The selectivity of the process was also estimated by $^{31}P\{^1H\}$ NMR: the spectrum of the crude reaction mixture contains two signals corresponding to the reaction products at δ_P = 18.49 and 18.65 ppm with the ratio of integral intensities 96:4. The structure of individual isomer **2d** was proved by ^{19}F NMR spectroscopy and was based on the remarkable fact that in perfluorinated naphthalenes the values of spin–spin coupling of the fluorine atoms in the *peri*-positions (1 and 8 or 4 and 5) are 50–70 Hz [20]. The ^{19}F NMR spectrum of product **2d**



Scheme 2. Schiff base **1** metallation.

Table 1
Nucleophilic aromatic substitution reaction of the Schiff base **1** carbanion with perfluoroarenes and perfluorohetarenes.



Entry	Ar_FF	Regioselectivity	Isolated product	Isolated yield (%)
1		Regiospecifically	 **2a**	70
2		Regiospecifically	 **2b**	25[a]
3		88:8:4	 **2c**	71
4		94:4	 **2d**	71

[a] *t*BuOK was used instead of KH.

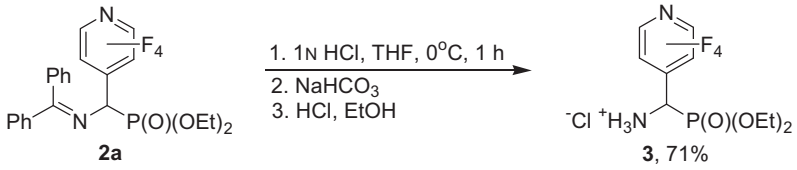
contains three well discernible doublets with the characteristic constants at δ_F = 148.78 ($J_{F,F}$ = 57.4 Hz), 146.37 ($J_{F,F}$ = 57.4 Hz), and 143.64 ppm ($J_{F,F}$ = 71.5 Hz) along with the broadened signal at δ_F = 116.01 ppm. Its position and width (~150 Hz) allow one to attribute it to the α-C_{Nf}F atom. The signal broadening and, as a consequence, the unresolved constant are related, probably, to steric overloading of the molecule and hindered rotation about the β-C_{Nf}–CP bond.

The diphenylmethylene protective group is easily removed by hydrolysis. Thus, the product **2a** was treated with a mixture of 1 N hydrochloric acid and THF to give diethyl amino(2,3,5,6-tetrafluoropyridin-4-yl)methanephosphonate hydrochloride (**3**) in 71% isolated yield (Scheme 3).

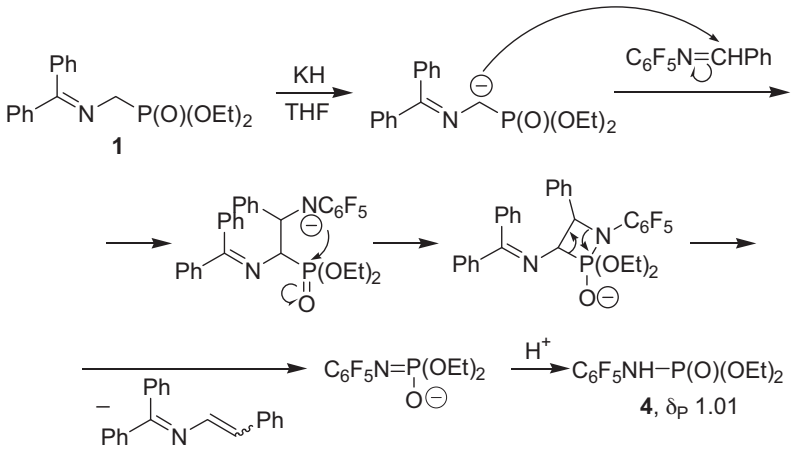
Interestingly, no diastereotopism of the ethoxy groups of the diethoxyphosphoryl moiety is manifested in the ^{1}H NMR spectrum of the hydrochloric salt. The same was observed earlier for salts of α-aminophosphonates (see, e.g. [6a]); however, the nature of this effect is not discussed in the literature.

The reaction of Schiff base **1** with *N*-benzylidenepentafluoroaniline gave an unexpected result: diethyl (pentafluorophenyl)amidophosphate (**4**) was isolated in 72% yield instead of the expected products of α-arylation or Mannich addition. It is known [15] that Schiff bases carbanions derived from phosphoglycine esters react with carbonyl compounds according to the Horner–Wadsworth–Emmons reaction type. Probably, the aza variant [21] of the same condensation takes place in this case. The plausible mechanism is presented in Scheme 4.

We failed to introduce pentafluorobenzene into the reaction with Schiff base **1**. The reason is evidently related to the known



Scheme 3. Removal of diphenylmethylene protective group; a representative example.



Scheme 4. A plausible mechanism of diethyl (pentafluorophenyl)amidophosphate (**4**) formation.

CH-acidity of this aromatic compound and, as a consequence, metallation of the latter by carbanion **1** and/or potassium hydride.

3. Conclusions

In summary, the results obtained indicate that potassium salt of phosphoglycine Schiff base **1** is the suitable nucleophile for the direct preparation of the phosphonic analogues of α-C-perfluoro(het)aryl-substituted glycine esters via S_NAr reaction with perfluoro(het)arenes. The new synthetic method provides the diethyl (diphenylmethyleneamino)(perfluoro(het)aryl)methanephosphonates under mild reaction conditions in high yields and with high regioselectivity.

4. Experimental

4.1. General

^1H, $^{13}C\{^1H\}$, ^{19}F, and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker Avance-400 instrument. Chemical shifts (δ) are reported in ppm relative to TMS (0 ppm for ^1H NMR), solvent $CDCl_3$ (77.0 for ^{13}C NMR), residual $CHCl_3$ (7.25 for ^1H NMR) or HDO (4.75 for ^1H NMR), external 85% H_3PO_4 (0 ppm for ^{31}P NMR) and $CFCl_3$ (0 ppm for ^{19}F NMR). Infrared spectra were obtained using SPECORD 75 IR and Carl Zeiss UR-20 spectrophotometers. Elemental analysis was performed on an Elementar Vario MICRO Cube analyzer.

THF was distilled from and stored under sodium benzophenon ketyl. Ethanol was dried over calcium ethoxide. Glacial acetic acid was purified by reiterated fractional freezing. Pentafluoropyridine, octafluorotoluene, octafluoronaphthalene, pentafluorobenzaldehyde, pentafluoroaniline, potassium hydride (with 65% paraffin oil, Merck), sodium hydride (60% dispersion in mineral oil, Aldrich), potassium *tert*-butoxide (98%, Acros), and hydrazine monohydrate (98%, Aldrich) are commercially available and were used as received.

4.2. Diethyl (diphenylmethyleneamino)methanephosphonate (1)

A solution of diethyl aminomethanephosphonate (prepared from diethyl *N*-phthalimidomethanephosphonate (7.16 g, 24.0 mmol) and hydrazine monohydrate (1.5 mL, 31.7 mmol) according to protocol [15]) in benzene (50 mL) was cooled to 10 °C and diphenylmethyleneimine (4.8 mL, 28.7 mmol) was added with stirring. *Warning*: Due to hazardous properties of benzene, all work should be performed in well ventilated chemical fume-hood. The mixture was stirred at room temperature under an inert atmosphere for 48 h. The solvent was distilled off on a rotary evaporator, and the product was recrystallized from petroleum ether. Schiff base **1** was obtained as colorless crystals in a yield of 6.35 g (80%). IR (Nujol): ν 1260, 1040, 1025, 980, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 6H, CH_3), 3.95 (d, $^2J_{H,P}$ = 17.5 Hz, 2H, PCH_2), 4.19 (m, 4H, OCH_2), 7.22 (m, 2H, arom.), 7.33 (t, $^3J_{H,H}$ = 7.4 Hz, 2H, arom.), 7.38–7.50 (m, 4H, arom.), 7.64 (d, $^3J_{H,H}$ = 7.5 Hz, 2H, arom.); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.73.

4.3. Diethyl (diphenylmethyleneamino)(2,3,5,6-tetrafluoropyridin-4-yl)methanephosphonate (2a); general procedure

A flame-dried, one-necked, 50-mL round-bottom flask equipped with a magnetic stirrer and filled with argon was charged with Schiff base **1** (300 mg, 0.91 mmol) and a microbeaker containing potassium hydride (with 65% paraffin oil, 310 mg, 2.71 mmol). The flask was connected to a vacuum line and thoroughly evacuated. THF (8 mL) was transferred by freezing from a volumetric ampule along the vacuum line. The reaction mixture was defrozen in an ice bath and stirred for 30 min. A weighed sample (237 mg, 1.40 mmol) of pentafluoropyridine was degassed by three cycles of freezing–evacuation–defreezing and then transferred into the reaction flask. The reaction mixture was stirred at 0 °C for 1.5 h and neutralized with acetic acid (240 mg, 4.00 mmol), which was preliminarily degassed and then transferred into the reaction flask as indicated above. Volatile components of the reaction mixture were removed *in vacuo*. The reaction flask was disconnected from the vacuum line, and benzene (15 mL) was added. The precipitate was filtered off and washed with benzene on the filter. The mother liquor was concentrated on a rotary evaporator, and the residue was recrystallized from petroleum ether. The crystals precipitated were filtered off and washed with hexane. Product **2a** was obtained as white crystals in a yield of 305 mg (70%). IR (Nujol): ν 1261, 1043, 1018, 980, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 4.14 (m, 2H, CH_2), 4.32 (m, 2H, CH_2), 5.53 (d, $^2J_{P,H}$ = 18.8 Hz, 1H, PCH), 7.15 (br.m, 2H, arom.), 7.35 (t, $^3J_{H,H}$ = 7.6 Hz, 2H, arom.), 7.42–7.48 (m, 4H, arom.), 7.71 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, arom.); ^{13}C NMR (101 MHz, $CDCl_3$): δ 16.04 ($^3J_{P,C}$ = 5.9 Hz, CH_3), 16.21 ($^3J_{P,C}$ = 6.0 Hz, CH_3), 58.65 ($^1J_{P,C}$ = 161.2 Hz, CP), 63.30 ($^2J_{P,C}$ = 6.9 Hz, CH_2), 64.26 ($^2J_{P,C}$ = 6.3 Hz, CH_2), 127.28 (2CH arom.), 128.06 (2CH arom.), 128.72 (2CH arom.), 128.93 (2CH arom.), 129.18 (CH arom.), 130.03 (C_{ArF}), 131.04 (CH arom.), 134.63 (C arom.), 138.42 (C arom.), 140.17 ($^1J_{F,C}$ = 263.0 Hz, 2CF), 143.42 ($^1J_{F,C}$ = 246.2 Hz, 2CF), 174.23 ($^3J_{P,C}$ = 17.6 Hz, C=N); ^{19}F NMR (376 MHz, $CDCl_3$): δ −91.17

(2F), −139.27 (2F); ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.89. Anal. Calcd. for $C_{23}H_{21}F_4N_2O_3P$: C, 57.51; H, 4.59; N, 5.76. Found: C, 57.50; H, 4.41; N, 5.83.

4.3.1. Diethyl (diphenylmethyleneamino)(2,3,5,6-tetrafluoro-4-trifluoromethylphenyl)methanephosphonate (2b)

Synthesized similarly to **2a** in 71% yield from Schiff base **1** (300 mg, 0.91 mmol), potassium hydride (with 65% paraffin oil, 310 mg, 2.71 mmol), and octafluorotoluene (333 mg, 1.40 mmol). Acetic acid (240 mg, 4.00 mmol) was used for neutralization. White crystals. IR (Nujol): ν 1270, 1165, 1055, 1030, 990, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 4.14 (m, 2H, CH_2), 4.30 (m, 2H, CH_2), 5.51 (d, $^2J_{P,H}$ = 18.6 Hz, 1H, PCH), 7.13 (br.m, 2H, arom.), 7.34 (t, $^3J_{H,H}$ = 7.6 Hz, 2H, arom.), 7.40–7.47 (m, 4H, arom.), 7.70 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, arom.); ^{13}C NMR (101 MHz, $CDCl_3$): δ 16.22 ($^3J_{P,C}$ = 5.9 Hz, CH_3), 16.37 ($^3J_{P,C}$ = 6.0 Hz, CH_3), 58.17 ($^1J_{P,C}$ = 163.8 Hz, CP), 63.36 ($^2J_{P,C}$ = 6.9 Hz, CH_2), 64.18 ($^2J_{P,C}$ = 6.1 Hz, CH_2), 119.38 (C_{ArF}), 121.10 (C_{ArF}), 122.56 ($^1J_{F,C}$ = 264.7 Hz, CF_3), 127.41 (2CH arom.), 128.17 (2CH arom.), 128.77 (2CH arom.), 129.04 (2CH arom.), 129.20 (CH arom.), 131.07 (CH arom.), 134.92 (C arom.), 138.65 (C arom.), 143.99 ($^1J_{F,C}$ = 258.8 Hz, 2CF), 145.10 ($^1J_{F,C}$ = 254.6 Hz, 2CF), 174.03 ($^3J_{P,C}$ = 16.9 Hz, C=N); ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.39 ($^4J_{F,F}$ = 21.6 Hz, 3F, CF_3); −135.76 (2F), −140.85 (2F); ^{31}P NMR (162 MHz, $CDCl_3$): δ 17.54. Anal. Calcd. for $C_{25}H_{21}F_7NO_3P$: C, 54.94; H, 4.09; N, 2.54. Found: C, 54.85; H, 3.87; N, 2.56.

4.3.2. Diethyl (diphenylmethyleneamino)(4-diethoxymethyl-2,3,5,6-tetrafluorophenyl)methanephosphonate (2c)

Synthesized similarly to **2a** in 71% yield from Schiff base **1** (300 mg, 0.91 mmol), potassium hydride (with 65% paraffin oil, 310 mg, 2.71 mmol), and diethoxymethylpentafluorobenzene [22] (380 mg, 1.40 mmol). Acetic acid (240 mg, 4.00 mmol) was used for neutralization. Yellow crystals. IR (Nujol): ν 1265, 1070, 1030, 960, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 1.24 (t, $^3J_{H,H}$ = 7.0 Hz, 3H, CH_3), 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3H, CH_3), 1.32 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 3.57 (m, 2H, CH_2), 3.75 (m, 2H, CH_2), 4.11 (m, 2H, CH_2), 4.28 (m, 2H, CH_2), 5.47 (d, $^2J_{P,H}$ = 18.1 Hz, 1H, PCH), 5.69 (s, 1H, $CH(OEt)_2$), 7.13 (br.m, 2H, arom.), 7.31 (t, $^3J_{H,H}$ = 7.6 Hz, 2H, arom.), 7.37–7.44 (m, 4H, arom.), 7.69 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, arom.); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.96 ($2CH_3$), 16.19 ($^3J_{P,C}$ = 5.9 Hz, CH_3), 16.34 ($^3J_{P,C}$ = 6.0 Hz, CH_3), 57.97 ($^1J_{P,C}$ = 165.2 Hz, CP), 63.10 ($^2J_{P,C}$ = 6.9 Hz, CH_2), 63.53 (CH_2), 63.62 (CH_2), 64.92 ($^2J_{P,C}$ = 6.2 Hz, CH_2), 96.56 ($CH(OEt)_2$), 116.42 (C_{ArF}), 117.06 (C_{ArF}), 127.49 (2CH arom.), 128.04 (2CH arom.), 128.61 (2CH arom.), 128.96 (3CH arom.), 130.79 (CH arom.), 135.01 (C arom.), 138.86 (C arom.), 144.37 ($^1J_{F,C}$ = 251.2 Hz, 2CF), 144.83 ($^1J_{F,C}$ = 255.4 Hz, 2CF), 173.26 ($^3J_{P,C}$ = 17.7 Hz, C=N); ^{19}F NMR (376 MHz, $CDCl_3$): δ −138.32 (2F), −143.60 (J = 21.7 Hz and 12.1 Hz, 2F); ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.54. Anal. Calcd. for $C_{28}H_{32}F_4NO_5P$: C, 59.75; H, 5.77; N, 2.55. Found: C, 59.89; H, 5.55; N, 2.41.

4.3.3. Diethyl (diphenylmethyleneamino)(1,3,4,5,6,7,8-heptafluoro-2-naphthyl)methanephosphonate (2d)

Synthesized similarly to **2a** in 75% yield from Schiff base **1** (300 mg, 0.91 mmol), potassium hydride (with 65% paraffin oil, 310 mg, 2.71 mmol), and octafluoronaphthalene (380 mg, 1.40 mmol). All reactants, including octafluoronaphthalene, were loaded into the flask before THF was added. Acetic acid (240 mg, 4.00 mmol) was used for neutralization. Yellow-brown crystals. IR (Nujol): ν 1270, 1070, 1033, 950, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 1.33 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 4.15 (m, 2H, CH_2), 4.29 (m, 2H, CH_2), 5,64 (d, $^2J_{P,H}$ = 18.6 Hz, 1H, PCH), 7.11 (br.m, 2H, arom.), 7.34 (t, $^3J_{H,H}$ = 7.4 Hz, 2H, arom.), 7.40–7.44 (m, 4H, arom.), 7.72 (d, $^3J_{H,H}$ = 7.8 Hz, 2H, arom.); ^{13}C NMR (101 MHz, $CDCl_3$): δ 16.24 ($^3J_{P,C}$ = 5.9 Hz, CH_3), 16.35 ($^3J_{P,C}$ = 6.0 Hz, CH_3), 58.26 ($^1J_{P,C}$ = 165.1 Hz, CP), 63.28 ($^2J_{P,C}$ = 6.6 Hz, CH2), 63.91 ($^2J_{P,C}$ = 6.2 Hz, CH_2), 107.66 (C_{ArF}), 110.93 (C_{ArF}), 115.30 (C_{ArF}), 127.42 (2CH arom.), 128.11 (2CH arom.), 128.68 (2CH arom.), 128.99 (2CH arom.), 129.07 (CH arom.), 130.92 (CH arom.), 135.13 (C arom.), 138.80 (C arom.), 138.53 ($^1J_{F,C}$ = 255.4 Hz, CF), 139.63 ($^1J_{F,C}$ = 254.6 Hz, CF), 140.84 ($^1J_{F,C}$ = 251.2 Hz, 2CF), 141.34 ($^1J_{F,C}$ = 258.8 Hz, CF), 146.55 ($^1J_{F,C}$ = 257.1 Hz, CF), 150.32 ($^1J_{F,C}$ = 256.3 Hz, CF), 173.64 ($^3J_{P,C}$ = 18.2 Hz, C=N); ^{19}F NMR (376 MHz, $CDCl_3$): δ −155.91 (1F), −153.43 (1F), −148.78 ($^4J_{F,F}$ = 57.4 Hz, 1F), −146.37 ($^4J_{F,F}$ = 57.4 Hz, 1F), −143.64 ($^4J_{F,F}$ = 71.5 Hz, 1F), −132.18 (1F), −116.01 (br., 1F); ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.49. Anal. Calcd. for $C_{28}H_{21}F_7NO_3P$: C, 57.56; H, 3.68; N, 2.53. Found: C, 57.64; H, 3.63; N, 2.40.

4.4. Diethyl amino(2,3,5,6-tetrafluoropyridin-4-yl)methanephosphonate hydrochloride (3)

A solution of phosphonate **2a** (48.4 mg, 0.1 mmol) in THF (8 mL) and 1 N hydrochloric acid (1 mL) was stirred at 0 °C for 1 h. THF was removed on a rotary evaporator. The residue was extracted with ether (3 × 3 mL) to remove benzophenone, neutralized with sodium hydrocarbonate, and extracted with chloroform (3 × 3 mL). The extract was dried over magnesium sulfate, and the solvent was removed on a rotary evaporator. The obtained diethyl amino(2,3,5,6-tetrafluoropyridin-4-yl)methanephosphonate was treated with an excess of HCl solution in ethanol. After removing of volatile components *in vacuo* hydrochloride **3** was obtained in a yield of 25.0 mg (71%). ^{1}H NMR (400 MHz, D_2O): δ 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 6H, CH_3), 4.27 (m, 4H, OCH_2), 5.52 (d, $^2J_{P,H}$ = 20.4 Hz, 1H, PCH); ^{31}P NMR (162 MHz, D_2O): δ 13.40.

4.5. Diethyl (pentafluorophenyl)amidophosphate (4)

Obtained in 72% yield similarly to **2a** from Schiff base **1** (300 mg, 0.91 mmol), potassium hydride (with 65% paraffin oil, 310 mg, 2.71 mmol), and *N*-benzylidenepentafluoroaniline [23] (380 mg, 1.40 mmol), which was added to the reaction mixture from a retort connected with the reaction flask. Acetic acid (240 mg, 4.00 mmol) was used for neutralization. White crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 6H, CH_3), 4.15–4.23 (m, 4H, OCH_2), 4.80 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.98 ($^3J_{P,C}$ = 6.7 Hz, CH_3), 63.61 ($^2J_{P,C}$ = 5.1 Hz, CH_2), 114.70 (C_{ArF}), 137.81 ($^1J_{F,C}$ = 249.6 Hz, 2CF), 138.15 ($^1J_{F,C}$ = 252.9 Hz, CF), 142.16 ($^1J_{F,C}$ = 256.3 Hz, 2CF); ^{19}F NMR (376 MHz, $CDCl_3$): δ −149.36 (2F), −160.98 ($^3J_{F,F}$ = 21.7 Hz, 1F), −126.99 (2F); ^{31}P NMR (162 MHz, $CDCl_3$): δ 1.01. Anal. Calcd. for $C_{10}H_{11}F_5NO_3P$: C, 37.81; H, 3.55; N, 4.43. Found: C, 37.63; H, 3.47; N, 4.39.

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