Three-component condensation of trifluoromethyl-substituted cyanovinylphosphonates, arylamines, and ketones and cytotoxic activity of products thus obtained

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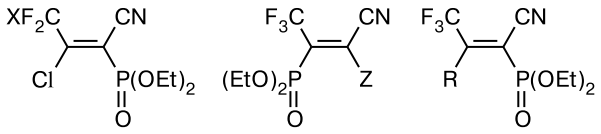
A three-component condensation of trifluoromethyl-substituted cyanovinylphosphonates, arylamines, and ketones (acetone, cyclopentanone, or cyclohexanone) has been studied. A possibility of using trifluoromethyl-substituted cyanovinylphosphonates as precursors of 1,4-dihydropyridines, 4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridines, 1,4,5,6,7,8-hexahydroquinolines, and 1,4,4a,5,6,7-hexahydroquinolines, modified with both trifluoromethyl and diethoxyphosphoryl groups, has been demonstrated. Using X-ray diffraction analysis, it was found that in some cases of the three-component condensation under study a mixture of 1-aryl-2-amino- and 2-arylamino-substituted products was formed. Migration of the multiple bond onto the ring fused with the dihydropyridine ring has been inferred from the NMR spectra and X-ray diffraction data. Cytotoxic activity of some compounds synthesized has been studied in the US National Cancer Institute.

Key words: trifluoromethyl-substituted cyanovinylphosphonates, arylamines, acetone, cyclopentanone, cyclohexanone, 1,4-dihydropyridines, 4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]-pyridines, 1,4,5,6,7,8-hexahydroquinolines, 1,4,4a,5,6,7-hexahydroquinolines, three-component condensation, migration of multiple bond, X-ray diffraction analysis, cytotoxic activity.

1,1-Dicyano-2-(trifluoromethyl)ethylenes and 3,3-dicyano-2-(trifluoromethyl)acrylic esters are convenient precursors of various trifluoromethyl-substituted nitrogen-containing heterocycles,[1—8] in particular, 1,4-dihydropyridines and 1,4-dihydropyrimidines possessing high insecticide activity.[1,6,8] Earlier, we have shown a possibility of using 2-chloro-1-cyano-1-diethoxyphosphoryl-2-(trifluoromethyl)ethylene (**1**) and its chlorodifluoromethyl analog **2** for the synthesis of fluoro-containing heterocyclic phosphonates,[9] developed a method for the synthesis[10] and studied reactions of vinylphosphonates **3—6** with some nitrogen-[11] and oxygen-containing[10] binucleophiles. We also studied cytotoxic activity *in vitro* of some fluoro-containing heterocyclic phosphonates synthesized against the standard panel consisting of 60 human tumor cell lines.[11] Thus, fluoro-containing vinylphosphonates[12,13] are important class of reactants, which open a possibility for the study of biological activity of fluoro-containing heterocycles[8,14,15] and for the search of new biologically active phosphonates.[16—22] The present work is devoted to the study of three-component condensation of trifluoromethyl-substituted cyanovinylphosphonates **3—6** with arylamines and ketones and cytotoxic activity of the condensation products.



1, **2** **3**, **4** **5**, **6**

X = F (**1**), Cl (**2**); Z = CN (**3**), CO_2Me (**4**); R = CF_3 (**5**), CO_2Et (**6**)

Results and Discussion

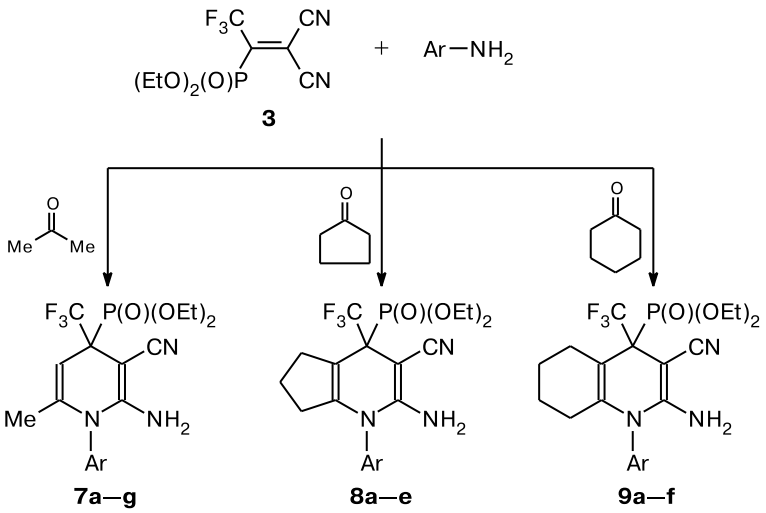
Fluorine-containing dicyanoethylenes react at room temperature with enamines, obtained both *in situ* and presynthesized from ketones and arylamines, leading to heterocyclic systems containing 1,4-dihydropyridine ring.[6,8] Trifluoromethyl-substituted cyanovinylphosphonates **3—6** also react in this way, however, a number of specific features is observed in this case: the formation of stable intermediate products of C-alkylation of enamines, the migra-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 143—159, January, 2010.

tion of the multiple bonds onto the ring fused with the dihydropyridine cycle, and the formation of side 2-arylamino-substituted 1,4-dihydropyridines.

Alkene **3** reacts with enamines the most readily and selectively, furnishing compounds **7—9** in from satisfactory to good yields (Scheme 1, Tables 1 and 2).

Scheme 1



Ar = 2,6-$Me_2C_6H_3$ (**7a**, **8a**), 4-$MeOC_6H_4$ (**7b**, **8b**), 4-ClC_6H_4 (**7c**, **8c**, **9a**), 2-ClC_6H_4 (**7d**, **8d**), 2,5-$Cl_2C_6H_3$ (**7e**, **8e**), 3-$CF_3C_6H_4$ (**7f**, **8f**), 4-$CF_3C_6H_4$ (**7g**, **9f**), 3,4-$Me_2C_6H_3$ (**9b**), 3-ClC_6H_4 (**9c**), 4-$PhOC_6H_4$ (**9d**), 2,6-$Cl_2C_6H_3$ (**9e**), 2,5-$(MeO)_2C_6H_3$ (**9g**)

Table 1. Physico-chemical characteristics of compounds **7—9**

Compound	Ar	Yield (%)	M.p./°C	Found / Calculated (%)						Molecular formula
				C	H	N	P	F	Cl	
7a	2,6-$Me_2C_6H_3$	67	152—154*	53.91 54.18	5.71 5.68	9.43 9.48	—	—	—	$C_{20}H_{25}F_3N_3O_3P$
7b	4-$MeOC_6H_4$	74	139—141*	51.49 51.24	5.24 5.21	9.36 9.40	6.83 6.91	12.54 12.80	—	$C_{19}H_{23}F_3N_3O_4P$
7c	4-ClC_6H_4	81	143—145*	47.74 48.07	4.55 4.48	9.27 9.34	6.80 6.89	12.42 12.67	8.30 7.88	$C_{18}H_{20}ClF_3N_3O_3P$
7d	2-ClC_6H_4	72.5	182—184*	48.00 48.07	4.52 4.48	9.30 9.34	—	—	—	$C_{18}H_{20}ClF_3N_3O_3P$
7e	2,5-$Cl_2C_6H_3$	67	190—191*	44.73 44.65	3.93 3.95	8.70 8.68	—	—	—	$C_{18}H_{19}Cl_2F_3N_3O_3P$
7f	3-$CF_3C_6H_4$	54	126—128	47.10 47.21	4.15 4.17	8.72 8.69	6.43 6.41	23.50 23.58	—	$C_{19}H_{20}F_6N_3O_3P$
7g	4-$CF_3C_6H_4$	76	114—116	47.27 47.21	4.17 4.17	8.66 8.69	—	—	—	$C_{19}H_{20}F_6N_3O_3P$
8a	2,6-$Me_2C_6H_3$	56	128—130*	56.53 56.29	5.81 5.80	8.90 8.95	—	—	—	$C_{22}H_{27}F_3N_3O_3P$
8b	4-$MeOC_6H_4$	62	111—113*	53.17 53.51	5.40 5.35	8.91 8.91	—	—	—	$C_{21}H_{25}F_3N_3O_4P$
8c	4-ClC_6H_4	39.5	118—120*	50.13 50.48	4.69 4.66	8.80 8.83	6.55 6.51	11.73 11.98	7.53 7.45	$C_{20}H_{22}ClF_3N_3O_3P$
8d	2-ClC_6H_4	44	147—150*	50.78 50.48	4.65 4.66	8.85 8.83	—	—	—	$C_{20}H_{22}ClF_3N_3O_3P$
8e	2,5-$Cl_2C_6H_3$	68	157—160*	47.30 47.08	4.10 4.15	8.21 8.23	—	—	—	$C_{20}H_{21}Cl_2F_3N_3O_3P$

(*to be continued*)

Table 1 (*continued*)

Compound	Ar	Yield (%)	M.p./°C	Found / Calculated (%)						Molecular formula
				C	H	N	P	F	Cl	
8f	3-$CF_3C_6H_4$	75	86—88	49.50 49.52	4.33 4.35	8.25 8.25	6.13 6.08	22.22 22.38	—	$C_{21}H_{22}F_6N_3O_3P$
9a	4-ClC_6H_4	47	132—134	51.81 51.49	4.90 4.94	8.58 8.58	6.30 6.32	11.60 11.63	7.29 7.24	$C_{21}H_{24}ClF_3N_3O_3P$
9b	3,4-$Me_2C_6H_3$	19	106—109*	57.01 57.14	6.06 6.05	8.71 8.69	—	—	—	$C_{23}H_{29}F_3N_3O_3P$
9c	3-ClC_6H_4	52	154—156*	51.34 51.49	4.92 4.94	8.62 8.58	—	—	—	$C_{21}H_{24}ClF_3N_3O_3P$
9d	4-$PhOC_6H_4$	47	118—121*	59.55 59.23	5.33 5.34	7.68 7.67	—	—	—	$C_{27}H_{29}F_3N_3O_4P$
9e	2,6-$Cl_2C_6H_3$	35.5	145—156*	48.00 48.11	4.38 4.42	8.00 8.01	—	—	—	$C_{21}H_{23}Cl_2F_3N_3O_3P$
9f	4-$CF_3C_6H_4$	54	97—98	50.50 50.48	4.62 4.62	8.00 8.03	5.96 5.92	21.83 21.78	—	$C_{22}H_{24}F_6N_3O_3P$
9g	2,5-$(MeO)_2C_6H_3$	36.5	116—128*	53.04 53.59	5.69 5.67	8.17 8.15	—	—	—	$C_{23}H_{29}F_3N_3O_5P$

* Melts with decomposition.

Table 2. ^1H, ^{19}F, and ^{31}P NMR spectra of compounds **7—9** (DMSO-d_6, δ, *J*/Hz)

Compound	^1H NMR	^{19}F NMR (3 F, CF_3)	^{31}P NMR (1 P, $P(O)(OEt)_2$)
7a	1.29 (m, 6 H, $OCH_2\underline{Me}$); 1.37 (br.s, 3 H, C(6)Me); 2.09, 2.16 (both s, 3 H each, Me); 4.15 (m, 4 H, $OC\underline{H}_2Me$); 4.77 (d, 1 H, H(5), $^3J_{H,P}$ = 5.9); 5.34 (br.s, 2 H, NH_2); 7.22 (m, 2 H, Ar); 7.31 (t, 1 H, Ar, *J* = 7.5)	8.72 (br.s)	15.40 (br.s)
7b[a]	1.39 (t, 6 H, $OCH_2\underline{Me}$, *J* = 7.1); 1.57 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 2.5); 3.88 (s, 3 H, OMe); 4.25 (m, 4 H, $OC\underline{H}_2Me$); 4.80 (d, 1 H, H(5), $^3J_{H,P}$ = 5.3); 4.84 (br.s, 2 H, NH_2); 7.08, 7.23 (both d, 2 H each, Ar, *J* = 8.7)	8.16 (br.s)	16.00 (br.s)
7c	1.29 (t, 6 H, $OCH_2\underline{Me}$, *J* = 7.2); 1.49 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 2.9); 4.16 (m, 4 H, $OC\underline{H}_2Me$); 4.75 (d, 1 H, H(5), $^3J_{H,P}$ = 5.2); 5.67 (s, 2 H, NH_2); 7.28, 7.56 (both d, 2 H each, Ar, *J* = 8.4)	9.70 (br.s)	15.83 (br.s)
7d[a,b]	1.39 (m, 6 H, $OCH_2\underline{Me}$);1.54 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 2.2); 4.27 (m, 4 H, $OC\underline{H}_2Me$); 4.88 (m, 3 H, H(5), NH_2); 7.44—7.68 (m, 4 H, Ar)	7.64, 8.23 (both br.s)	15.39, 15.75 (both br.s)
7e[c]	1.28 (m, 6 H, $OCH_2\underline{Me}$); 1.48 (m, 3 H, C(6)Me); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 4.77 (m, 1 H, H(5)); 5.82, 5.85 (both s, 2 H, NH_2); 7.51—7.68 (m, 3 H, Ar)	9.31, 9.52 (both br.s)	15.18, 15.57 (both br.s)
7f	1.29 (t, 6 H, $OCH_2\underline{Me}$, *J* = 7.2); 1.48 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 3.1); 4.16 (m, 4 H, $OC\underline{H}_2Me$); 4.80 (d, 1 H, H(5), $^3J_{H,P}$ = 4.7); 5.88 (s, 2 H, NH_2); 7.59, 7.86 (both d, 1 H each, Ar, *J* = 7.8); 7.63 (s, 1 H, Ar); 7.74 (t, 1 H, Ar, *J* = 7.8)	9.96 (br.s); 17.19 (s, 3 F, $\underline{C}F_3C_6H_4$)	16.40 (q, $^3J_{F,P}$ = 1.3)
7g	1.29 (t, 6 H, $OCH_2\underline{Me}$, *J* = 7.2); 1.49 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 3.1); 4.16 (m, 4 H, $OC\underline{H}_2Me$); 4.79 (d, 1 H, H(5), $^3J_{H,P}$ = 5.0); 5.84 (s, 2 H, NH_2); 7.50, 7.88 (both d, 2 H each, Ar, *J* = 8.4)	9.85 (br.s); 17.17 (s, 3 F, $\underline{C}F_3C_6H_4$)	16.33 (br.s)
8a	1.28 (m 6 H, $OCH_2\underline{Me}$); 1.74 (m, 4 H, $(CH_2)_3$); 2.07, 2.14 (both s, 3 H each, Me); 2.44, 2.71 (both m, 1 H each, $(CH_2)_3$); 4.13 (m 4 H, $OC\underline{H}_2Me$); 5.49 (s, 2 H, NH_2); 7.20 (m, 2 H, Ar); 7.29 (t, 1 H, Ar, *J* = 7.5)	13.04 (br.s)	15.14 (q, $^3J_{F,P}$ = 1.5)

(*to be continued*)

Table 2 (*continued*)

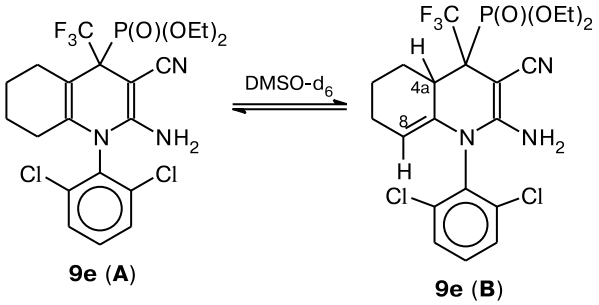
Compound	^{1}H NMR	^{19}F NMR (3 F, CF_3)	^{31}P NMR (1 P, P(O)(OEt)$_2$)
8b[a]	1.39 (m, 6 H, $OCH_2\underline{Me}$); 1.84 (m, 2 H, $(CH_2)_3$); 2.16, 2.82 (both m, 1 H each, $(CH_2)_3$); 2.43 (m, 2 H, $(CH_2)_3$, H_2O); 3.87 (s, 3 H, OMe); 4.24 (m, 4 H, $OC\underline{H}_2Me$); 4.88 (br.s, 2 H, NH_2); 7.07 (m, 2 H, Ar); 7.22 (br.s, 2 H, Ar)	12.88 (br.s)	15.72 (q, $^3J_{F,P} = 1.7$)
8c	1.28 (m, 6 H, $OCH_2\underline{Me}$); 1.75 (m, 2 H, $(CH_2)_3$); 1.85, 2.14, 2.39, 2.70 (all m, 1 H each, $(CH_2)_3$); 4.17 (m, 4 H, $OC\underline{H}_2Me$); 5.81 (s, 2 H, NH_2); 7.27, 7.55 (both d, 2 H each, Ar, $J = 8.5$)	14.14 (br.s)	15.49 (q, $^3J_{F,P} = 2.0$)
8d[d]	1.28 (m, 6 H, OCH_2Me); 1.85 (m, 4 H, $(CH_2)_3$); 2.43, 2.74 (both m, 1 H each, $(CH_2)_3$); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 5.63, 5.67 (both s, 2 H, NH_2); 7.45 (m, 3 H, Ar); 7.64 (d, 1 H, Ar, $J = 7.5$)	13.52, 13.74 (both br.s)	14.75, 15.15 (both br.s)
8e[e]	1.28 (m, 6 H, $OCH_2\underline{Me}$); 1.93 (m, 4 H, $(CH_2)_3$); 2.43, 2.73 (both m, 1 H each, $(CH_2)_3$); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 5.87, 5.92 (both br.s, 2 H, NH_2); 7.45—7.68 (m, 3 H, Ar)	13.69 (br.s)	14.85, 15.11 (both br.s)
8f	1.29 (m, 6 H, $OCH_2\underline{Me}$); 1.78 (m, 3 H, $(CH_2)_3$); 2.18, 2.41, 2.69 (all m, 1 H each, $(CH_2)_3$); 4.10 (m, 4 H, $OC\underline{H}_2Me$); 5.95 (s, 2 H, NH_2); 7.57 (m, 2 H, Ar); 7.73 (t, 1 H, Ar, $J = 7.8$); 7.84 (d, 1 H, Ar, $J = 7.8$)	14.30 (br.s); 17.18 (s, 3 F, $\underline{C}F_3C_6H_4$)	15.96 (q, $^3J_{F,P} = 2.2$)
9a	1.30 (m, 6 H, $OCH_2\underline{Me}$); 1.39 (m, 2 H, $(CH_2)_4$); 1.55 (m, 3 H, $(CH_2)_4$); 1.72, 2.02, 2.59 (all m, 1 H each, $(CH_2)_4$); 4.13 (m, 4 H, $OC\underline{H}_2Me$); 5.41 (br.s, 2 H, NH_2); 7.32, 7.56 (both d, 2 H each, Ar, $J = 8.4$)	17.11 (br.s)	16.82 (q, $^3J_{F,P} = 4.1$)
9b	1.29 (m, 6 H, $OCH_2\underline{Me}$); 1.37 (m, 2 H, $(CH_2)_4$); 1.55 (m, 3 H, $(CH_2)_4$); 1.71, 2.00, 2.60 (all m, 1 H each, $(CH_2)_4$); 4.13 (m, 4 H, $OC\underline{H}_2Me$); 5.20 (br.s, 2 H, NH_2); 7.01 (m, 2 H, Ar); 7.26 (d, 1 H, Ar, $J = 7.5$)	16.72 (br.s)	16.65 (q, $^3J_{F,P} = 4.2$)
9c	1.30 (m, 6 H, $OCH_2\underline{Me}$); 1.41 (m, 2 H, $(CH_2)_4$); 1.57 (m, 3 H, $(CH_2)_4$); 1.77, 2.00, 2.58 (all m, 1 H each, $(CH_2)_4$); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 5.50 (s, 2 H, NH_2); 7.30—7.56 (m, 4 H, Ar)	17.27 (br.s)	16.90 (br.s)
9d	1.30 (m, 6 H, $OCH_2\underline{Me}$); 1.40 (m, 2 H, $(CH_2)_4$); 1.57 (m, 3 H, $(CH_2)_4$); 1.75, 2.00, 2.60 (all m, 1 H each, $(CH_2)_4$); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 5.39 (br.s, 2 H, NH_2); 7.07, 7.27 (both d, 2 H each, Ar, $J = 8.7$); 7.11 (d, 2 H, Ar, $J = 8.1$); 7.20 (t, 1 H, Ar, $J = 7.5$); 7.44 (dd, 2 H, Ar, $J = 7.5, 8.1$)	16.96 (br.s)	16.82 (q, $^3J_{F,P} = 4.2$)
9e	**A**: 58%; 1.27 (m, 6 H, $OCH_2\underline{Me}$); 1.35—2.25 (m, 7 H, $(CH_2)_4$); 2.70 (m, 1 H, $(CH_2)_4$); 4.12 (m, 4 H, $OC\underline{H}_2Me$); 5.61 (br.s, 2 H, NH_2); 7.48—7.66 (m, 3 H, Ar) **B**: 42%; 1.27 (m, 6 H, $OCH_2\underline{Me}$); 1.35—2.25 (m, 6 H, $=CH(CH_2)_3$); 3.03 (m, 1 H, H(4a)); 4.41 (m, 1H, H(8)); 4.12 (m, 4 H, $OC\underline{H}_2Me$); 5.61 (br.s, 2 H, NH_2); 7.48—7.66 (m, 3 H, Ar)	15.66 (br.s) 15.73 (br.s)	15.82 (br.s) 17.74 (br.s)
9f	1.30 (m, 6 H, $OCH_2\underline{Me}$); 1.41 (m, 3 H, $(CH_2)_4$); 1.57 (m, 2 H, $(CH_2)_4$); 1.73, 2.01, 2.59 (all m, 1 H each, $(CH_2)_4$); 4.14 (m, 4 H, $OC\underline{H}_2Me$); 5.60 (br.s, 2 H, NH_2); 7.55, 7.88 (both d, 2 H each, Ar, $J = 8.4$)	17.24 (s, 3 F, $\underline{C}F_3C_6H_4$); 17.30 (d, $^3J_{F,P} = 3.7$)	16.90 (q, $^3J_{F,P} = 3.7$)
9g[f]	1.31(m, 6 H, $OCH_2\underline{Me}$); 1.40—1.72 (m, 6 H, $(CH_2)_4$); 2.00, 2.62 (both m, 1 H each, $(CH_2)_4$); 3.73, 3.76 (both s, 3 H each, OMe); 4.15 (m, 4 H, $OC\underline{H}_2Me$); 5.16, 5.24 (both br.s, 2 H, NH_2); 6.72 (br.s, 1 H, Ar); 7.10 (m, 2 H, Ar)	14.97, 17.21 (both br.s)	15.59, 16.98 (both br.s)

[a] The spectrum was recorded in CD_3CN.
[b] A mixture of atropoisomers 1.4 : 1.
[c] A mixture of atropoisomers 1.35 : 1.
[d] A mixture of atropoisomers 1.39 : 1.
[e] A mixture of atropoisomers 1.25 : 1.
[f] A mixture of atropoisomers 1.72 : 1.

Compounds **7d,e**, **8d,e**, and **9g** containing a substituent at *ortho*-position of the aromatic ring are formed as a mixture of atropoisomers (the ratio is given in Table 2). The isomerism in these substances is explained by the hindrance of rotation around the N—Ar bond and the presence of asymmetric carbon atom C(4) in the dihydropyridine ring. In the case of compound **7d**, individual isomers were successfully isolated by preparative thin-layer chromatography, however, rather rapid interconversion of the atropoisomers occurs in CD_3CN.

In the ^1H NMR spectrum of compound **9e** recorded in DMSO-d_6 along with signals, which correspond to the structure **A**, other signals are observed, from which two characteristic signals at δ 3.03 and 4.41 could be separated. These signals, apparently, correspond to the protons H(4a) and H(8) in the structure **B**. The ^{19}F and ^{31}P NMR spectra also contain double sets of signals for the trifluoromethyl and diethoxyphosphoryl groups. It is possible that upon dissolution of **9e**, its equilibrium isomerization occurs (Scheme 2). Integration of the corresponding signals of two isomeric forms in the NMR spectra indicates a small predominance of form **A** (58%) over form **B** (42%). Such a phenomenon has been assumed earlier based on the NMR spectral data, including two-dimensional experiments COSY and NOESY, for 4-(difluorodiethoxyphosphoryl)-methyl-substituted hexahydroquinolines.[23]

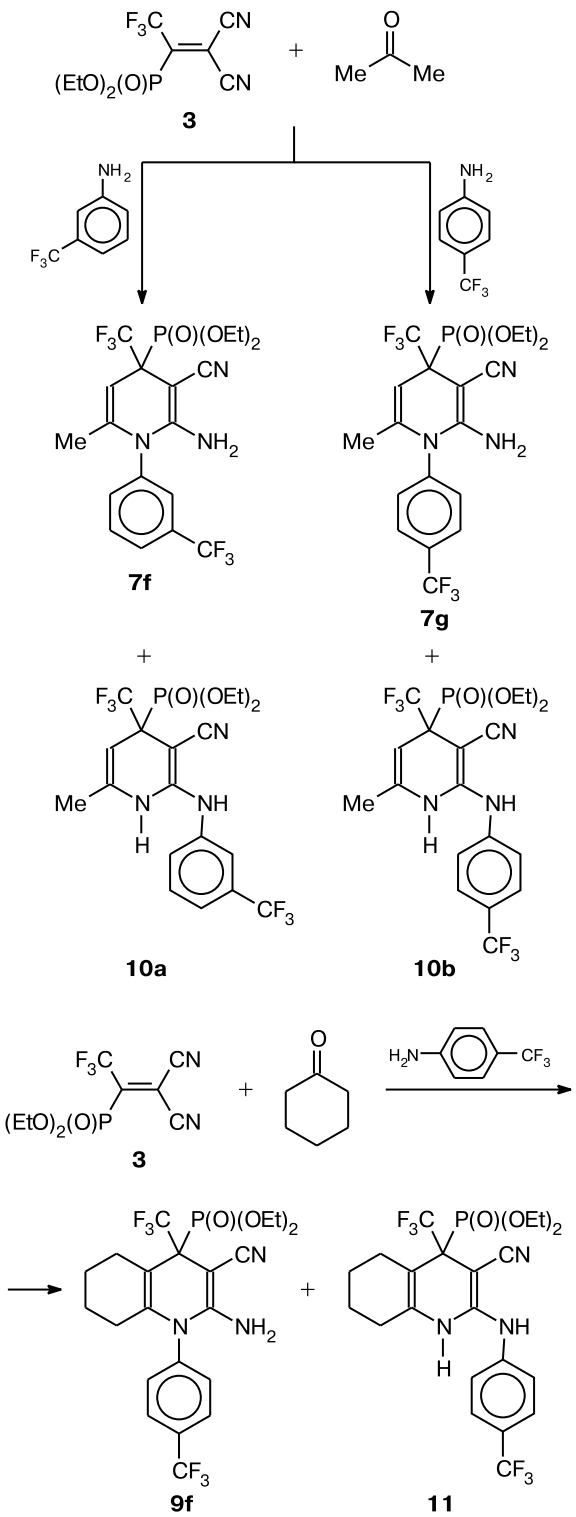
Scheme 2



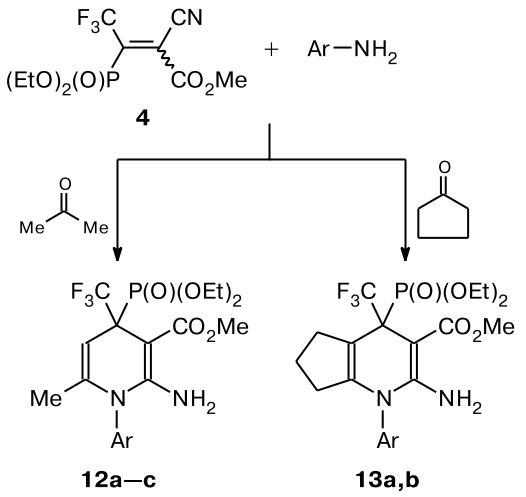
It should be noted that a number of specific features is observed for the three-component condensation of vinylphosphonate **3** with trifluoromethyl-substituted anilines and ketones, depending on the structure of the latter. For instance, the reaction with acetone, in addition to the major 2-aminodihydropyridines **7f,g**, gives 11% and 4% (the ^1H and ^{19}F NMR spectral data of the reaction mixture) of 2-arylamino-substituted compounds **10a** and **10b**, respectively. The reaction of **3** with 4-(trifluoromethyl)aniline and cyclohexanone also leads to 2-arylaminohexahydroquinoline **11**, which was successfully isolated (6% yield) and characterized (Scheme 3). At the same time, no formation of such side products was observed in the reaction with cyclopentanone.

Alkene **4** reacts with arylamines and ketones considerably slower than **3**, the reaction is always accompanied by formation of a number of side compounds and the yields of cyclization products at the nitrile group of compounds **12** and **13** do not exceed 60% (Scheme 4).

Scheme 3



Scheme 4



Ar = 2,6-$Me_2C_6H_3$ (**12a**, **13b**), 4-$MeOC_6H_4$ (**12b**, **13a**), 4-$CF_3C_6H_4$ (**12c**)

In the reaction of alkene **4** with *p*-anisidine and cyclopentanone (Scheme 5), in addition to the target product **13a**, compound **15** containing no diethoxyphosphoryl group was isolated, the formation of which can be explained by intramolecular cyclization at the methoxycarbonyl group and subsequent elimination of the phosphonate group from the intermediate **14**. The structure of compound **15** was confirmed by the X-ray diffraction data (Fig. 1).

Compound **5** under conditions of such three-component condensation very often forms stable intermediate products of C-alkylation of the enamine obtained *in situ*. The reaction of **5** with substituted anilines and acetone in CCl_4 at 20 °C rapidly leads to compounds **16a—c**, compounds **16a,b** were isolated by preparative thin-layer chromatography and characterized (compound **16c** was used for the synthesis of **18c** without chromatographic purification). No intramolecular cyclization to 1,4-dihydropyridine derivatives was observed upon prolonged keeping of the reaction mixtures at room temperature, rather a slow

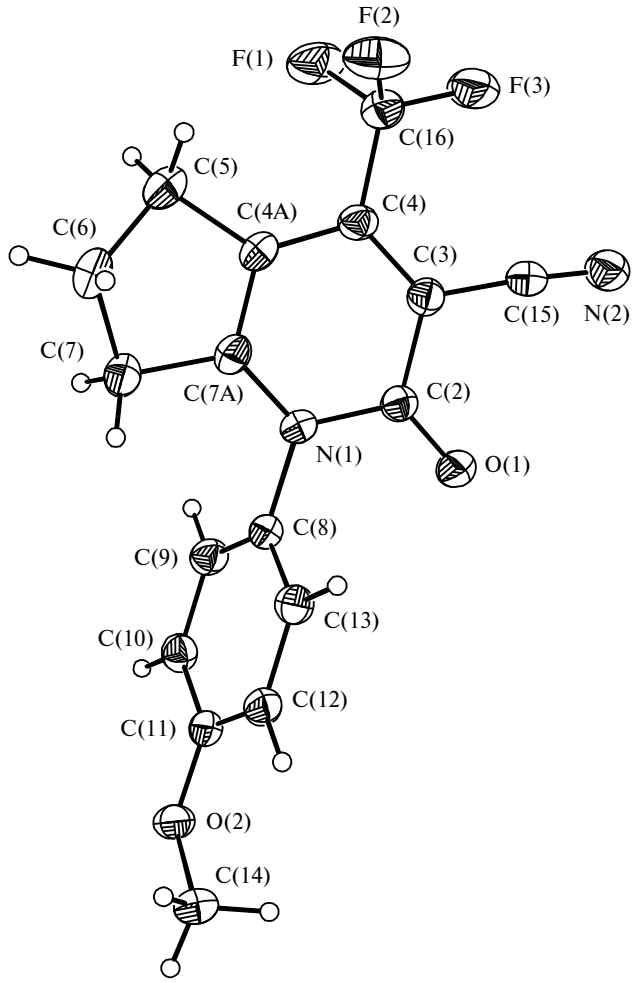
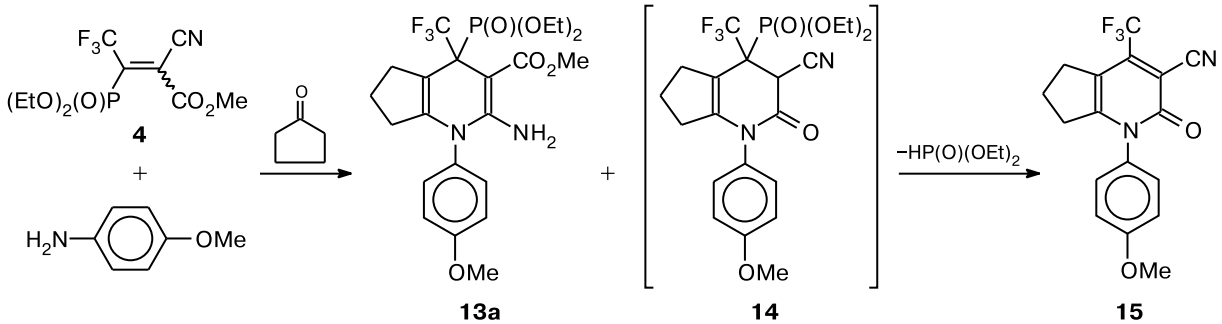


Fig. 1. General view of the molecule **15** in representation of atoms by ellipsoids of atomic displacements with 50% probability.

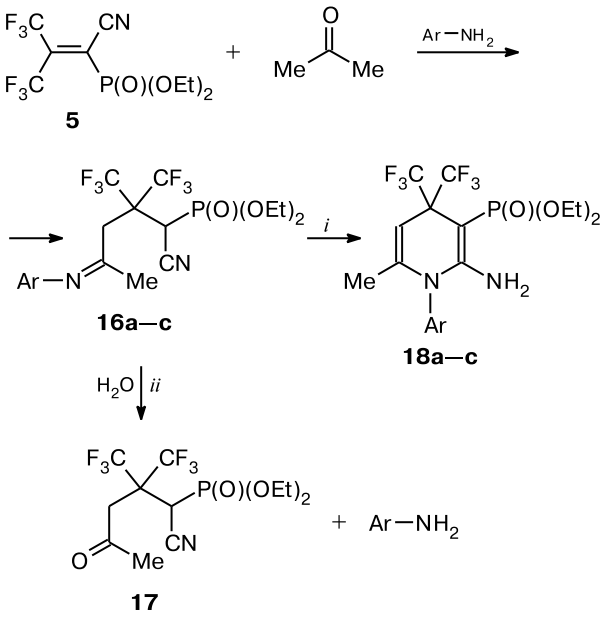
hydrolysis of compounds **16a—c** (due to the water liberating in the first step of the process) to the starting arylamines took place (confirmed by TLC data) and the product of acetone alkylation **17**. The target 2-amino-1-aryl-3-diethoxyphosphoryl-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyridines **18a—c** were obtained upon pro-

Scheme 5



longed reflux of compounds **16a—c** in carbon tetrachloride (Scheme 6, Tables 3 and 4).

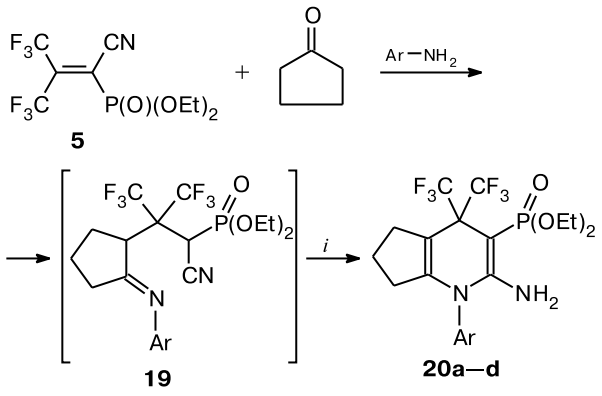
Scheme 6



i. CCl_4, reflux, 18 h; *ii*. 20 °C, 120 h.
Ar = 4-$MeOC_6H_4$ (**16a**, **18a**), 4-ClC_6H_4 (**16b**, **18b**), 4-$PhOC_6H_4$ (**16c**, **18c**)

Similarly to the preceding transformation, the reaction of alkene **5** with arylamines and cyclopentanone also leads to the intermediate C-alkylation products **19** (detected by TLC), which undergo intramolecular cyclization to 4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine derivatives **20a—d** already at 20 °C (Scheme 7, see Tables 3 and 4).

Scheme 7



i. 20 °C, 48—120 h.
Ar = 4-$MeOC_6H_4$ (**20a**), 3-$CF_3C_6H_4$ (**20b**), 4-$CF_3C_6H_4$ (**20c**), 2-ClC_6H_4 (**20d**)

We also studied behavior of vinylphosphonate **5** in the three-component condensation with arylamines and cy-

Table 3. Physico-chemical characteristics of compounds **18**, **20**, **21**

Compound	Ar	Yield (%)	M.p./°C	Found / Calculated (%)						Molecular formula
				C	H	N	P	F	Cl	
18a	4-$MeOC_6H_4$	50	98—100	46.63 46.73	4.75 4.78	5.74 5.73	—	—	—	$C_{19}H_{23}F_6N_2O_4P$
18b	4-ClC_6H_4	48	128—129	43.70 43.87	4.11 4.09	5.70 5.68	6.27 6.29	23.05 23.13	7.27 7.19	$C_{18}H_{20}ClF_6N_2O_3P$
18c	4-$PhOC_6H_4$	41	*	52.45 52.37	4.58 4.59	5.07 5.09	—	—	—	$C_{24}H_{25}F_6N_2O_4P$
20a	4-$MeOC_6H_4$	76	147—148	49.00 49.03	4.91 4.90	5.45 5.45	—	22.00 22.16	—	$C_{21}H_{25}F_6N_2O_4P$
20b	3-$CF_3C_6H_4$	37	164—165	45.68 45.66	4.01 4.01	5.07 5.07	—	30.90 30.95	—	$C_{21}H_{22}F_9N_2O_3P$
20c	4-$CF_3C_6H_4$	37	188—189	45.41 45.66	4.01 4.03	5.07 5.02	—	—	—	$C_{21}H_{22}F_9N_2O_3P$
20d	2-ClC_6H_4	28	113—115	46.15 46.30	4.29 4.27	5.43 5.40	—	—	—	$C_{20}H_{22}ClF_6N_2O_3P$
21a	4-$MeOC_6H_4$	57	134—135	50.06 50.01	5.14 5.15	5.32 5.30	5.89 5.86	21.43 21.57	—	$C_{22}H_{27}F_6N_2O_4P$
21b	3-$CF_3C_6H_4$	26	164—165	46.78 46.65	4.29 4.27	4.94 4.95	—	29.89 30.19	—	$C_{22}H_{24}F_9N_2O_3P$

* Amorphous substance.

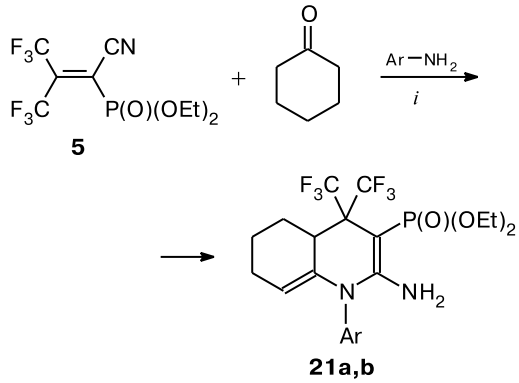
Table 4. ^{1}H, ^{19}F, and ^{31}P NMR spectra of compounds **18**, **20**, **21** ($CDCl_3$, δ, *J*/Hz)

Compound	^{1}H NMR	^{19}F NMR	^{31}P NMR (1 P, P(O)(OEt)$_2$)
18a	1.31 (t, 6 H, $OCH_2\underline{Me}$, J = 7.1); 1.57 (s, 3 H, C(6)Me); 3.85 (s, 3 H, OMe); 4.05 (m, 4 H, $OC\underline{H}_2Me$); 4.77 (d, 1 H, H(5), $^{4}J_{H,P}$ = 5.6); 6.40 (br.s, 2 H, NH_2); 6.97, 7.12 (both d, 2 H each, Ar, J = 8.8)	7.73 (s, 6 F, 2 CF_3)	26.59 s
18b	1.32 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.58 (s, 3 H, C(6)Me); 4.06 (m, 4 H, $OC\underline{H}_2Me$); 4.81 (d, 1 H, H(5), $^{4}J_{H,P}$ = 5.6); 6.38 (br.s, 2 H, NH_2); 7.18, 7.47 (both d, 2 H each, Ar, J = 8.7)	7.77 (s, 6 F, 2 CF_3)	26.06 s
18c	1.32 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.61 (s, 3 H, C(6)Me); 4.07 (m, 4 H, $OC\underline{H}_2Me$); 4.80 (d, 1 H, H(5), $^{4}J_{H,P}$ = 5.9); 6.44 (br.s, 2 H, NH_2); 7.03—7.43 (m, 9 H, Ar)	7.73 (s, 6 F, 2 CF_3)	26.37 s
20a	1.32 (t, 6 H, $OCH_2\underline{Me}$, J = 7.1); 1.83 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, J = 7.3); 2.10, 2.67 (both m, 2 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 3.84 (s, 3 H, OMe); 4.05 (m, 4 H, $OC\underline{H}_2Me$); 6.55 (br.s, 2 H, NH_2); 6.94, 7.13 (both d, 2 H each, Ar, J = 8.8)	10.53 (s, 6 F, 2 CF_3)	27.51 s
20b	1.32 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.87, 2.10, 2.69 (all br.m, 2 H each, $(CH_2)_3$); 4.07 (m, 4 H, $OC\underline{H}_2Me$); 6.47 (br.s, 2 H, NH_2); 7.45 (d, 1 H, Ar, J = 7.5); 7.51 (br.s, 1 H, Ar); 7.63 (dd, 1 H, Ar, J = 7.5, 7.8); 7.73 (d, 1 H, Ar, J = 7.8)	10.59 (s, 6 F, 2 CF_3); 15.02 (s, 3 F, $\underline{C}F_3C_6H_4$)	26.55 s
20c	1.32 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.87 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.11, 2.68 (both br.m, 2 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 4.06 (m, 4 H, $OC\underline{H}_2Me$); 6.47 (br.s, 2 H, NH_2); 7.38, 7.75 (both d, 2 H each, Ar, J = 8.4)	10.58 (s, 6 F, 2 CF_3); 15.00 (s, 3 F, $\underline{C}F_3C_6H_4$)	26.62 s
20d	1.32 (br.m, 6 H, $OCH_2\underline{Me}$); 1.85 (br.s, 2 H, $CH_2C\underline{H}_2CH_2$); 1.96—2.20 (br.m, 2 H each, $(CH_2)_3$); 2.69 (br.s, 2 H, $(CH_2)_3$); 4.06 (br.m, 4 H, $OC\underline{H}_2Me$); 6.45 (br.s, 2 H, NH_2); 7.30—7.56 (m, 4 H, Ar)	10.15, 11.99 (both q, 3 F each, CF_3, $^{4}J_{F,F}$ = 10.6)	27.33 br.s
21a	1.30 (m, 6 H, $OCH_2\underline{Me}$); 1.38 (m, 1 H, =$CH(CH_2)_3$); 1.79—2.02 (m, 4 H, =$CH(CH_2)_3$); 2.14 (br.s, 1 H, =$CH(CH_2)_3$); 3.32 (br.s, 1 H, H(4a)); 3.85 (s, 3 H, OMe); 4.03 (m, 4 H, $OC\underline{H}_2Me$); 4.31 (br.m, 1H, H(8)); 6.58 (br.s, 2 H, NH_2); 6.94—7.08 (m, 4 H, Ar)	13.38 (q, 3 F, CF_3, $^{4}J_{F,F}$ = 10.0); 16.51 (br.q, 3 F, CF_3, $^{4}J_{F,F}$ = 10.0)	27.34 s
21b	1.31 (m, 6 H, $OCH_2\underline{Me}$); 1.40 (m, 1 H, =$CH(CH_2)_3$); 1.81—2.02 (br.m, 4 H, =$CH(CH_2)_3$); 2.16 (br.s, 1 H, =$CH(CH_2)_3$); 3.50 (br.s, 1 H, H(4a)); 4.03 (br.m, 4 H, $OC\underline{H}_2Me$); 4.11 (br.m, 1 H, H(8)); 6.49 (br.s, 2 H, NH_2); 7.40 (d, 1 H, Ar, J = 7.6); 7.46 (br.s, 1 H, Ar); 7.65 (dd, 1 H, Ar, J = 7.6, 7.3); 7.71 (d, 1 H, Ar, J = 7.3)	13.45 (q, 3 F, CF_3, $^{4}J_{F,F}$ = 10.1); 16.55 (br.q, 3 F, CF_3, $^{4}J_{F,F}$ = 10.1); 15.08 (s, 3 F, $CF_3C_6H_4$)	26.52 s

clohexanone. It turned out that intermediate C-alkylation products of enamines fairly fast are converted to the substituted hexahydroquinolines **21a,b** and, like compound **9e**, there is observed migration of the multiple bond onto the ring fused with the dihydropyridine cycle (Scheme 8, see Tables 3 and 4). The structures of products **21a,b** were confirmed by NMR spectroscopy and X-ray diffraction data for compound **21a** (Fig. 2).

Vinylphosphonate **6** also reacts with anilines differently depending on the ketone structure. For instance, in the case of acetone, the reaction takes place only with arylamines containing electron-donating substituents in the aromatic ring, resulting in the low yields of mixtures of two isomeric products **22** and **23** (Scheme 9, Tables 5 and 6). It should be noted that both isomers **22b** and **23b** were isolated only in the case of the reaction of alkene **6** with acetone and *p*-anisidine.

Scheme 8



i. 20 °C, 48 h.
Ar = 4-$MeOC_6H_4$ (**21a**), 3-$CF_3C_6H_4$ (**21b**)

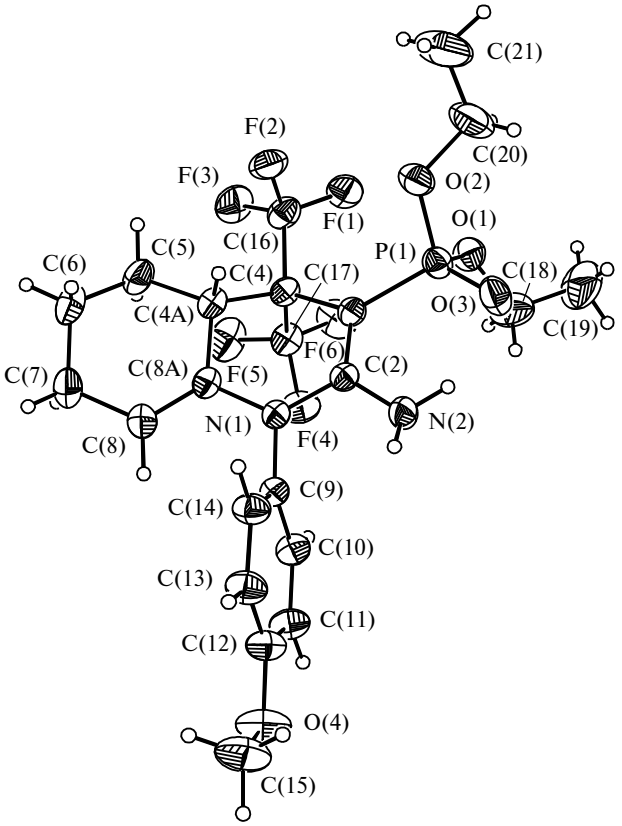


Fig. 2. General view of the molecule **21a** in representation of atoms by ellipsoids of atomic displacements with 50% probability.

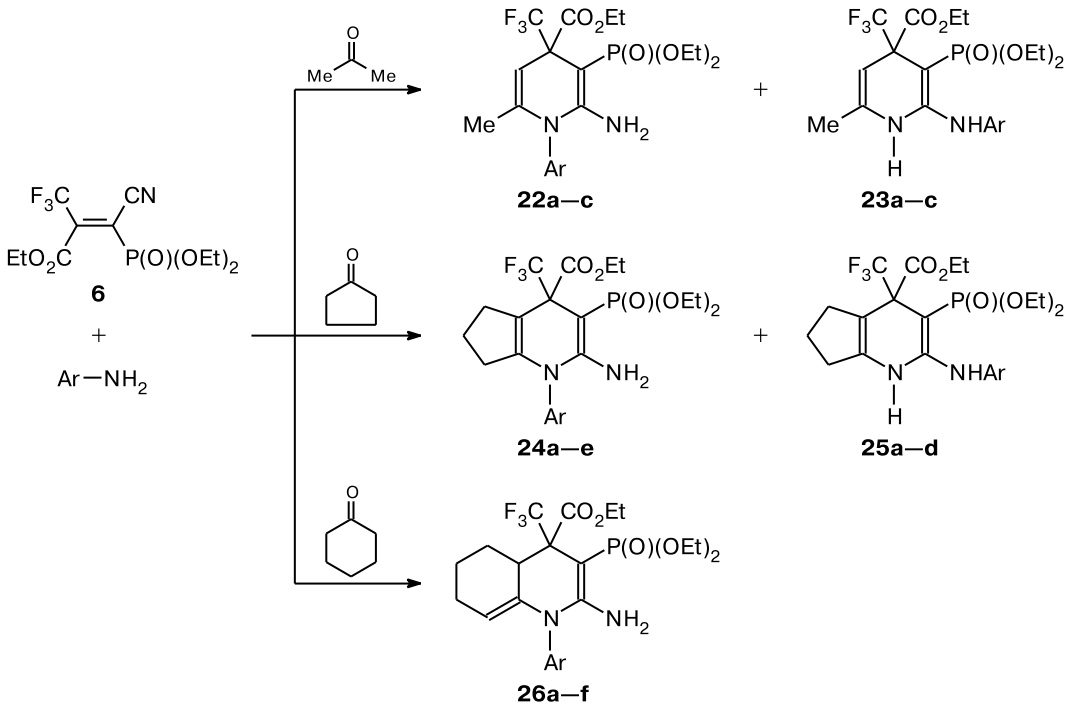
Two products **24** and **25** were as well obtained in the three-component condensation of vinylphosphonate **6** with cyclopentanone and most of the arylamines studied by us. The overall yields were 60—70% and both isomers **24a—d** and **25a—d** can be isolated (see Scheme 9, Tables 5 and 6). However, in the case of 2,6-dimethylaniline no formation of noticeable amount of the side product was observed in this transformation and only compound **24e** was successfully isolated. The structures of products **24** and **25** were confirmed by X-ray diffraction of compounds **24c** (Fig. 3) and **25c** (Fig. 4).

In the reaction of alkene **6** with cyclohexanone and anilines, likewise in the case of alkene **5**, migration of the multiple bond and formation of hexahydroquinoline derivatives **26a—f** were observed (see Scheme 9, Tables 5 and 6). It should be noted that compounds **26a—f** are formed as a mixture of diastereomers (the ratio is given in Table 6).

In conclusion, we studied the reaction of trifluoromethyl-substituted cyanovinylphosphonates **3—6** with enamines obtained *in situ* from arylamines and ketones (acetone, cyclopentanone, and cyclohexanone). We demonstrated a possibility of using alkenes **3—6** as precursors of 1,4-dihydropyridines, 4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridines, 1,4,5,6,7,8-hexahydroquinolines, and 1,4,4a,5,6,7-hexahydroquinolines, modified with both trifluoromethyl and diethoxyphosphoryl groups.

Cytotoxic activity of some compounds synthesized was studied *in vitro* at the US National Cancer Institute against

Scheme 9



Ar = 2,6-$Me_2C_6H_3$ (**22a**, **24e**, **26b**), 4-$MeOC_6H_4$ (**22b**, **23b**, **26c**), 4-$PhOC_6H_4$ (**22c**, **24a**, **25a**), Ph (**23a**, **26a**), 2,5-$(MeO)_2C_6H_3$ (**23c**), 4-$CF_3C_6H_4$ (**24b**, **25b**, **26f**), 4-FC_6H_4 (**24c**, **25c**), 3-ClC_6H_4 (**24d**, **25d**, **26e**), 3,5-$(MeO)_2C_6H_3$ (**26d**)

Table 5. Physico-chemical characteristics of compounds **22—26**

Compound	Ar	Yield (%)	M.p./°C	Found / Calculated (%)						Molecular formula
				C	H	N	P	F	Cl	
22a	2,6-$Me_2C_6H_3$	35	*	53.90 53.88	6.19 6.17	5.75 5.71	6.31 6.32	11.45 11.62	—	$C_{22}H_{30}F_3N_2O_5P$
22b	4-$MeOC_6H_4$	9	121—123	51.11 51.22	5.72 5.73	5.73 5.69	—	—	—	$C_{21}H_{28}F_3N_2O_6P$
22c	4-$PhOC_6H_4$	9	168—170	56.12 56.32	5.46 5.45	5.02 5.05	—	—	—	$C_{26}H_{30}F_3N_2O_6P$
23a	Ph	14	*	52.10 51.95	5.66 5.67	6.05 6.06	6.75 6.70	12.21 12.33	—	$C_{20}H_{26}F_3N_2O_5P$
23b	4-$MeOC_6H_4$	4	*	51.16 51.22	5.75 5.73	5.63 5.69	—	—	—	$C_{21}H_{28}F_3N_2O_6P$
23c	2,5-$(MeO)_2C_6H_3$	13	*	51.04 50.58	5.80 5.79	5.35 5.36	—	—	—	$C_{22}H_{30}F_3N_2O_7P$
24a	4-$PhOC_6H_4$	35	164—165	57.99 57.93	5.57 5.56	4.81 4.83	—	—	—	$C_{28}H_{32}F_3N_2O_6P$
24b	4-$CF_3C_6H_4$	17	182—183	49.69 49.65	4.89 4.89	5.02 5.03	—	—	—	$C_{23}H_{27}F_6N_2O_5P$
24c	4-FC_6H_4	24	132—133	52.33 52.18	5.39 5.37	5.55 5.53	—	14.85 15.01	—	$C_{22}H_{27}F_4N_2O_5P$
24d	3-ClC_6H_4	9	*	50.51 50.54	5.22 5.20	5.35 5.36	5.95 5.92	11.00 10.90	6.69 6.78	$C_{22}H_{27}ClF_3N_2O_5P$
24e	2,6-$Me_2C_6H_3$	23	*	55.99 55.81	6.26 6.24	5.39 5.42	—	—	—	$C_{24}H_{32}F_3N_2O_5P$
25a	4-$PhOC_6H_4$	32	117—118	57.98 57.93	5.55 5.56	4.83 4.83	—	—	—	$C_{28}H_{32}F_3N_2O_6P$
25b	4-$CF_3C_6H_4$	43.5	158—159	49.49 49.65	4.88 4.89	5.06 5.03	—	—	—	$C_{23}H_{27}F_6N_2O_5P$
25c	4-FC_6H_4	47.5	178—180	52.10 52.18	5.37 5.37	5.54 5.53	6.10 6.12	14.95 15.01	—	$C_{22}H_{27}F_4N_2O_5P$
25d	3-ClC_6H_4	46	183—185	50.59 50.54	5.21 5.20	5.35 5.36	—	10.87 10.90	6.83 6.78	$C_{22}H_{27}ClF_3N_2O_5P$
26a	Ph	41	135—137	54.55 54.98	6.04 6.02	5.56 5.58	6.19 6.16	11.22 11.34	—	$C_{23}H_{30}F_3N_2O_5P$
26b	2,6-$Me_2C_6H_3$	19	93—95	56.51 56.60	6.47 6.46	5.25 5.28	—	—	—	$C_{25}H_{34}F_3N_2O_5P$
26c	4-$MeOC_6H_4$	55	156—158	54.00 54.13	6.06 6.06	5.27 5.26	—	—	—	$C_{24}H_{32}F_3N_2O_6P$
26d	3,5-$(MeO)_2C_6H_3$	50.5	144—146	53.54 53.38	6.07 6.09	4.98 4.98	—	—	—	$C_{25}H_{34}F_3N_2O_7P$
26e	3-ClC_6H_4	49	133—135	51.43 51.45	5.44 5.44	5.21 5.22	5.79 5.77	10.58 10.62	6.69 6.60	$C_{23}H_{29}ClF_3N_2O_5P$
26f	4-$CF_3C_6H_4$	38	209—210	50.40 50.53	5.14 5.12	4.91 4.91	—	19.75 19.98	—	$C_{24}H_{29}F_6N_2O_5P$

* Amorphous substance.

a standard panel consisting of 60 human tumor cell lines[24] (Table 7). The data given should be considered as the results of the first step in the study of compounds of this series allowing us to find promising compounds for further research.

Most of compounds studied possess moderate cytotoxic activity with the absence of clear selectivity of action against the cell cultures belonging to various subpanels, excluding absolutely inactive compound **25d**. Compounds of the dihydropyridine series **7c** and **7e** exhibited similar

Table 6. ^{1}H, ^{19}F, and ^{31}P NMR spectra of compounds **22—26** (DMSO-d_6, δ, *J*/Hz)

Compound	^{1}H NMR	^{19}F NMR (3 F, CF_3)	^{31}P NMR (1 P, P(O)(OEt)$_2$)
22a	1.15—1.23 (m, 9 H, $OCH_2\underline{Me}$); 1.34 (c, 3 H, C(6)Me); 2.09, 2.12 (both s, 3 H each, Me); 3.90 (m, 4 H, $OC\underline{H}_2Me$); 4.04, 4.14 (both m, 1 H each, $OC\underline{H}_2Me$); 4.66 (d, 1 H, H(5), $^{4}J_{H,P}$ = 5.9); 5.23 (s, 2 H, NH_2); 7.21—7.31 (m, 3 H, Ar)	5.11 s	25.86 s
22b[a]	1.25—1.36 (m, 9 H, $OCH_2\underline{Me}$); 1.55 (s, 3 H, C(6)Me); 3.85 (s, 3 H, OMe); 4.07 (br.m, 4 H, $OC\underline{H}_2Me$); 4.27 (br.m, 2 H, $OC\underline{H}_2Me$); 4.64 (d, 1 H, H(5), $^{4}J_{H,P}$ = 4.7); 5.11 (br.s, 2 H, NH_2); 6.96 (d, 2 H, Ar, *J* = 8.7); 7.15 (br.m, 2 H, Ar)	3.38 s	25.74 s
22c	1.15—1.24 (m, 9 H, $OCH_2\underline{Me}$); 1.53 (s, 3 H, C(6)Me); 3.90 (br.m, 4 H, $OC\underline{H}_2Me$); 4.10 (br.m, 2 H, $OC\underline{H}_2Me$); 4.36 (br.d, 1 H, H(5), $^{4}J_{H,P}$ = 3.4); 5.35 (s, 2 H, NH_2); 6.93—7.45 (m, 9 H, Ar)	3.83 s	25.03 s
23a	0.94, 1.11, 1.20 (all t, 3 H each, $OCH_2\underline{Me}$, *J* = 7.2); 1.81 (s, 3 H, C(6)Me); 3.81 (m, 4 H, $OC\underline{H}_2Me$); 4.04, 4.15 (both m, 1 H each, $OC\underline{H}_2Me$); 4.38 (d, 1 H, H(5), $^{4}J_{H,P}$ = 5.0); 6.91—6.95 (m, 3 H, Ar); 7.28 (dd, 2 H, Ar, *J* = 7.5, 8.1); 7.40 (s, 1 H, NH); 9.16 (d, 1 H, NH, $^{4}J_{H,P}$ = 3.4)	3.51 s	25.59 s
23b	1.04 (br.t, 3 H, $OCH_2\underline{Me}$, *J* = 7.1); 1.15, 1.21 (both br.t, 3 H each, $OCH_2\underline{Me}$, *J* = 7.1); 1.78 (s, 3 H, C(6)Me); 3.72 (s, 3 H, OMe); 3.85 (br.m, 4 H, $OC\underline{H}_2Me$); 4.05, 4.13 (both br.m, 1 H each, $OC\underline{H}_2Me$); 4.34 (br.s, 1 H, H(5)); 6.91 (br.m, 4 H, Ar); 7.43 (s, 1 H, NH); 8.75 (br.s, 1 H, NH)	3.91 s	24.17 s
23c	0.95 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.2); 1.19 (m, 6 H, $OCH_2\underline{Me}$); 1.83 (s, 3 H, C(6)Me); 3.67, 3.78 (both s, 3 H each, OMe); 3.80—4.18 (m, 6 H, $OC\underline{H}_2Me$); 4.39 (d, 1 H, H(5), $^{4}J_{H,P}$ = 4.7); 6.46—6.50 (m, 2 H, Ar); 6.93 (d, 1 H, Ar, *J* = 9.0); 7.32 (s, 1 H, NH); 9.22 (d, 1 H, NH, $^{4}J_{H,P}$ = 2.8)	3.57 s	22.84 s
24a	1.18—1.24 (m, 9 H, $OCH_2\underline{Me}$); 1.81 (br.m, 2 H, $CH_2C\underline{H}_2CH_2$); 1.93, 2.14, 2.31, 2.41 (br.m, 1 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 3.90 (m, 4 H, $OC\underline{H}_2Me$); 4.06, 4.16 (both m, 1 H each, $OC\underline{H}_2Me$); 5.34 (s, 2 H, NH_2); 7.06—7.45 (m, 9 H, Ar)	5.47 s	25.42 s
24b	1.18—1.25 (m, 9 H, $OCH_2\underline{Me}$); 1.83 (br.m, 3 H, $(CH_2)_3$); 2.17 (br.m, 1 H, $(CH_2)_3$); 2.39 (br.m, 2 H, $(CH_2)_3$); 3.92 (br.m, 4 H, $OC\underline{H}_2Me$); 4.06, 4.19 (both m, 1 H each, $OC\underline{H}_2Me$); 5.42 (s, 2 H, NH_2); 7.48, 7.87 (both d, 2 H each, Ar, *J* = 8.4)	5.46 s, 17.21 (s, 3 F, $\underline{C}F_3C_6H_4$)	24.97 s
24c	1.18—1.24 (m, 9 H, $OCH_2\underline{Me}$); 1.82 (br.m, 3 H, $(CH_2)_3$); 2.15, 2.31, 2.40 (all m, 1 H each, $(CH_2)_3$); 3.91 (br.m, 4 H, $OC\underline{H}_2Me$); 4.06, 4.17 (both m, 1 H each, $OC\underline{H}_2Me$); 5.33 (s, 2 H, NH_2); 7.26—7.35 (m, 4 H, Ar)	−34.64 (s, 1 F, FC_6H_4); 5.43 s	23.99 s
24e	1.17—1.24 (m, 9 H, $OCH_2\underline{Me}$); 1.79 (br.m, 3 H, $(CH_2)_3$); 1.92, 2.15, 2.43 (all br.m, 1 H each, $(CH_2)_3$); 2.09, 2.11 (both s, 3 H each, Me); 3.92 (m, 4 H, $OC\underline{H}_2Me$); 4.07, 4.18 (both m, 1 H each, $OC\underline{H}_2Me$); 5.15 (s, 2 H, NH_2); 7.20—7.31(m, 3 H, Ar)	6.83 s	28.25 s
25a	1.01, 1.15, 1.21 (all t, 3 H each, $OCH_2\underline{Me}$, *J* = 7.2); 1.89 (br.m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.07, 2.34 (both br.m, 1 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 2.42 (br.m, 2 H, $C\underline{H}_2CH_2C\underline{H}_2$); 3.77, 4.05, 4.18 (all m, 1 H each, $OC\underline{H}_2Me$); 3.95 (m, 2 H, $OC\underline{H}_2Me$); 6.93—7.38 (m, 10 H, Ar, NH); 9.36 (d, 1 H, NH, $^{4}J_{H,P}$ = 3.1)	5.79 s	23.98 s
25b	0.91, 1.08, 1.23 (all t, 3 H each, $OCH_2\underline{Me}$, *J* = 7.2); 1.92 (br.m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.08, 2.36 (both br.m, 1 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 2.44 (br.m, 2 H, $C\underline{H}_2CH_2C\underline{H}_2$); 3.72, 4.06, 4.19 (all m, 1 H each, $OC\underline{H}_2Me$); 3.85 (m, 3 H, $OC\underline{H}_2Me$); 7.03, 7.58 (both d, 2 H each, Ar, *J* = 8.7); 7.68 (s, 1 H, NH); 9.65 (d, 1 H, NH, $^{4}J_{H,P}$ = 3.7)	5.88 s, 18.55 (s, 3 F, $\underline{C}F_3C_6H_4$)	22.14 s

(*to be continued*)

Table 6 (*continued*)

Compound	^{1}H NMR	^{19}F NMR (3 F, CF_3)	^{31}P NMR (1 P, P(O)(OEt)$_2$)
25c	0.99, 1.14, 1.21 (all t, 3 H each, $OCH_2\underline{Me}$, J = 7.2); 1.89 (br.m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.07 (br.m, 1 H, $C\underline{H}_2CH_2C\underline{H}_2$); 2.37 (br.m, 3 H, $C\underline{H}_2CH_2C\underline{H}_2$); 3.77, 4.05, 4.18 (all m, 1 H each, $OC\underline{H}_2Me$); 3.88 (m, 3 H, $OC\underline{H}_2Me$); 6.99, 7.13 (both m, 2 H each, Ar); 7.30 (s, 1 H, NH); 9.35 (d, 1 H, NH, $^4J_{H,P}$ = 3.1)	–43.86 (s, 1 F, FC_6H_4); 5.76 s	22.53 s
25d	0.95, 1.10, 1.21 (all t, 3 H each, $OCH_2\underline{Me}$, J = 6.9); 1.91 (br.m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.08, 2.33 (both br.m, 1 H each, $C\underline{H}_2CH_2C\underline{H}_2$); 2.45 (br.m, 2 H, $C\underline{H}_2CH_2C\underline{H}_2$); 3.75, 4.06, 4.18 (br.m, 1 H each, $OC\underline{H}_2Me$); 3.87 (br.m, 3 H, $OC\underline{H}_2Me$); 6.85, 6.93 (both br.d, 1 H each, Ar, J = 7.5, 7.8); 7.26 (dd, 1 H, Ar, J = 7.5, 7.8); 7.42 (br.s, 1 H, NH); 9.54 (br.d, 1 H, NH, $^4J_{H,P}$ = 3.4)	5.65 s	22.67 s
26a[a,b]	1.28 (m, 6 H, $OCH_2\underline{Me}$); 1.34 (t, 3 H, $OCH_2\underline{Me}$, J = 7.2); 1.47, 2.01 (both br.m, 1 H each, $=CH(CH_2)_3$); 1.72—1.91 (br.m, 4 H, $=CH(CH_2)_3$); 3.47 (br.m, 1 H, H(4a)); 4.06 (m, 4 H, $OC\underline{H}_2Me$); 4.15—4.45 (br.m, 3 H, $OC\underline{H}_2Me$, H(8)); 4.86 (br.s, 2 H, NH_2); 7.16—7.51 (m, 5 H, Ar)	11.82, 13.84 both br.s	26.20 br.m
26b[a,c]	1.28 (m, 6 H, $OCH_2\underline{Me}$); 1.36 (t, 3 H, $OCH_2\underline{Me}$, J = 6.9); 1.44, 2.03 (both br.m, 1 H each, $=CH(CH_2)_3$); 1.71—1.96 (br.m, 4 H, $=CH(CH_2)_3$); 2.12, 2.15 (both s, 3 H each, Me); 3.39 (br.m, 1 H, H(4a)); 4.06 (m, 4 H, $OC\underline{H}_2Me$); 4.18—4.48 (br.m, 3 H, $OC\underline{H}_2Me$, H(8)); 4.82 (br.s, 2 H, NH_2); 7.15—7.27 (m, 3 H, Ar)	12.72, 14.48 both br.s	25.99 br.m
26s[d,h]	1.29 (m, 6 H, $OCH_2\underline{Me}$); 1.35 (t, 3 H, $OCH_2\underline{Me}$, J = 7.2); 1.45, 2.01 (both br.m, 1 H each, $=CH(CH_2)_3$); 1.73—1.92 (br.m, 4 H, $=CH(CH_2)_3$); 3.48 (br.m, 1 H, H(4a)); 3.85 (s, 3 H, OMe); 4.07 (m, 4 H, $OC\underline{H}_2Me$); 4.18—4.45 (br.m, 3 H, $OC\underline{H}_2Me$, H(8)); 4.87, 4.90 (both br.s, 2 H, NH_2); 6.93—7.14 (m, 4 H, Ar)	11.77, 13.80 both br.s	25.28 br.m
26d[e]	1.14—1.25 (m, 9 H, $OCH_2\underline{Me}$); 1.34—2.11 (br.m, 6 H, $=CH(C\underline{H}_2)_3$); 3.37 (br.m, 1 H, H(4a)); 3.76 (br.s, 6 H, OMe); 3.87 (br.m, 4 H, $OC\underline{H}_2Me$); 3.95—4.25 (br.m, 3 H, $OC\underline{H}_2Me$, H(8)); 5.21 (br.s, 2 H, NH_2); 5.98—6.64 (br.m, 3 H, Ar)	13.35, 15.36 both br.s	23.99, 23.95 both br.s
26e[a,f]	1.30 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.35 (t, 3 H, $OCH_2\underline{Me}$, J = 7.2); 1.46, 2.01 (both br.m, 1 H each, $=CH(CH_2)_3$); 1.70—1.95 (br.m, 4 H, $=CH(CH_2)_3$); 3.48 (m, 1 H, H(4a)); 4.08 (m, 4 H, $OC\underline{H}_2Me$); 4.17—4.44 (br.m, 3 H, $OC\underline{H}_2Me$, H(8)); 4.85, 4.88 (both br.s, 2 H, NH_2); 7.04—7.47 (br.m, 4 H, Ar)	11.85, 13.81 both br.s	25.71, 25.80 both br.s
26f[a,g]	1.30 (t, 6 H, $OCH_2\underline{Me}$, J = 7.2); 1.36 (t, 3 H, $OCH_2\underline{Me}$, J = 7.2); 1.41—2.05 (m, 6 H, $=CH(C\underline{H}_2)_3$); 3.50 (br.m, 1 H, H(4a)); 4.00—4.16 (br.m, 5 H, $OC\underline{H}_2Me$, H(8)); 4.20—4.40 (br.m, 2 H, $OC\underline{H}_2Me$); 4.82, 4.85 (both br.s, 2 H, NH_2); 7.37 (m, 2 H, Ar); 7.74, 7.77 (both d, 2 H, Ar, J = 8.4)	11.86, 13.96 both br.s; 15.01 (br.s, 3 F, $\underline{C}F_3C_6H_4$)	25.55, 25.62 both br.s

[a] The spectrum was recorded in $CDCl_3$.
[b] A mixture of diastereomers 3.3 : 1.
[c] A mixture of diastereomers 1.1 : 1.
[d] A mixture of diastereomers 2.7 : 1.
[e] A mixture of diastereomers 3.4 : 1.
[f] A mixture of diastereomers 1.77 : 1.
[g] A mixture of diastereomers 2.27 : 1.
[h] The ^{1}H and ^{19}F spectra were recorded in $CDCl_3$.

moderate cytotoxicity independent of the substituent on the nitrogen atom of the dihydropyridine ring. At the same time, compound **18b** has proved considerably less active when two trifluoromethyl groups are present at position 4 and when cyano group is replaced with the diethoxyphosphoryl residue. Compounds **8e**, **8b**, and **20a** containing, respectively, 2,5-dichlorophenyl (**8e**) and 4-methoxyphenyl (**8b** and **20a**) substituents on the nitrogen atom of the

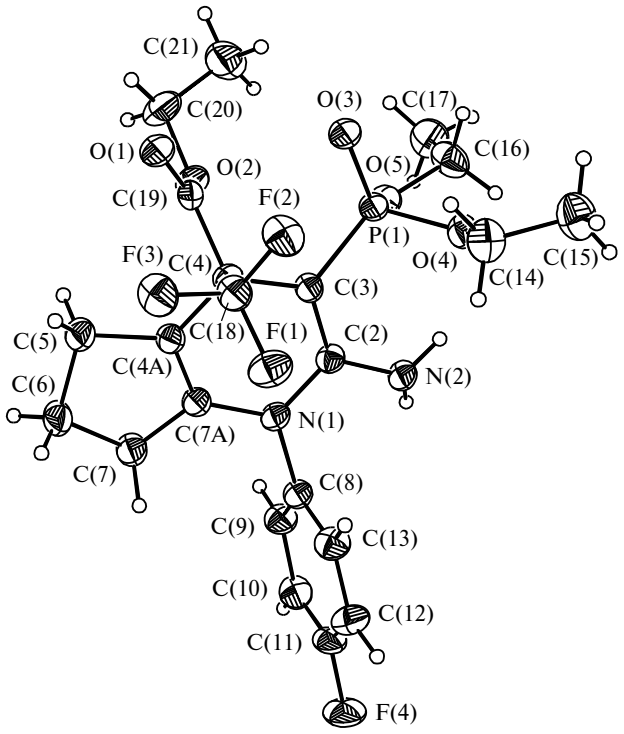


Fig. 3. General view of the molecule **24c** in representation of atoms by ellipsoids of atomic displacements with 50% probability (the solvate molecule of diethyl ether is not shown).

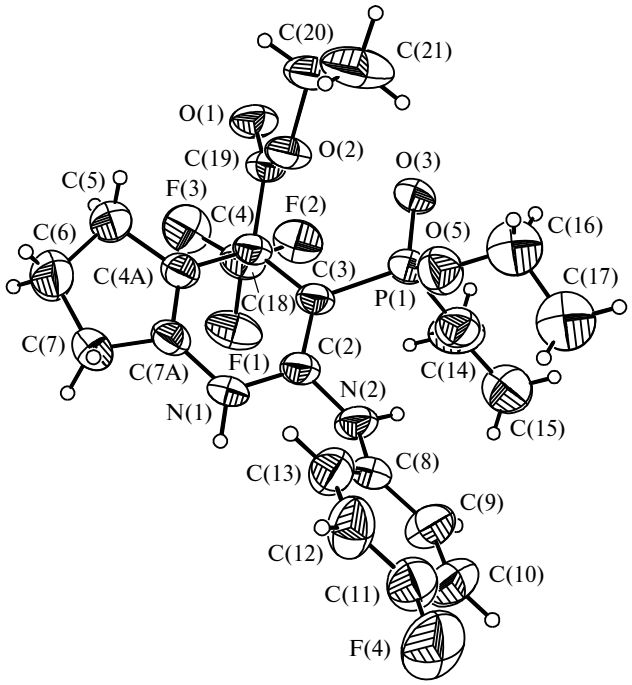


Fig. 4. General view of the molecule **25c** in representation of atoms by ellipsoids of atomic displacements with 50% probability.

dihydropyridine ring exhibited noticeable cytotoxic activity against the most tumor cells in contrast to the aforementioned compound **25d** containing no substituent at this position. Compounds of hexahydroquinoline series **9g**, **26c**, and **26d** displayed very similar moderate cytotoxic properties having minimum structural differences. Appar-

Table 7. Results of the study of cytotoxic activity of compounds

Cell cultures	GI_{50}/μmol L^{-1}									
	7c	**7e**	**8b**	**8e**	**9g**	**18b**	**20a**	**25d**	**26c**	**26d**
					Leukemia					
CCRF-CEM	13.2	—	25.2	10.8	19.4	78.0	20.2	>100	25.5	20.6
HL-60(TB)	14.2	5.76	16.6	16.7	18.9	—	10.3	>100	13.8	25.2
K-562	10.0	>100	21.6	21.2	19.3	>100	17.1	>100	23.9	20.0
MOLT-4	9.46	3.33	15.4	14.4	27.8	1.35	6.53	>100	14.9	9.88
RPMI-8226	16.0	12.5	16.9	13.7	17.1	5.84	14.8	>100	14.7	19.8
SR	4.51	19.5	15.9	15.5	12.5	0.126	15.5	>100	24.4	17.6
					Non-Small Cell Lung Cancer					
A549/ATCC	51.3	52.1	40.3	31.0	36.7	>100	11.7	54.8	27.4	15.9
EKVX	23.8	69.0	33.2	22.2	30.0	>100	12.1	>100	37.1	24.2
HOP-62	>100	99.5	94.6	17.3	47.1	>100	15.7	>100	47.6	17.0
HOP-92	12.5	37.0	13.7	16.7	22.8	4.15	13.21	>100	5.05	12.9
NCI-H226	22.3	—	42.6	23.1	45.2	>100	5.0	>100	57.0	16.8
NCI-H23	28.7	37.0	34.7	33.6	38.3	>100	15.5	>100	43.2	20.5
NCI-H322M	—	>100	38.5	28.6	37.0	—	13.2	>100	53.5	29.1
NCI-H460	49.1	49.4	31.0	15.7	18.9	>100	14.8	>100	27.2	16.4
NCI-H522	20.3	27.4	17.4	17.4	19.1	66.2	14.5	47.7	32.0	17.8

(*to be continued*)

Table 7 (*continued*)

Cell cultures	GI_{50}/μmol L^{-1}									
	7c	**7e**	**8b**	**8e**	**9g**	**18b**	**20a**	**25d**	**26c**	**26d**
					Colon Cancer					
COLO 205	17.1	39.1	26.6	20.9	27.8	>100	17.5	>100	19.2	16.8
HCC-2998	24.8	70.1	32.6	19.2	30.7	>100	16.1	>100	52.8	19.4
HCT-116	14.8	39.2	17.5	28.4	30.3	53.8	11.3	85.4	22.1	13.8
HCT-15	13.1	49.4	31.3	26.0	31.3	>100	14.7	>100	29.7	18.9
HT 29	30.5	51.0	41.5	20.1	24.3	>100	12.4	>100	27.1	16.7
KM 12	1.21	55.5	21.5	22.3	89.7	>100	12.5	>100	32.5	20.4
SW-620	14.6	97.8	19.9	23.5	24.2	>100	14.2	>100	32.0	18.3
					CNS Cancer					
SF-268	29.6	56.1	30.8	15.7	17.1	>100	11.6	>100	33.6	16.7
SF-295	35.0	—	21.9	18.3	17.2	38.3	13.5	>100	24.6	16.5
SF-539	34.4	96.8	30.2	17.0	17.0	>100	15.6	>100	27.5	17.4
SNB-19	>100	66.3	71.7	18.8	35.9	>100	13.1	>100	44.3	16.3
SNB-75	21.3	59.8	26.5	24.5	20.0	>100	8.11	40.7	24.13	13.4
U251	26.6	73.5	32.0	18.3	38.9	>100	14.1	>100	4.9	18.1
					Melanoma					
LOX IMVI	11.7	>100	27.0	17.1	20.4	>100	13.6	>100	20.5	16.1
MALME-3M	0.726	37.7	40.4	23.2	30.0	>100	13.2	>100	23.5	21.2
M14	30.4	38.9	34.8	18.5	23.8	>100	13.5	>100	33.2	15.8
SK-MEL-2	89.4	39.9	18.7	20.6	3.92	>100	13.9	>100	24.6	18.5
SK-MEL-28	16.3	60.7	26.9	21.7	31.2	>100	14.4	>100	50.8	17.9
SK-MEL-5	18.6	31.4	15.8	15.7	25.1	>100	12.0	>100	14.6	14.4
UACC-257	34.6	65.4	51.7	—	15.1	>100	12.3	>100	24.6	16.5
UACC-62	20.8	37.5	22.9	17.6	32.1	>100	10.0	>100	28.7	15.9
					Ovarian Cancer					
IGROV1	6.51	6.12	15.8	13.3	22.0	88.8	—	—	25.4	—
OVCAR-3	15.7	47.5	18.5	16.0	21.9	>100	13.0	>100	25.0	20.0
OVCAR-4	22.8	50.3	27.1	34.5	27.0	>100	12.9	>100	26.3	20.5
OVCAR-5	15.9	44.7	68.4	28.1	65.0	>100	14.7	>100	26.9	22.9
OVCAR-8	31.9	89.9	38.7	31.7	31.0	>100	16.5	>100	33.2	22.4
SK-OV-3	>100	66.2	99.6	24.5	24.9	>100	17.0	>100	44.6	24.0
					Renal Cancer					
768-0	66.0	72.1	60.0	19.2	35.6	>100	14.5	>100	52.0	62.1
A498	—	41.9	—	23.5	33.0	—	11.2	>100	25.8	29.0
ACHN	10.2	53.0	32.6	28.9	34.7	78.0	14.8	>100	25.8	>100
CAKI-1	15.2	66.2	16.8	19.1	19.4	41.4	8.81	>100	23.8	>100
RXF-393	20.8	51.7	43.4	19.3	53.4	>100	14.2	39.9	37.6	32.1
SN12C	45.5	>100	39.6	22.8	32.8	>100	12.4	>100	37.0	40.6
TK-10	3.04	>100	48.8	32.9	29.0	55.1	13.5	>100	40.1	>100
UO-31	20.6	7.61	18.7	14.2	24.5	>100	11.0	>100	23.3	35.4
					Prostate Cancer					
PC-3	19.1	31.8	19.8	15.9	24.8	4.27	11.8	>100	13.2	64.1
DU-145	17.4	>100	20.3	20.4	25.2	>100	15.7	>100	40.0	37.8
					Breast Cancer					
MCF7	25.3	37.6	32.7	16.6	10.2	>100	14.2	>100	26.8	54.1
NCI/ADR-RES	46.0	41.4	35.7	28.6	26.1	>100	12.6	>100	27.2	59.7
MDA-MB-231/A	21.3	46.0	13.3	16.9	25.2	>100	12.4	51.7	25.2	28.8
HS 578T	2.26	41.8	13.4	21.2	22.1	79.8	10.0	70.7	26.8	49.3
MDA-MB-435	32.6	63.3	27.5	18.9	—	>100	12.6	>100	32.8	40.9
MDA-N	—	—	—	—	—	—	—	—	—	—
BT-549	15.1	44.8	17.7	16.0	12.8	>100	15.4	48.2	35.8	33.1
T-47D	11.3	31.3	46.4	18.6	25.9	>100	12.4	>100	33.4	53.6

Note. GI_{50} is the concentration of compound causing 50% retardation of the cell culture growth rates.

ently, the presence of the methoxyphenyl and chlorophenyl substituent on the nitrogen atom of the pyridine ring is a necessary condition for the cytotoxic activity to be exhibited by all the compounds represented in this series. The results obtained give us substantiation of further search for cytotoxic agents in the series under study, as well as among other fluorine-containing heterocycles.

Experimental

^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra of compounds synthesized were recorded on a Bruker AMX-400 spectrometer (400.13, 100.61, and 160.62 MHz, respectively), ^{19}F NMR spectra were recorded on a Bruker WP-200SY and Bruker AMX-400 spectrometers (188.31 and 376.47 MHz, respectively). Chemical shifts ^{1}H and ^{13}C were determined relatively to the residual signal of the deuterated solvent and recalculated to $SiMe_4$. Chemical shifts of ^{19}F and ^{31}P were determined relatively to the external standards, CF_3COOH and 85% aq. H_3PO_4, respectively.

Compounds **15**, **21a**, **24c**, and **25c** were studied by X-ray diffraction analysis. The X-ray diffraction experiments of single crystals of **15**, **21a**, **24c**, and **25c** were performed on a SMART 1000 CCD diffractometer (λ(Mo-*K*α) = 0.71073 Å, a graphite monochromator, ω-scanning). The main crystal and structural parameters are given in Table 8. Analysis of measured intensities was performed using the SAINT Plus[25] and SADABS programs.[26] The structures were solved by the direct method and refined by the full-matrix least squares method in anisotropic approximation for nonhydrogen atoms against F^2_{hkl} using the SHELXTL-97 program package (see Ref. 27). Hydrogen atoms were placed in the geometrically calculated positions and refined by the riding model (U_{iso}(H) = nU_{eq}(C), where n = 1.5 for the carbon atoms of the methyl group, n = 1.2 for other C atoms). The disorder of the ethyl group in compound **25c** over two positions was an exception, the both components of which were refined isotropically. The hydrogen atoms of the amino groups were localized from the differential synthesis of electron density and then the N—H distance was normalized by the value of 0.9 Å. Hydrogen atoms were refined by the riding model (U_{iso}(H) = nU_{eq}(N), where n = 1.2). The independent part of the unit cell contains one

Table 8. Crystallographic data and parameters of X-ray diffraction experiments for compounds **15**, **21a**, **24c**, **25c**

Parameter	**15**	**21a**	**24c**	**25c**
Molecular formula	$C_{17}H_{13}F_3N_2O_2$	$C_{22}H_{27}F_6N_2O_4P$	$C_{26}H_{37}F_4N_2O_6P$	$C_{22}H_{27}F_4N_2O_5P$
Molecular weight	334.29	528.43	580.55	506.43
T/K	110(2)	295(2)	110(2)	230(2)
Crystal system	Monoclinic	Triclinic	Orthorhombic	Monoclinic
Space group	*C*2/*c*	*P*-1	$P2_12_12_1$	$P2_1/n$
a/Å	23.390(5)	9.918(5)	9.149(2)	12.548(3)
b/Å	7.6033(16)	10.040(5)	13.981(4)	15.156(4)
c/Å	18.145(4)	13.247(7)	22.486(6)	12.548(3)
α/deg	90	87.48(4)	90	90
β/deg	111.081(5)	68.34(4)	90	109.139(5)
γ/deg	90	85.17(4)	90	90
V/Å^3	3011.0(11)	1221.5(11)	2876.2(13)	2447.3(10)
Z	8	2	4	4
Absorption coefficient μ/mm^{-1}	0.123	0.190	0.163	0.178
F(000)	1376	548	1224	1056
d_{calc}/g cm^{-3}	1.475	1.437	1.341	1.374
Scanning range on θ/deg.	1.87—29.00	2.04—26.06	1.72—30.07	1.92—25.99
Number of reflections				
measured	11234	5094	31466	19802
independent	3988	4800	8368	4718
(R_{int})	(0.0419)	(0.0151)	(0.0475)	(0.0291)
with $I \geq 2\sigma(I)$	2026	3863	5448	3270
Number of parameters	218	320	357	308
Data completeness (%)	99.2	99.0	99.3	98.0
GOOF	1.011	1.171	0.993	1.006
Convergence of refinement from reflections ($R_1(F)$) with $I > 2\sigma(I)$[a]	0.0506	0.0469	0.0553	0.0649
Convergence of refinement from all the reflections ($wR_2(F^2)$)[b]	0.1089	0.1482	0.1151	0.1508
Residual electron density (max/min), e/Å^{-3}	0.318/−0.241	0.347/−0.324	0.650/−0.316	0.985/−0.508

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma(F_o)$.
[b] $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$.

molecule for all the compounds except **24c**, which also includes a solvate molecule of diethyl ether.

Compounds **3—6** were synthesized as described earlier.[10]

Diethyl [2-amino-3-cyano-1-(2,6-dimethylphenyl)-6-methyl-4-(trifluoromethyl)-1,4-dihydropyridin-4-yl]phosphonate (7a). A solution of alkene **3** (0.31 g, 1.1 mmol) in acetone (1.5 mL) was added to a solution of 2,6-dimethylaniline (0.12 g, 0.99 mmol) in acetone (2.0 mL) at 20 °C with stirring. The reaction mixture was stirred for 24 h at 20 °C. The solvent was evaporated *in vacuo*. Carbon tetrachloride (7 mL) was added to the residue, a precipitate was filtered off and washed with pentane to obtain the product (0.29 g, 67%) (see Tables 1 and 2). ^{13}C NMR (DMSO-d_6), δ: 16.8 (m, $OCH_2\underline{Me}$); 17.2, 17.4, and 19.8 (all s, Me); 46.3 (m, C(3)); 63.6 (m, $O\underline{C}H_2Me$); 91.7 (d, C(5), $^2J_{C,P}$ = 8 Hz); 121.0 (s, CN); 122.4 (dq, CF_3, $^1J_{C,F}$ = 283 Hz and $^2J_{C,P}$ = 15 Hz); 129.3 and 129.4 (both s, C(2′) and C(6′)); 130.1 (s, C(3′), C(5′)); 134.1 (s, C(1′)); 138.1 (s, C(4′)); 138.3 (d, C(6), $^3J_{C,P}$ = 9 Hz); 155.0 (d, C(2), $^3J_{C,P}$ = 3 Hz).

Compounds **7b—g** were synthesized similarly from alkene **3**, acetone, and corresponding arylamines (see Tables 1 and 2).

Diethyl [2-amino-3-cyano-1-(4-methoxyphenyl)-4-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridin-4-yl]phosphonate (8b). A solution of alkene **3** (0.31 g, 1.1 mmol) in CCl_4 (1.0 mL) was added to a solution of *p*-anisidine (0.12 g, 0.98 mmol) and cyclopentanone (0.10 g, 1.2 mmol) in CCl_4 (5.0 mL) at 20 °C with stirring. The reaction mixture was stirred for 24 h at 20 °C, a precipitate formed was filtered off and washed with pentane to obtain the product (0.29 g, 62%) (see Tables 1 and 2).

Compounds **8a,c—g** were synthesized similarly from alkene **3**, cyclopentanone, and corresponding arylamines (see Tables 1 and 2). In the case of compounds **8a,c,f,g**, the products were isolated by preparative TLC on silica gel using an ethyl acetate—light petroleum (3 : 1) solvent mixture as an eluent.

Diethyl 2-amino-1-(4-chlorophenyl)-3-cyano-4-trifluoromethyl-1,4,5,6,7,8-hexahydroquinolin-4-ylphosphonate (9a). A solution of alkene **3** (0.31 g, 1.1 mmol) in CCl_4 (1.0 mL) was added to a solution of 4-chloroaniline (0.13 g, 1.02 mmol) and cyclohexanone (0.12 g, 1.2 mmol) in CCl_4 (5.0 mL) at 20 °C with stirring. The reaction mixture was stirred for 48 h at 20 °C, the solvent was evaporated *in vacuo*. The product (0.23 g, 47%) was isolated by preparative TLC on silica gel using an ethyl acetate—light petroleum (3 : 1) solvent mixture as an eluent (see Tables 1 and 2).

Compounds **9b—g** were synthesized similarly from alkene **3**, cyclohexanone, and corresponding arylamines (see Tables 1 and 2).

Diethyl 3-cyano-4-trifluoromethyl-2-(4-trifluoromethylphenylamino)-1,4,5,6,7,8-hexahydroquinolin-4-yl]phosphonate (11) and diethyl {2-amino-3-cyano-4-trifluoromethyl-1-[4-(trifluoromethyl)phenyl]-1,4,5,6,7,8-hexahydroquinolin-4-yl} phosphonate (9f). A solution of alkene **3** (0.30 g, 1.1 mmol) in CCl_4 (0.5 mL) was added to a solution of 4-(trifluoromethyl)aniline (0.16 g, 1.00 mmol) and cyclohexanone (0.12 g, 1.22 mmol) in CCl_4 (3.5 mL) at 20 °C with stirring. The reaction mixture was stirred for 16 h at 20 °C, a precipitate formed was filtered off and washed with pentane to obtain compound **11** (0.06 g, 11.5%). Found (%): C, 50.33; H, 4.68; F, 21.56; N, 8.10; P, 5.99. $C_{22}H_{24}F_6N_3O_3P$. Calculated (%): C, 50.48; H, 4.62; F, 21.78; N, 8.03; P, 5.92. ^{19}F NMR (DMSO-d_6), δ: 17.30 (d, 3 F, CF_3, $^3J_{F,P}$ = 4.0 Hz); 18.51 (s, 3 F, $\underline{C}F_3$—C_6H_4). ^{31}P NMR (DMSO-d_6), δ: 17.80 (q, 1 P, $P(O)(OEt)_2$, $^3J_{F,P}$ = 4.0 Hz). ^{1}H NMR (DMSO-d_6), δ: 1.29 (m, 6 H, $OCH_2\underline{Me}$); 1.50 and 1.65 (both m, 2 H each, $(CH_2)_4$); 1.96 and 2.57 (both m, 1 H each, $(CH_2)_4$); 2.09 (br.s, 2 H, $(CH_2)_4$); 4.12 (m, 4 H, $OC\underline{H}_2Me$); 7.06 and 7.57 (both d, 2 H each, Ar, *J* = 8.4 Hz); 8.90 and 9.08 (both s, 1 H each, NH). ^{13}C NMR (DMSO-d_6), δ: 21.4 and 21.6 (both d, $OCH_2\underline{Me}$, $^3J_{C,P}$ = 5 Hz); 26.2, 26.8, 30.3, and 31.7 (all s, C(5), C(6), C(7), C(8)); 68.0, and 68.8 (both d, $O\underline{C}H_2Me$, $^2J_{C,P}$ = 7 Hz); 104.6 (d, C(4a), $^2J_{C,P}$ = 6 Hz); 121.5 (s, C(2′), C(6′)); 124.0 (s, CN); 125.3 (q, C(4′), $^2J_{C,F}$ = 32 Hz); 129.3 (dq, C(4)$\underline{C}F_3$, $^1J_{C,F}$ = 287 Hz and $^2J_{C,P}$ = 12 Hz); 129.9 (q, C(4′)$\underline{C}F_3$, $^1J_{C,F}$ = 271 Hz); 131.5 (q, C(3′), C(5′), $^3J_{C,F}$ = 3 Hz); 139.2 (d, C(8a), $^3J_{C,P}$ = 7 Hz); 151.1 (s, C(1′)); 155.1 (s, C(2)).

The solvent from the filtrate was evaporated *in vacuo*. Compound **9f** (0.35 g, 54%) was isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (6 : 1) (see Tables 1 and 2). ^{13}C NMR (DMSO-d_6), δ: 21.4 and 21.6 (both d, $OCH_2\underline{Me}$, $^3J_{C,P}$ = 5 Hz); 27.0, 27.1, 30.8, and 33.4 (all s, C(5), C(6), C(7), C(8)); 53.5 (m, C(3)); 56.6 (dq, C(4), $^2J_{C,F}$ = 25 Hz and $^1J_{C,P}$ = 146 Hz); 68.1 and 68.5 (both d, $O\underline{C}H_2Me$, $^2J_{C,P}$ = 8 Hz); 108.3 (d, C(4a), $^2J_{C,P}$ = 7 Hz); 125.6 (s, CN); 129.1 (q, C(4′)$\underline{C}F_3$, $^1J_{C,F}$ = 272 Hz); 129.7 (dq, C(4)$\underline{C}F_3$, $^1J_{C,F}$ = 287 Hz and $^2J_{C,P}$ = = 12 Hz); 132.0 (q, C(3′), C(5′), $^3J_{C,F}$ = 4 Hz); 134.7 (q, C(4′), $^2J_{C,F}$ = 32 Hz); 136.6 (s, C(2′), C(6′)); 139.9 (d, C(8a), $^3J_{C,P}$ = = 8 Hz); 146.3 (s, C(1′)); 160.6 (s, C(2)).

Methyl 2-amino-4-diethoxyphosphoryl-1-(2,6-dimethylphenyl)-6-methyl-4-(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (12a). A solution of alkene **4** (0.34 g, 1.09 mmol) in acetone (1.0 mL) was added to a solution of 2,6-dimethylaniline (0.12 g, 0.99 mmol) in acetone (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 72 h at 20 °C. The product (0.27 g, 57%) was isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (3 : 1)), m.p. 89—90 °C. Found (%): C, 52.97; H, 5.94; F, 11.86; N, 5.89; P, 6.46. $C_{21}H_{28}F_3N_2O_5P$. Calculated (%): C, 52.94; H, 5.92; F, 11.96; N, 5.88; P, 6.50. ^{19}F NMR ($CDCl_3$), δ: 7.92 (d, 3 F, CF_3, $^3J_{F,P}$ = 2.4 Hz). ^{31}P NMR ($CDCl_3$), δ: 20.57 (br.s, 1 P, $P(O)(OEt)_2$). ^{1}H NMR ($CDCl_3$), δ: 1.33 (m, 6 H, $OCH_2\underline{Me}$); 1.46 (br.s, 3 H, C(6)Me); 2.18 (s, 6 H, Me); 3.70 (s, 3 H, CO_2Me); 4.19 (m, 4 H, $OC\underline{H}_2Me$); 5.13 (d, 1 H, H(5), $^3J_{H,P}$ = 7.8 Hz); 6.76 (br.s, 2 H, NH_2); 7.17 (m, 2 H, Ar); 7.26 (m, 1 H, Ar).

Compounds **12b,c** were synthesized similarly from alkene **4**, acetone, and corresponding arylamines.

Methyl 2-amino-4-diethoxyphosphoryl-1-(4-methoxyphenyl)-6-methyl-4-trifluoromethyl-1,4-dihydropyridine-3-carboxylate (12b). The yield was 48%, m.p. 111—113 °C. Found (%): C, 50.30; H, 5.49; F, 11.70; N, 5.86. $C_{20}H_{26}F_3N_2O_6P$. Calculated (%): C, 50.21; H, 5.48; F, 11.91; N, 5.86. ^{19}F NMR (DMSO-d_6), δ: 10.20 (br.s, 3 F, CF_3). ^{31}P NMR (DMSO-d_6), δ: 22.35 (q, 1 P, $P(O)(OEt)_2$, $^3J_{F,P}$ = 1.6 Hz). ^{1}H NMR (DMSO-d_6), δ: 1.24 (m, 6 H, $OCH_2\underline{Me}$); 1.49 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 1.9 Hz); 3.51 (s, 3 H, CO_2Me); 3.81 (s, 3 H, OMe); 4.05 (m, 4 H, $OC\underline{H}_2Me$); 4.87(d, 1 H, H(5), $^3J_{H,P}$ = 8.1 Hz); 7.07(m, 4 H, Ar); 7.15 (br.s, 2 H, NH_2).

Methyl 2-amino-4-diethoxyphosphoryl-6-methyl-4-trifluoromethyl-1-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3-carboxylate (12c). The yield was 41%. Found (%): C, 46.40; H, 4.58; F, 21.84; N, 5.44. $C_{20}H_{23}F_6N_2O_5P$. Calculated (%): C, 46.52; H, 4.49; F, 22.07; N, 5.42. ^{19}F NMR (DMSO-d_6), δ: 10.37 (br.s, 3 F, CF_3); 17.16 (s, 3 F, CF_3). ^{31}P NMR (DMSO-d_6), δ: 19.92 (q, 1 P, $P(O)(OEt)_2$, $^3J_{F,P}$ = 2.2 Hz). ^{1}H NMR (DMSO-d_6), δ: 1.26 (t, 6 H, $OCH_2\underline{Me}$, *J* = 7.2 Hz); 1.50 (d, 3 H, C(6)Me, $^5J_{H,P}$ = 1.6 Hz); 3.54 (s, 3 H, CO_2Me); 4.09 (m, 4 H, $OC\underline{H}_2Me$); 4.96 (d, 1 H, H(5), $^3J_{H,P}$ = 8.1 Hz); 7.36 (br.s, 2 H, NH_2); 7.50 and 7.90 (both d, 2 H each, Ar, *J* = 8.1 Hz).

Methyl 2-amino-4-diethoxyphosphoryl-1-(4-methoxyphenyl)-4-trifluoromethyl-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (13a) and **1-(4-methoxyphenyl)-2-oxo-4-trifluoromethyl-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (15).** A solution of alkene **4** (0.34 g, 1.09 mmol) in CCl_4 (1.0 mL) was added to a solution of *p*-anisidine (0.06 g, 0.49 mmol) and cyclopentanone (0.06 g, 0.7 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 72 h at 20 °C. The products were isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (3 : 1)). Compound **13a** (0.05 g, 20%) was an amorphous substance. Found (%): C, 51.69; H, 5.65; N, 5.53. $C_{22}H_{28}F_3N_2O_6P$. Calculated (%): C, 52.38; H, 5.59; N, 5.55. ^{19}F NMR ($CDCl_3$), δ: 14.99 (br.s, 3 F, CF_3). ^{31}P NMR (DMSO-d_6), δ: 19.80 (br.s, 1 P, P(O)(OEt)$_2$). ^{1}H NMR (DMSO-d_6), δ: 1.24 (m, 6 H, $OCH_2\underline{Me}$); 1.65 (m, 2 H, $(CH_2)_3$); 1.87, 2.03, 2.42, and 2.87 (all m, 1 H each, $(CH_2)_3$); 3.53 (s, 3 H, CO_2Me); 3.81 (s, 3 H, OMe); 4.04 (m, 4 H, $OC\underline{H}_2Me$); 7.04—7.16 (m, 6 H, Ar and NH_2).

Compound **15** (0.06 g, 37%), m.p. 151 °C. Found (%): C, 61.00; H, 3.93; F, 16.98; N, 8.38. $C_{17}H_{13}F_3N_2O_2$. Calculated (%): C, 61.08; H, 3.92; F, 17.05; N, 8.38. ^{19}F NMR (DMSO-d_6), δ: 15.32 (s, 3 F, CF_3). ^{1}H NMR (DMSO-d_6), δ: 2.11, 2.66, and 3.03 (all m, 2 H each, $(CH_2)_3$); 3.87 (s, 3 H, OMe); 7.03 and 7.13 (both d, 2 H each, Ar, J = 8.7 Hz).

Methyl 2-amino-1-(2,6-dimethylphenyl)-4-diethoxyphosphoryl-4-trifluoromethyl-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (13b) was obtained similarly to **13a** from 2,6-dimethylaniline, cyclopentanone, and alkene **4**. The yield was 51%, m.p. 83—85 °C. Found (%): C, 54.90; H, 6.03; F, 11.55; N, 5.56. $C_{23}H_{30}F_3N_2O_5P$. Calculated (%): C, 54.98; H, 6.02; F, 11.34; N, 5.58. ^{19}F NMR (DMSO-d_6,), δ: 16.34 (br.s, 3 F, CF_3). ^{31}P NMR (DMSO-d_6), δ: 20.26 (q, 1 P, P(O)(OEt)$_2$, $^3J_{F,P}$ = = 2.8 Hz). ^{1}H NMR (DMSO-d_6), δ: 1.22 (m, 6 H, $OCH_2\underline{Me}$); 1.75 (m, 4 H, $(CH_2)_3$); 2.07 and 2.11 (both s, 3 H each, Me); 2.42 and 2.91 (both m, 1 H each, $(CH_2)_3$); 3.52 (s, 3 H, CO_2Me); 4.09 (m, 4 H, $OC\underline{H}_2Me$); 7.18—7.31 (m, 5 H, Ar and NH_2).

Diethyl 1-cyano-4-(4-methoxyphenylimino)-2,2-bis(trifluoromethyl)pentylphosphonate (16a). A solution of alkene **5** (0.20 g, 0.62 mmol) in CCl_4 (1.0 mL) was added to a suspension of *p*-anisidine (0.07 g, 0.57 mmol), acetone (0.1 g, 1.7 mmol), and anhydrous sodium sulfate in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was stirred for 2 h at 20 °C. The drying agent was filtered off and washed with CCl_4 (10 mL), the solvent was evaporated *in vacuo*. Compound **16a** (0.27 g, 96%) was isolated by preparative TLC on silica gel (eluent: chloroform—acetone (15 : 1)) as light yellow oily substance. Found (%): C, 46.90; H, 4.77; F, 23.16; N, 5.66; P, 6.30. $C_{19}H_{23}F_6N_2O_4P$. Calculated (%): C, 46.73; H, 4.75; F, 23.34; N, 5.74; P, 6.34. ^{19}F NMR ($CDCl_3$), δ: 9.04 (q, 3 F, CF_3, $^4J_{F,F}$ = 9.8 Hz); 13.58 (br.q, 3 F, CF_3, $^4J_{F,F}$ = 9.8 Hz). ^{31}P NMR ($CDCl_3$), δ: 11.78 (br.s, 1 P, P(O)(OEt)$_2$). ^{1}H NMR ($CDCl_3$), δ: 1.33 and 1.41 (both t, 3 H each, $OCH_2\underline{Me}$, J = 7.1 Hz); 1.90 (s, 3 H, Me); 3.40 (AB-system, 2 H, CH_2, ^2J_H = −16.5 Hz); 3.81 (s, 3 H, OMe); 4.18 (br.m, 2 H, $OC\underline{H}_2Me$); 4.30 (m, 2 H, $OC\underline{H}_2Me$); 6.25 (d, 1 H, CH, $^2J_{H,P}$ = 28.8 Hz); 6.62 and 6.87 (both d, 2 H each, Ar, J = 8.8 Hz).

Diethyl 4-(4-chlorophenylimino)-1-cyano-2,2-bis(trifluoromethyl)pentylphosphonate (16b) was obtained similarly to **16a** from alkene **5**, acetone, and 4-chloroaniline as light brown oily substance. The yield was 93.5%. Found (%): C, 43.70; H, 4.12; Cl, 7.26; F, 22.81; N, 5.71. $C_{18}H_{20}ClF_6N_2O_3P$. Calculated (%): C, 43.87; H, 4.09; Cl, 7.19; F, 23.13; N, 5.68. ^{19}F NMR ($CDCl_3$), δ: 9.08 (q, 3 F, CF_3, $^4J_{F,F}$ = 10.6 Hz); 13.56 (dq, 3 F, CF_3, $^4J_{F,F}$ = = 10.6 Hz, $^4J_{F,P}$ = 2.4 Hz). ^{1}H NMR ($CDCl_3$), δ: 1.31 and 1.41 (both t, 3 H each, $OCH_2\underline{Me}$, J = 7.1 Hz); 1.88 (m, 3 H, Me); 3.41 (AB-system, 2 H, CH_2, ^2J_H = −16.9 Hz); 4.19 (br.m, 2 H, $OC\underline{H}_2Me$); 4.31 (m, 2 H, $OC\underline{H}_2Me$); 6.07 (d, 1 H, CH, $^2J_{H,P}$ = 28.7 Hz); 6.61 and 7.29 (both dd, 2 H each, Ar, J = 8.4 Hz and 1.6 Hz).

Diethyl 1-cyano-4-oxo-2,2-bis(trifluoromethyl)pentylphosphonate (17). A solution of alkene **5** (0.25 g, 0.77 mmol) in CCl_4 (1.0 mL) was added to a solution of 4-chloroaniline (0.085 g, 0.67 mmol) and acetone (0.1 g, 1.7 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 120 h at 20 °C. The product (0.26 g, 90%) was isolated by preparative TLC on silica gel (eluent: chloroform—acetone (15 : 1)), m.p. 92—93 °C. Found (%): C, 37.65; H, 4.21; F, 29.68; N, 3.66; P, 8.02. $C_{12}H_{16}F_6NO_4P$. Calculated (%): C, 37.61; H, 4.21; F, 29.74; N, 3.65; P, 8.08. ^{19}F NMR ($CDCl_3$), δ: 9.32 (q, 3 F, CF_3, $^4J_{F,F}$ = 10.6 Hz); 11.85 (dq, 3 F, CF_3, $^4J_{F,F}$ = 10.6 Hz, $^4J_{F,P}$ = 2.4 Hz). ^{31}P NMR ($CDCl_3$), δ: 11.26 (q, 1 P, P(O)(OEt)$_2$, $^4J_{F,P}$ = 2.4 Hz). ^{1}H NMR ($CDCl_3$), δ: 1.42 (m, 6 H, $OCH_2\underline{Me}$); 2.26 (s, 3 H, Me); 3.50 (AB-system, 2 H, CH_2, ^2J_H = −18.1 Hz); 3.81 (s, 3 H, OMe); 4.28 (m, 4 H, $OC\underline{H}_2Me$); 5.19 (d, 1 H, CH, $^2J_{H,P}$ = 28.0 Hz).

Compound **17** was isolated similarly from the reaction mixtures obtained by the reaction of alkene **5**, acetone, and *p*-anisidine and alkene **5**, acetone, and 4-phenoxyaniline. The yields were 93% and 89%, respectively.

Diethyl 2-amino-1-(4-methoxyphenyl)-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyridin-3-ylphosphonate (18a). A solution of compound **16a** (0.09 g) in CCl_4 (5 mL) was refluxed for 18 h. The solvent was evaporated *in vacuo*. Compound **18a** (0.045 g, 50%) was isolated by preparative TLC on silica gel (eluent: chloroform—acetone (60 : 5)) (see Tables 3 and 4).

Compound **18b** was synthesized similarly from **16b**. The yield was 48% (see Tables 3 and 4).

Diethyl 2-amino-6-methyl-1-(4-phenoxyphenyl)-4,4-bis(trifluoromethyl)-1,4-dihydropyridin-3-ylphosphonate (18c). A solution of alkene **5** (0.25 g, 0.76 mmol) in CCl_4 (1.0 mL) was added to a suspension of 4-phenoxyaniline (0.13 g, 0.70 mmol), acetone (0.12 g, 2.07 mmol), and anhydrous sodium sulfate (1.5 g) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was stirred for 2 h at 20 °C. The drying agent was filtered off and washed with CCl_4 (10 mL), the solvent was evaporated *in vacuo*. The residue (**16c**) was dissolved in CCl_4 (5 mL) and refluxed for 18 h. The solvent was evaporated *in vacuo*. Compound **18c** (0.16 g, 41%) was isolated by preparative TLC on silica gel (eluent: chloroform—acetone (60 : 5)) (see Tables 3 and 4).

Diethyl 2-amino-1-(4-methoxyphenyl)-4,4-bis(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridin-3-ylphosphonate (20a). A solution of alkene **5** (0.21 g, 0.65 mmol) in CCl_4 (1.0 mL) was added to a solution of *p*-anisidine (0.07 g, 0.57 mmol) and cyclopentanone (0.09 g, 1.07 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 48 h at 20 °C. The product (0.22 g, 76%) was isolated by preparative TLC on silica gel (eluent: chloroform—acetone (10 : 1)) (see Tables 3 and 4).

Compounds **20b—d** were synthesized similarly from alkene **5**, cyclopentanone, and corresponding arylamines (the reaction time was 120 h) (see Tables 3 and 4).

Diethyl 2-amino-1-(4-methoxyphenyl)-4,4-bis(trifluoromethyl)-1,4,4a,5,6,7-hexahydroquinolin-3-ylphosphonate (21a). A solution of alkene **5** (0.21 g, 0.65 mmol) in CCl_4 (1.0 mL) was

added to a solution of *p*-anisidine (0.07 g, 0.57 mmol) and cyclohexanone (0.13 g, 1.3 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 48 h at 20 °C. The product (0.17 g, 57%) was isolated by preparative TLC on silica gel (eluent: CCl_4—acetone (5 : 1)) (see Tables 3 and 4).

Compound **21b** (26%) was obtained similarly from alkene **5**, cyclohexanone, and 3-(trifluoromethyl)aniline (the reaction time was 120 h) (see Tables 3 and 4).

Ethyl 2-amino-3-diethoxyphosphoryl-1-(2,6-dimethylphenyl)-6-methyl-4-trifluoromethyl-1,4-dihydropyridine-4-carboxylate (22a). A solution of alkene **6** (0.16 g, 0.48 mmol) in CCl_4 (1.0 mL) was added to a solution of 2,6-dimethylaniline (0.05 g, 0.41 mmol) and acetone (0.1 g, 1.7 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 48 h at 20 °C. The product (0.07 g, 35%) was isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (4 : 1)) (see Tables 5 and 6).

Compounds **22b,c** were obtained similarly from alkene **6**, acetone, and corresponding arylamines (the reaction time was 72 h) (see Tables 5 and 6).

Ethyl 2-amino-3-diethoxyphosphoryl-6-methyl-2-phenylamino-4-trifluoromethyl-1,4-dihydropyridine-4-carboxylate (23a). A solution of alkene **6** (0.41 g, 1.25 mmol) in CCl_4 (1.0 mL) was added to a solution of aniline (0.1 g, 1.08 mmol) and acetone (0.15 g, 2.59 mmol) in CCl_4 (1.5 mL) at 20 °C with stirring. The reaction mixture was kept for 72 h at 20 °C. The product (0.07 g, 14%) was isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (2 : 3)) (see Tables 5 and 6).

Compounds **23b,c** were obtained similarly from alkene **6**, acetone, and corresponding arylamines (the reaction time was 72 h) (see Tables 5 and 6).

Ethyl 2-amino-3-diethoxyphosphoryl-1-(4-phenoxyphenyl)-4-trifluoromethyl-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-4-carboxylate (24a) and **ethyl 3-diethoxyphosphoryl-2-(4-phenoxyphenylamino)-4-trifluoromethyl-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-4-carboxylate (25a).** A solution of alkene **6** (0.20 g, 0.61 mmol) in CCl_4 (1.0 mL) was added to a solution of 4-phenoxyaniline (0.1 g, 0.54 mmol) and cyclopentanone (0.09 g, 1.07 mmol) in CCl_4 (1.5 mL) at 20 °C with stirring. The reaction mixture was kept for 72 h at 20 °C. Compounds **24a** (0.11 g) and **25a** (0.10 g) were isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (2 : 1)) (see Tables 5 and 6).

Compounds **24b—e** and **25b—d** were obtained similarly from alkene **6**, cyclopentanone, and corresponding arylamines (see Tables 5 and 6).

Ethyl 2-amino-3-diethoxyphosphoryl-1-phenyl-4-trifluoromethyl-1,4,4a,5,6,7-hexahydroquinoline-4-carboxylate (26a). A solution of alkene **6** (0.36 g, 1.11 mmol) in CCl_4 (1.0 mL) was added to a solution of aniline (0.09 g, 0.97 mmol) and cyclohexanone (0.19 g, 1.94 mmol) in CCl_4 (1.0 mL) at 20 °C with stirring. The reaction mixture was kept for 72 h at 20 °C. Compound **26a** (0.20 g, 41%) was isolated by preparative TLC on silica gel (eluent: ethyl acetate—light petroleum (3 : 1)) (see Tables 5 and 6).

Compounds **26b—f** were obtained similarly from alkene **6**, cyclohexanone, and corresponding arylamines (see Tables 5 and 6).

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Received October 14, 2009;
in revised form October 30, 2009