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PREPARATION OF PYRIMIDINE DERIVATIVES THROUGH THREE-COMPONENT REACTIONS OF DIALKYL (2-OXO-3,3,3-TRIFLUOROPROPYL)PHOSPHONATES

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Methods are proposed for the preparation of fluorophosphorus-containing pyrimidines through three-component reactions of dialkyl (3,3,3-trifluoro-2-oxopropyl)phosphonates. Cyclocondensation of these phosphonates with urea and aryl aldehydes gave 6-aryl-4-hydroxy-2-oxo-4-trifluoromethylhexahydropyrimidin-5-ylphosphonates and reaction with urea and trialkyl orthoformates led to 4-alkoxy-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidin-5-ylphosphonates.

Keywords: hexahydropyrimidinone, dihydropyrimidinone, orthoformate, oxophosphonate, tetrahydropyrimidinone, trifluoromethyl group, Biginelli reaction, multicomponent reaction.

Progress in the chemistry of multicomponent reactions and an increasing interest when compared with traditional, multistage syntheses is evidence for the high synthetic potential of this route which is both a simple and rapid method for preparing different classes of compounds [1].

Multicomponent reactions leading to formation of nitrogen-containing heterocyclic systems such as pyridine and pyrimidine [2, 3] have recently been studied. Derived compounds show a broad spectrum of biological activity [4, 5] hence preparation of novel representatives of this class of compounds is an urgent challenge in the chemistry of heterocycles [6]. Amongst a significant number of synthesized, functionally substituted pyrimidines finding use in pharmaceutical chemistry [7, 8], pyrimidines containing phosphorus substituents remain little studied due to the limited number of methods of preparing them.

One of the most widely used methods currently in use for preparing pyrimidines is the three- component Biginelli reaction. The use of traditional methodology in this reaction for the cyclocondensation of dialkyl 2-oxopropylphosphonates, aryl aldehydes, and urea is inefficient, the 4-aryl-5-(*O*,*O*-dialkylphosphoryl)-3,4-dihydropyrimidin-2-ones being obtained only under catalysis with the use of $Yb(OTf)_3$ [9]. A further reported method for preparing hexahydropyrimidine-5-phosphonates is the reaction of *N*-(1-tosylprop-1-yl)thiourea with 2-oxopropylphosphonate enolates [10].

We have found that diethyl (3,3,3-trifluoropropyl-2-oxo)phosphonate (**1a**) reacts with aryl aldehydes and urea under Biginelli conditions to give the diethyl (6-aryl-4-hydroxy-2-oxo-4-trifluoromethylhexahydropyrimidin-5-yl)phosphonates **2a-c**.

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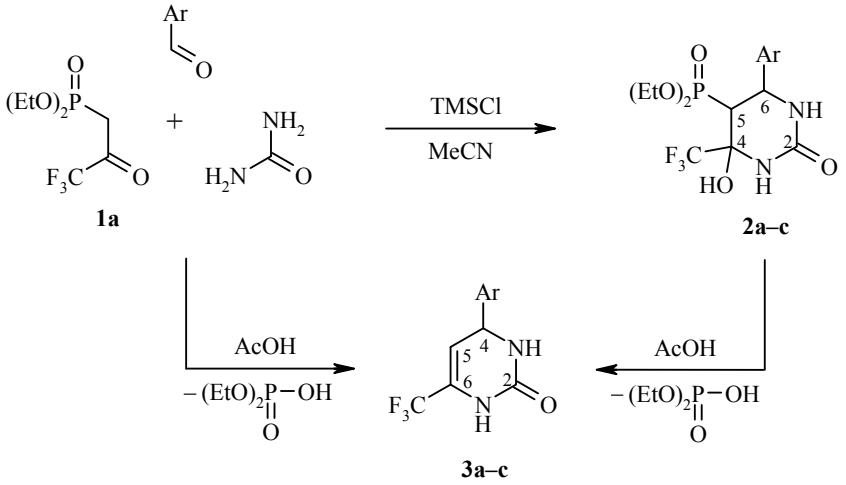
In our study of this three-component cyclization, we have employed conditions used for similar condensations of β-dicarbonyl compounds, i.e. stirring in acetonitrile at room temperature with a catalytic amount of trimethylchlorosilane [11, 12]. As in the examples of the Biginelli reaction of β-dicarbonyl compounds with fluoroalkyl groups [12-16], the cyclization products of the oxophosphonate **1a** are the 4-hydroxytetrahydropyrimidin-2-ones (**2a-c**) but dehydratation and formation of classical 3,4-dihydropyrimidin-2-one Biginelli reaction products are not observed.



2, 3 a Ar = Ph, **b** Ar = *p*-$MeOC_6H_4$, **c** Ar = *p*-BrC_6H_4

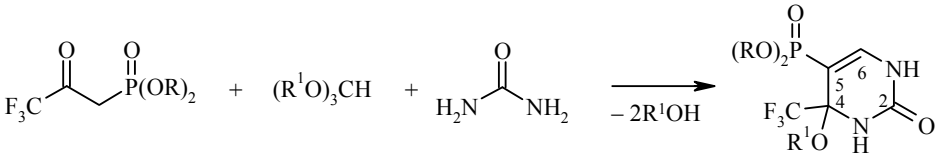
The tetrahydropyrimidin-2-ones **2a-c** contain three asymmetric carbon atoms which supposes the possible formation of four diastereomers. However, according to the ^{1}H NMR spectroscopic data for the crude products, only a single diastereomer is formed in all of the examples we studied. The ^{13}C NMR spectra of compounds **2a-c** showed a highly characteristic signal for the C-4 atom of the pyrimidine ring at around 81 ppm which appears as a quartet of doublets and confirms the formation of the tetrahydropyrimidinone ring. It is not possible to make an unambiguous assignment of the stereochemistry of compounds **2a-c** on the basis of just the data obtained.

Compounds **2a-c** are unstable in DMSO-d_6 solutions. Measured after one week the ^{1}H NMR spectra show the presence of an aryl aldehyde signal and the ^{19}F and ^{31}P NMR spectra show signals for the oxophosphonate hydrate **1a** and diethyl phosphate $(EtO)_2P(O)OH$. Formation of the latter can be the result of dephosphonylation and this was confirmed by heating compounds **2a-c** in acetic acid. In these conditions the 4-aryl-6-trifluoromethyl-3,4-dihydropyrimidin-2-ones **3a-c** were formed in good yields as the dephosphonylation products of the 1,2,3,4-tetrahydropyrimidin-2-ones **2a-c**.

Carrying out the initial multicomponent reaction in acetic acid was also accompanied by dephosphonylation of the Biginelli reaction products formed at the initial step to give the corresponding dihydropyrimidin-2-one dephosphorylation products **3a-c**. The course of the reaction was monitored by ^{19}F and ^{31}P NMR spectroscopy of the reaction solutions. The ^{19}F NMR spectra of the initial reaction step show the presence of a signal at -82 ppm corresponding to the trifluoromethyl group signal of the products **2a-c** which disappears over time and is replaced by a signal at -70 ppm corresponding to formation of compounds **3a-c**. In the ^{31}P NMR spectra the signal for the diethyl phosphonate group at 23 ppm for compounds **2a-c** disappears and a signal for diethyl phosphate appears at 2 ppm.

We have also discovered a simple and efficient method for preparing stable phosphorus-containing pyrimidinones based on the three-component reaction of dialkyl (2-oxo-3,3,3-trifluoropropyl)phosphonates **1a,b** with urea and trialkyl orthoformates. Refluxing a mixture of oxophosphonate **1** and urea in an excess of the trialkyl orthoformate gives the dialkyl 4-(alkoxy(hydroxy)-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydro-

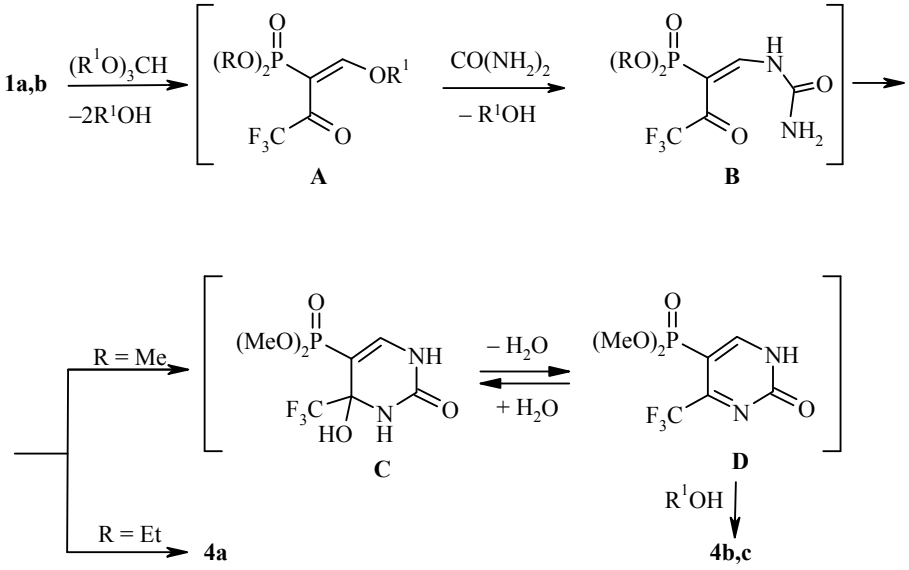
pyrimidin-5-yl)phosphonates **4a-c** which precipitate from the mixture during the reaction process.



1a,b **4a–c**

1 a R = Et; **b** R = Me; **4 a** R = Et, R^1 = H; **b** R = R^1 = Me; **c** R = Me, R^1 = Et

Evidently, the reaction occurs *via* intermediate **A**, formation of which has been reported by us in the reaction of 3-arylsulfonyl-1,1,1-trifluoropropan-2-ones with orthoformates [17]. The intermediate ester **A** condenses with urea to form the acyclic intermediate **B**. Subsequent intramolecular cyclization gives the pyrimidine heterocyclic system.



The 4-hydroxy derivative **C** formed in the condensation process can dehydrate under thermal conditions to the pyrimidin-2-one **D**. The double bond of the CF_3–C=N fragment in pyrimidine **D** is quite electrophilic and adds a molecule of the alcohol liberated in the initial stages of the reaction to form the dimethylphosphonyl-substituted 4-alkoxypyrimidines **4b,c**. The difference in structure for the products of this reaction can evidently be explained by their different solubility in the reaction medium. The diethylphosphonyl-substituted 4-hydroxypyrimidinone **4a** precipitated from the reaction mixture with heating while the dimethylphosphonyl analog **C** is soluble in the mixture and dehydrates upon subsequent refluxing to the intermediate **D** (which then adds a molecule of the alcohol to give the difficultly soluble 4-alkoxypyrimidinones **4b,c**).

It should be noted that, with use of fluorinated β-oxophosphonates in the three-component reaction, the condensation (which consists of three consecutive stages) occurs in a one pot. In analogous reactions of β-dicarbonyl compounds reported in the literature the construction of a pyrimidine ring occurs in two stages with separation of intermediates of type **A** [18] or **B** [19], cyclization of which to pyrimidin-2-ones in the subsequent step demands more rigorous conditions and the use of base.

Hence we have developed a simple synthetic route to fluoroalkyl-containing phosphonyl-substituted pyrimidinones through three-component heterocyclization reactions of dialkyl (3,3,3-trifluoro-2-oxopropyl)-phosphonates with urea and trialkyl orthoformates.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer for KBr tablets. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) and ^{13}C NMR, APT, ^{1}H–^{1}H COSY, and ^{13}C–^{1}H HETCOR spectra on a Bruker Avance 400 (400 and 100 MHz, respectively) for solutions in DMSO-d_6 with residual solvent signals at 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C used as standard. ^{19}F and ^{31}P NMR spectra were recorded on a Varian Gemini-200 instrument (188 and 81 MHz respectively) with C_6F_6 (-162.9 ppm relative to $CFCl_3$) and H_3PO_4 (0.00 ppm) as internal standards. Mass spectra were taken on an Agilent 1100 series LC/MSD SL instrument with chemical ionization at atmospheric pressure (APCI) as the ionization method. Melting points were determined on a Boetius apparatus.

The oxophosphonates **1a,b** were prepared by acylation of the lithium salts of dimethyl- or diethyl methylphosphonate using ethyl trifluoroacetate according to method [20].

Hexahydropyrimidines 2a-c (General Method). A mixture of the oxophosphonate **1a** (0.5 g, 2 mmol), the corresponding aryl aldehyde (2 mmol), urea (0.12 g, 2 mmol), and trimethylchlorosilane (0.06 ml, 0.5 mmol) in acetonitrile (4 ml) was stirred at room temperature for 5-8 h. The precipitate formed was filtered off and crystallized from acetonitrile.

Diethyl (4-Hydroxy-2-oxo-4-trifluoromethyl-6-phenylhexahydropyrimidin-5-yl)phosphonate (2a). Yield 60%; mp 150-151ºC (MeCN). IR spectrum, ν, cm^{-1}: 1690 (C=O), 2950, 3000, 3110, 3220. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, t, ^{3}J = 7.1, CH_3); 1.12 (3H, t, ^3J = 7.1, CH_3); 2.81 (1H, dd, $^2J_{H–P}$ = 20.5, $^3J_{5,6}$ = 6.8, H-5); 3.60-4.10 (4H, m, 2CH_2); 4.79 (1H, dm, $^3J_{6,5}$ = 6.8, H-6); 7.09 (1H, s, NH); 7.25-7.36 (6H, m, H Ph + NH); 7.65 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz); 15.7 (d, $^3J_{C–P}$ = 6.3, CH_3); 15.9 (d, $^3J_{C-P}$ = 6.0, CH_3); 45.3 (d, $J_{C–P}$ = 145.0, C-5); 52.1 (s, C-6); 60.8 (d, $^2J_{C–P}$ = 6.7, CH_2); 61.1 (d, $^2J_{C–P}$ = 6.5, CH_2); 81.1 (qd, $^2J_{C–F}$ = 31.5, $^2J_{C–P}$ = 3.1, C-4); 123.3 (qd, $J_{C–F}$ = 290.0, $^3J_{C–P}$ = 5.0, CF_3); 126.9, 127.3, 127.9 (s, C Ph); 140.7 (d, $^3J_{C–P}$ = 7.1, *ipso*-C Ph); 154.5 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -82.18 (s, CF_3). ^{31}P NMR spectrum, δ, ppm: 23.01 (m). Mass spectrum, *m/z* (I_{rel}, %): 397 $[M+H]^+$ (5), 379 $[M+H-H_2O]^+$ (40), 337 $(M+H\text{-urea})^+$ (100), 106 (20). Found, %: C 45.73; H 5.00; N 7.01. $C_{15}H_{20}F_3N_2O_5P$. Calculated, %: C 45.46; H 5.09; N 7.07.

Diethyl [4-Hydroxy-6-(4-methoxyphenyl)-2-oxo-4-trifluoromethylhexahydropyrimidin-5-yl]-phosphonate (2b). Yield 57%; mp 139-141ºC (MeCN). IR spectrum, ν, cm^{-1}: 1680 (C=O), 2940, 3000, 3110, 3220. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, t, ^3J = 6.6, CH_3); 1.11 (3H, t, ^3J = 6.6, CH_3); 2.75 (1H, dd, $^2J_{H–P}$ = 20.5, $^3J_{5,6}$ = 7.1, H-5); 3.60-4.10 (4H, m, 2CH_2); 3.73 (3H, s, OCH_3); 4.73 (1H, m, H-6); 6.89 (2H, m, H Ar); 7.10 (1H, s, NH); 7.15-7.20 (3H, m, H Ar + NH); 7.65 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 15.7 (d, $^3J_{C–P}$ = 5.9, CH_3); 16.0 (d, $^3J_{C–P}$ = 6.2, CH_3); 46.1 (d, $J_{C–P}$ = 145.3, C-5); 51.8 (s, C-6); 55.1 (s, OCH_3); 60.7 (d, $^2J_{C–P}$ = 6.5, CH_2); 62.3 (d, $^2J_{C–P}$ = 6.9, CH_2); 81.2 (qd, $^2J_{C–F}$ = 32.2, $^2J_{C–P}$ = 3.1, C-4); 113.4 (s, *m*-C Ar); 123.5 (qd, $J_{C–F}$ = 289.3, $^3J_{C–P}$ = 3.9, CF_3); 128.6 (s, *o*-C Ar); 132.3 (d, $^3J_{C–P}$ = 7.3, *ipso*-C Ar); 154.8 (s, C=O); 158.8 (s, *p*-C Ar). ^{19}F NMR spectrum, δ, ppm: -82.03 (s, CF_3). ^{31}P NMR spectrum, δ, ppm: 22.59 (m). Mass spectrum, *m/z* (I_{rel}, %): 427 $[M+H]^+$ (5), 409 $[M+H-H_2O]^+$ (50), 367 $[M+H\text{-urea}]^+$ (20), 162 (100). Found, %: C 45.23; H 5.00; N 6.39. $C_{16}H_{22}F_3N_2O_6P$. Calculated, %: C 45.08; H 5.20; N 6.57.

Diethyl [6-(4-Bromophenyl)-4-hydroxy-2-oxo-4-trifluoromethyl-6-hexahydropyrimidin-5-yl]phosphonate (2c). Yield 55%; mp 164-165ºC (MeCN). IR spectrum, ν, cm^{-1}: 1710 (C=O), 2950, 3000, 3120, 3230. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.06 (3H, t, ^3J = 7.0, CH_3); 1.13 (3H, t, ^3J = 7.0, CH_3); 2.82 (1H, dd, $^2J_{H–P}$ = 20.7, $^3J_{5,6}$ = 7.0, H-5); 3.70-4.10 (4H, m, 2CH_2); 4.81 (1H, ddd, $^3J_{H–P}$ = 9.2, $^3J_{6,5}$ = 7.0, $^3J_{6,1}$ = 2.0, H-6); 6.88 (1H, t, $^3J_{1,6}$ = 2.0, $^4J_{H–P}$ = 1.8, 1-NH); 7.20 (1H, s, 3-NH); 7.26 (2H, AA'XX', $^3J_{AX}$ = 8.5, H Ar); 7.52 (2H, AA'XX', $^3J_{AX}$ = 8.5, H Ar); 7.55 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 15.6 (d, $^3J_{C–P}$ = 6.0, CH_3); 15.8 (d, $^3J_{C–P}$ = 6.0, CH_3); 45.1 (d, $J_{C–P}$ = 145.0, C-5); 51.7 (s, C-6); 61.1 (d, $^2J_{C–P}$ = 6.8, CH_2); 62.2 (d, $^2J_{C–P}$ = 6.8, CH_2); 81.1 (qd, $^2J_{C–F}$ = 32.2, $^2J_{C–P}$ = 3.5, C-4); 120.5 (s, *p*-C Ar); 124.2 (qd, $J_{C–F}$ = 289.0, $^3J_{C–P}$ = 4.0, CF_3); 129.4 (s, *m*-C Ar); 130.8 (s, *o*-C Ar); 139.9 (d, $^3J_{C–P}$ = 7.2, ipso-C Ar); 154.3 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -81.89 (s, CF_3). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 22.01 (m). Mass spectrum, *m/z* (I_{rel}, %): 417

and 415 $[M+H\text{-urea}]^+$ (100 and 95), 185 and 187 (20 and 20). Found, %: C 38.06; H 3.93; N 6.00. $C_{15}H_{19}BrF_3N_2O_5P$. Calculated, %: C 37.91; H 4.03; N 5.90.

Dihydropyrimidines 3a-c (General Method). A solution of the oxophosphonate **1a** (0.5 g, 2 mmol), the corresponding aryl aldehyde (2 mmol), and urea (0.12 g, 2 mmol) in acetic acid (4 ml) was heated for 5-7 h on an oil bath at 80ºC. The end of the reaction was determined by ^{19}F and ^{31}P NMR spectroscopy of the reaction mixture. The mixture was poured into water (6 ml) and the precipitate formed was filtered off, washed with water (2 ml), dried, and crystallized.

4-Phenyl-6-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (3a). Yield 70%; mp 124-125ºC (EtOH) (mp 120-121ºC [21]). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.15 (1H, m, H-4); 5.53 (1H, m, H-5); 7.30-7.45 (5H, m, H Ph); 7.48 (1H, s, NH); 9.34 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz); 54.1 (s, C-4); 103.3 (q, $^3J_{C-F}$ = 5.1, C-5); 120.1 (q, J_{C-F} = 272.6, CF_3); 125.9 (q, $^2J_{C-F}$ = 34.6, C-6); 126.2, 127.8, 128.8 (s, C Ar); 143.4 (s, *ipso*-C Ar); 152.4 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -69.18 (s, CF_3). Mass spectrum, *m/z* (I_{rel}, %): 243 $[M+H]^+$ (40), 77 (100). Found, %: C 54.75; H 3.92; N 11.49. $C_{11}H_9F_3N_2O$. Calculated, %: C 54.55; H 3.75; N 11.57.

4-Methoxyphenyl-6-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (3b). Yield 69%; mp 168-170ºC (H_2O-EtOH, 1: 1). IR spectrum, ν, cm^{-1}: 1700 (C=O); 2870, 2970, 3110, 3220, 3300. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.74 (3H, s, CH_3); 5.08 (1H, m, H-4); 5.48 (1H, m, H-5); 6.94 (2H, AA'XX', $^3J_{AX}$ = 8.1, H Ar); 7.21 (2H, AA'XX', $^3J_{AX}$ = 8.1, H Ar); 7.39 (1H, s, NH); 9.28 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 53.5 (s, C-4); 55.2 (s, CH_3); 103.6 (q, $^3J_{C-F}$ = 4.8, C-5); 114.2 (s, m-C Ar); 120.1 (q, J_{C-F} = 272.0, CF_3); 126.0 (q, $^2J_{C-F}$ = 34.5, C-6); 127.4 (s, *o*-C Ar); 135.5 (s, *ipso*-C Ar); 152.4 (s, C=O); 158.9 (s, *p*-C Ar). ^{19}F NMR spectrum, δ, ppm: -69.16 (s, CF_3). Mass spectrum, *m/z* (I_{rel}, %): 273 $[M+H]^+$ (100). Found, %: C 53.05; H 4.00; N 10.40. $C_{12}H_{11}F_3N_2O_2$. Calculated, %: C 52.94; H 4.07; N 10.29.

4-Bromophenyl-6-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (3c). Yield 65%; mp 147-149ºC (H_2O-EtOH). IR spectrum, ν, cm^{-1}: 1690 (C=O), 2880, 2970, 3110, 3220, 3320. ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.15 (1H, m, H-4); 5.53 (1H, m, H-5); 7.24 (2H, AA'XX', $^3J_{AX}$ = 8.1, H Ar); 7.52 (1H, s, NH); 7.58 (2H, AA'XX', $^3J_{AX}$ = 8.1, H Ar); 9.41 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 53.5 (s, C-4); 102.9 (q, $^3J_{C-F}$ = 5.1, C-5); 120.9 (s, *p*-C Ar); 126.5 (q, $^2J_{C-F}$ = 34.9, C-6); 128.5 (s, *o*-C Ar); 131.8 (s, *m*-C Ar); 142.8 (s, *ipso*-C Ar); 152.3 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -69.28 (s, CF_3). Mass spectrum, *m/z* (I_{rel}, %): 321 and 323 $[M+H]^+$ (100 and 95). Found, %: C 41.40; H 2.56; N 8.91. $C_{11}H_8BrF_3N_2O$. Calculated, %: C 41.15; H 2.51; N 8.72.

Tetrahydropyrimidines 4a-c (General Method). A mixture of the corresponding oxophosphonate **1a,b** (4 mmol), urea (0.24 g, 4 mmol), and the corresponding trialkyl orthoformate (16 mmol) was refluxed for 2-4 h. The precipitate formed on refluxing was cooled to room temperature and filtered. After liquid chromatography the purity of the products **4a-c** was greater than 95%; for analytical purposes the samples were recrystallized from acetonitrile.

Diethyl (4-hydroxy-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidin-5-yl)phosphonate (4a) was prepared from phosphonate **1a**, urea, and trimethyl- or triethyl orthoformate. Yield 70%; mp 162-164ºC (MeCN). IR spectrum, ν, cm^{-1}: 1710 (C=O), 2940, 3000, 3110, 3220. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (6H, t, ^3J = 7.0, $2CH_3$); 3.80-4.00 (4H, m, ^3J = 7.2, $2CH_2$); 7.11 (1H, dd, $^3J_{H-P}$ = 14.3, $^3J_{6,5}$ = 5.8, H-6); 7.42 (1H, br. s, OH); 8.41 (1H, d, $^3J_{1,6}$ = 5.8, 1-NH); 9.88 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 16.0 (d, $^3J_{C-P}$ = 6.8, CH_3); 16.1 (d, $^3J_{C-P}$ = 6.8, CH_3); 61.3 (d, $^2J_{C-P}$ = 5.3, CH_2); 61.6 (d, $^2J_{C-P}$ = 5.6, CH_2); 82.3 (qd, $^2J_{C-F}$ = 33.7, $^2J_{C-P}$ = 11.0, C-4); 93.2 (d, J_{C-P} = 203.2, C-5); 123.0 (q, J_{C-F} = 288.3, CF_3); 143.0 (d, $^3J_{C-P}$ = 15.4, C-6); 149.8 (s, C=O). ^{19}F NMR spectrum, δ, ppm:-82.64 (s, CF_3). ^{31}P NMR spectrum, δ, ppm: 17.54 (m). Mass spectrum, *m/z* (I_{rel}, %): 301 $[M+H\text{-}H_2O]^+$ (25), 157 (20). Found, %: C 33.90; H 4.49; N 8.96. $C_9H_{14}F_3N_2O_5P$. Calculated, %: C 33.97; H 4.43; N 8.80.

Dimethyl (4-methoxy-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidin-5-yl)phosphonate (4b) was prepared from phosphonate **1b**, urea, and triethyl orthoformate. Yield 68%; mp 148-150ºC (MeCN). IR spectrum, ν, cm^{-1}: 1720 (C=O), 2940, 3130, 3230, 3320. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (3H, s, CH_3); 3.58 (3H, d, $^3J_{H-P}$ = 11.2, CH_3); 3.62 (3H, d, $^3J_{H-P}$ = 11.2, CH_3); 7.33 (1H, dd, $^3J_{H-P}$ = 14.2, ^2J = 5.8, H-6); 8.57 (1H, d, ^2J = 5.8, 1-NH); 10.16 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 49.1 (s, CH_3); 52.0 (d, $^2J_{C-P}$ =5.6,

CH_3); 52.3 (d, $^2J_{C–P}$ = 5.6, CH_3); 87.3 (dq, $^2J_{C–F}$ = 33.1, $^2J_{C–P}$ = 11.1, C-4); 88.3 (d, $J_{C–P}$ = 205.5, C-5); 122.1 (q, J_{C-F} = 288.0, CF_3); 145.9 (d, $^3J_{C–P}$ = 15.1, C-6); 150.0 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -81.38 (s, CF_3). ^{31}P NMR spectrum, δ, ppm: 19.86 (m). Mass spectrum, *m/z* (I_{rel}, %): 273 $[M+H-MeOH]^+$ (100), 157 (10). Found, %: C 31.70; H 3.92; N 9.40. $C_8H_{12}F_3N_2O_5P$. Calculated, %: C 31.59; H 3.98; N 9.21.

Dimethyl (4-ethoxy-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidin-5-yl)phosphonate (4c) was prepared from phosphonate **1b**, urea, and triethyl orthoformate. Yield 65%; mp 129-131ºC (MeCN). IR spectrum, ν, cm^{-1}: 1700 (C=O); 2960, 3100, 3230, 3300. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, t, ^3J = 6.9, CH_3); 3.38 (2H, q, ^3J = 6.9, CH_2); 3.58 (3H, d, $^3J_{H–P}$ = 10.6, OCH_3); 3.62 (3H, d, $^3J_{H–P}$ = 10.6, OCH_3); 7.29 (1H, dd, $^3J_{H–P}$ = 14.3, ^2J = 4.8, H-6); 8.55 (1H, d, ^2J = 4.8, 1-NH); 10.12 (1H, s, 2-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.6 (s, CH_3); 52.4 (d, $^2J_{C–P}$, OCH_3); 52.7 (d, $^2J_{C–P}$ = 6.6, OCH_3); 57.9 (s, CH_2); 87.0 (qd, $^2J_{C–F}$ = 32.9, $^2J_{C–P}$ = 11.0, C-4); 88.7 (d, $J_{C–P}$ = 206.1, C-5); 122.4 (q, $J_{C–F}$ = 287.5, CF_3); 146.1 (d, $^3J_{C–P}$ = 15.3, C-6); 150.5 (s, C=O). ^{19}F NMR spectrum, δ, ppm: -81.61 (s, CF_3). ^{31}P NMR spectrum, δ, ppm: 19.52 (m). Mass spectrum, *m/z* (I_{rel}, %): 273 $[M+H-EtOH]^+$ (5), 157 (100). Found, %: C 34.05; H 4.53; N 8.95. $C_9H_{14}F_3N_2O_5P$. Calculated, %: C 33.97; H 4.43; N 8.80.

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