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To the 85th Anniversary of birthday of late Yu.G. Gololobov

Synthesis and Some Transformations of Diethyl (5-Trifluoromethylfur-2-yl)methanephosphonate

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Abstract—By the interaction of 2-bromomethyl-5-trifluoromethyfuran with triethyl phosphite under the Arbuzov reaction conditions diethyl (5-trifluoromethylfur-2-yl)methanephosphonate was prepared. Due to deactivation of the furan ring this substance does not enter chloromethylation even at 70°C. Because of CH-acidity of the diethoxyphosphorylmethyl fragment diethyl (5-trifluoromethylfur-2-yl)methanephosphonate in the presence of sodium foil enters the Claisen reaction with ethyl formate and diethyl oxalate. Respective derivatives of furylacetaldehyde and furylpyruvic acid and their sodium salts were isolated and characterized. Reactions of the compounds obtained with methyl iodide and diethyl chlorophosphate were studied. It was shown that trifluoromethyl derivative of phosphorylated furylacetaldehyde forms stable enol ethers and esters. The furylpyruvic acid derivative is alkylated with methyl iodide at the carbon atom adjacent to phosphorus and the compound formed undergoes cleavage to 1-(5-trifluoromethylfur-2-yl)ethanephosphonate.

Keywords: trifluoromethylfurans, Arbuzov reaction, Claisen condensation, ethyl formate, diethyl oxalate, enol ethers, enol phosphates

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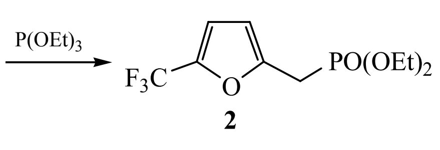
Phosphorus-containing furan derivatives are known for a comparatively long time. Some of them are used in biology. For example, the phosphorylared furylalanine is the non-hydrolysable analog of 1-phosphonohystidine used while studying the pathways of signal transfer in bacteria and eukaryotes [1]. Not long ago [2] it was found that the introduction of trifluoromethyl group in the structure of a broad class of substances leads to the appearance of immunomodulating effect in acute diseases of lung cells. This fact permits to suggest that phosphorylated derivatives of trifluoromethylfuran may be promising objects for the search of new physiologically active compounds.

In our studies we have chosen 5-trifluoromethyl-2-bromomethylfuran **1** as the starting substance. Via its phosphopylation under the conditions of the Arbusov reaction (5-trifluoromethylfur-2-yl)methanephosphonate **2** was synthesized in 78% yield (Scheme 1).

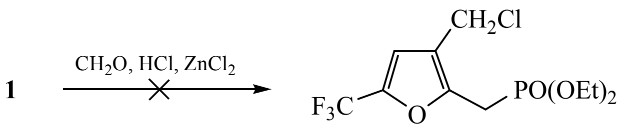
Molecule of compound **2** contains two reactive fragments, the furan ring and the methylene group adjacent to phosphorus atom, and we made an attempt to carry out the reactions characteristic of both these sites.

As is known, furans easily enter the electrophylic substitution reactions [3]. As the model reaction we have chosen chloromethylation which even in the case of the furoic acid derivatives proceeds at 30–35°C. The reaction was carried out in dichloroethane at the phosphonate **2** : paraformaldehyde : zinc chloride molar ratio 1 : 1.5 : 0.25 under the conditions of

Scheme 1.



saturation of the reaction mixture with dry hydrogen chloride. It was found unexpectedly that no reaction takes place even when heating this mixture for 4 h at 70°C. Even sterically loaded derivatives of furoic acids are easily chloromethylated under these conditions [4]. Hence, simultaneous presence of trifluoromethyl and diethoxyphosphoryl groups strongly deactivates the furan ring.

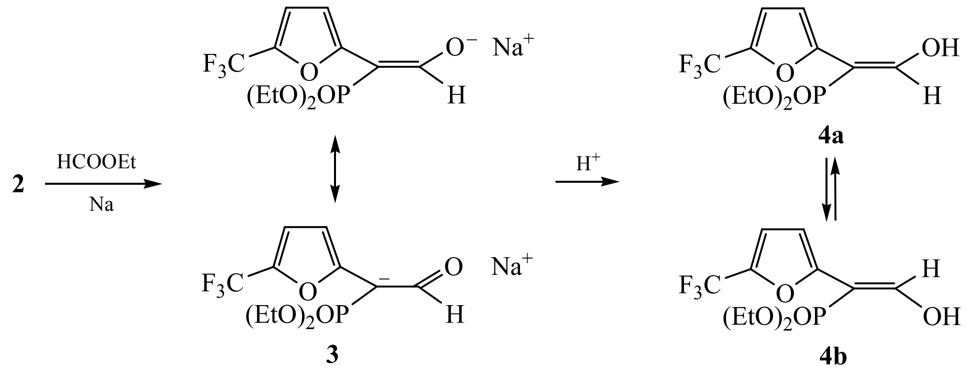


Methylene group contiguous to the phosphorus atom in the furan ring is the CH-acid center which in the presence of strong bases is acylated with ethyl formate and diethyl oxalate. This reaction was studied recently by an example of 2-furyl and 3-furylmethanephosphonates. It was shown that the presence of such electron-acceptor substituents as ester or cyano group facilitates proceeding of this reaction and stabilizes the condensation products [5–8]. Both these groups are σ- and π-acceptors. Trifluoromethyl group is one of rare strong pure σ-acceptors, and that is why investigation of its influence on the proceeding of this version of Claisen reaction presents definite interest.

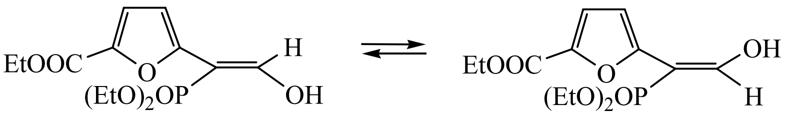
The condensation of phosphonate **2** with ethyl formate was carried out according to [4] in anhydrous toluene in the presence of sodium foil. The reaction was accompanied by a small heat evolution. The dissolution of sodium proceeded in the course of 3 h. At the dilution of the reaction mixture with petroleum ether the formation of the precipitate of sodium salt **3** was observed. It is a stable white crystalline substance of mp 164°C. In the presence of ethanol liberating in the course of the reaction it is considerably well soluble in the mixture of toluene with petroleum ether. Therefore after removing compound **3** and the workup of the filtrate a derivative of the furylacetic aldehyde **4** was isolated as yellow crystals of mp 82–83°C. The conversion of phosphonate **2** in this reaction was 87%, and the total yield of the formyl derivative calculated with respect to the sodium salt was 92% (Scheme 2).

The structure of formyl derivative **4** and its salt **3** was established by NMR spectroscopy. In the ^{31}P NMR spectrum of compound **4** (in DMSO-d_6) the signal at 18.02 ppm was observed. Signal of fluorine atom in this compound was detected at –62.42 ppm. Protons of the furan ring resonate at 6.63 ppm (H^3, d, J_{HH} 3.6 Hz) and 7.17 ppm (H^4, br.s). The downfield signals include a doublet at 7.50 ppm (=CHO, J_{PH} 10.0 Hz) and a broad signal of the enol hydroxy group at 12.04 ppm. Considering the value of J_{PH} it is possible to conclude that in DMSO the formyl derivative exists as *E*-enol **4a**. In the ^{13}C NMR spectrum signals of carbon atom of the vinyl fragment appear at 79.16 ppm (PC=, d, $^1J_{PC}$ 200.7 Hz) and 177.80 ppm (=CO, $^2J_{PC}$ 18.3 Hz). In the ^1H and the ^{13}C NMR spectra in deuterochloroform two sets of signals with the intensity ratio 5.5 : 1 are observed. In the set of signals with higher intensity the furan ring protons give a doublet at 6.18 ppm (H^3, J_{HH} 3.2 Hz) and a broadened signal at 6.74 ppm (H^4). Vinyl proton resonates as a doublet at 7.87 ppm (=CHO, J_{PH} 38.8 Hz). The broad signal of the enol proton is observed at 11.50 ppm. In the ^{13}C NMR spectrum signals of carbon atoms of the vinyl fragment appear at 91.31 ppm (PC=, $^1J_{PC}$ 179.6 Hz) and 151.27 ppm (=CO, $^2J_{PC}$ 17.0 Hz). Chemical shift of phosphorus in this compound is 20.56 ppm. These spectral data characterize *Z*-enol **4b**. The second, less intense set of signals belongs to *E*-enol **4a**. Protons of the furan ring appear at 6.24 ppm (H^3, d, J_{HH} 3.6 Hz) and 6.80 ppm (H^4, br.s). Doublet of the vinyl proton was observed at

Scheme 2.



Scheme 3.



4c

7.68 ppm (=CHO, J_{PH} 10.4 Hz). The exchange signal of the enol hydroxy group was common for both sets. Signals of the vinyl carbon atoms in the ^{13}C NMR spectrum were found at 91.58 ppm (PC=, $^1J_{PC}$ 179.2 Hz) and 152.41 ppm (=CO, $^{21}J_{PC}$ 17.0 Hz). Chemical shift of phosphorus atom of this form was appeared at 19.00 ppm. The fluorine atom in both forms has the same chemical shift equal to –63.93 ppm.

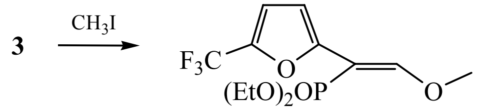
After establishing spectral parameters of *E*- and *Z*-enols **4a, 4b** we can analyze spectral characteristics of salt **3**. Signal of phosphorus atom in the ^{31}P NMR spectrum of this substance is observed at 29.62 ppm, namely, in the common range of sodium salts of the dialkyl furylmethanephosphonates [5–7]. In the downfield part of the ^{1}H NMR spectrum a doublet at 8.67 ppm (J_{PH} 2.0 Hz) is observed. Signals of the side chain carbon atoms have chemical shifts 79.16 ppm (d, $^1J_{PC}$ 200.7 Hz) and 177.80 ppm (d, $^2J_{PC}$ 18.3 Hz). They are very close to the above-presented values characterizing *E*-enol **4a** (DMSO-d_6).

On the other hand, the comparison of these data with spectral characteristics of the phosphorylated furylacetic aldehyde **4c** and its sodium salt **3a** [4, 8] shows following picture. In the ^{1}H NMR spectrum in deuterated chloroform a doublet of the vinyl proton at 8.00 ppm (=CHO, J_{PH} 38.8 Hz) and a broad signal of the enol hydroxy group at 11.53 ppm are observed. Signals of carbon atoms of the vinyl fragment appeared at 91.57 ppm (P–C=, $^1J_{PC}$ 179.1 Hz) and 152.40 ppm (=CO, $^2J_{PC}$ 17.2 Hz). Therefore in chloroform compound **4c** exists as *Z*-enol. We have also taken ^{1}H, ^{13}C, and ^{31}P NMR spectra of this substance in DMSO-d_6. The doublet of vinyl proton in this case is observed at 7.51 ppm ($^2J_{PH}$ 6.0 Hz), and a broadened signal of the enol proton, at 12.03 ppm. Signals of carbon atoms of the vinyl fragment were registered at 94.32 ppm (P–C=, $^1J_{PC}$ 195.5 Hz) and 153.38 ppm (=CO, $^2J_{PC}$ 20.0 Hz). Hence, in DMSO *E*-enol form of compound **4c** prevails (Scheme 3).

The presented data show that in the case of compound **4c** difference in chemical shifts of carbon atoms in the side chain for the enol forms prevailing in different solvents is not large. Besides, these spectral characteristics are sufficiently close to the data characteristic of enol forms of the fluorinated product **4a** and **4b** in deuterochloroform and strikingly differ from the data for DMSO solutions.

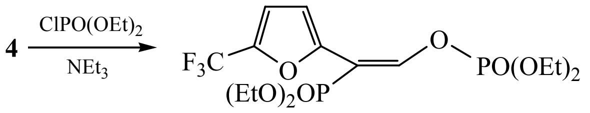
In the ^{1}H NMR spectrum of sodium salt **3a** in DMSO-d_6 signal of the vinyl proton is observed at 8.67 ppm (=CHO, $^2J_{PH}$ 2.4 Hz), and carbon atoms of the vinyl fragment give signals at 81.27 ppm (P–C=, $^1J_{PC}$ 199.7 Hz) and 177.97 ppm (=CO, $^2J_{PC}$ 19.1 Hz). These data well agree with that for the salt **3** and the enol **4a** obtained in DMSO. From these data follows that negative charge in the anions **3** and **3a** is significantly delocalized, and these substances cannot be regarded as pure carbanions of enolates. On the other hand, evidently due to the additional polarization effect of trifluoromethyl group the electron density distribution in compound **4** dissolved in DMSO resembles that existing in the anion of salt **3**. Chemical shift of phosphorus atom shows that no real ionization of fluorinated derivative **4** takes place. Most probably we deal with the tight ion pair whose structure is best of all described by the formula **4a** with *cis*-location of proton and phosphorus atoms. In its turn, structure of anions **3, 3a** on the basis of J_{PH} values may be approximately regarded as the resonance hybride of the formyl carbanion and *E*-enolate anion.

Sodium salt **3** was exposed to alkylation with methyl iodide. The reaction was carried out in dioxane at 55–60°C for 8 h. It occurred that alkylation proceeds only at the oxygen with the formation of *Z*-enol ether **5**. Doublet of the double bond proton was observed at 7.37 ppm with the characteristic coupling constant J_{PH} 32.4 Hz.



5

One of interesting classes of organophosphorus compounds taking part in biochemical transformations is enol phosphates. In connection with that we made an attempt to introduce phosphate group in the compound **4**. The reaction was carried out according to [8] in ethyl acetate in the presence of triethylamine. Diethyl chlorophosphate was used as the acylating agent.



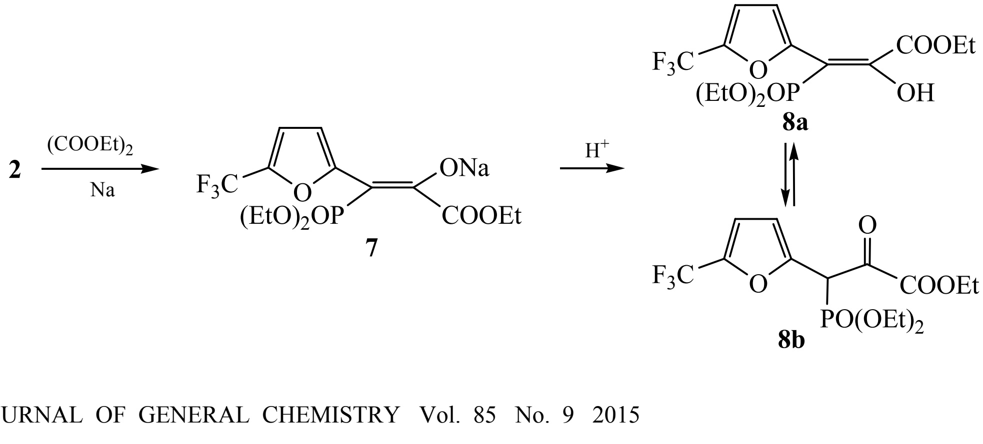
6

In the ^{31}P NMR spectrum of the reaction product **6** two signals of prosphorus atoms at 13.65 ppm and –5.59 ppm belonging to the phosphonate and the phosphate groups respectively were found. No coupling constant between them was observed. Signal of the vinyl proton in the ^{1}H NMR spectrum was a doublet of doublets at 7.50 ppm with the coupling constants J_{PH} 10.6 Hz and J_{POH} 6.6 Hz. Hence, the phosphonate phosphorus and the vinyl proton are located by the one side in relation to the double bond, and phosphorus-containing groups are remote from one another. Analogous configuration of the vinyl fragment of phosphonatophosphates was observed previously for the derivatives of the furylacetic aldehyde carrying the ester group in the furan ring in the cases when the substituents were not located in neighboring positions of the heterocycle [8].

The condensation of phosphonate **2** with diethyl oxalate in the presence of sodium foil was also carried out in toluene according to procedure [7]. The reaction was accompanied by a significant heat evolution and foaming. A complete dissolution of sodium was achieved in 5 h. The reaction product was sodium salt **7** which crystallized after removing volatile products while trituration of the residue in the 4 : 1 mixture of petroleum ether and ethyl acetate. The conversion of starting substance was 64% and the yield of the reaction product 55%. In the ^{19}F and ^{31}P NMR spectra signals of the corresponding nuclei were observed at –61.19 and 25.82 ppm. In the downfield part of the ^{1}H NMR spectrum only the furan ring proton signals were observed. It proves that substitution of the acidic hydrogen atom with sodium took place. Signals of the side chain carbon atoms in the salt **7** were observed at 74.68 ppm (PC=, $^{1}J_{\mathrm{PC}}$ 201.1 Hz), 176.16 ppm (=CO, $^{2}J_{\mathrm{PC}}$ 18.2 Hz), and 169.20 ppm (C=O). No splitting of the carbonyl group carbon atom signal shows that it is *cis*-located with respect to phosphorus. These data well agree with the spectral characteristics of salt **3**. This means that in the case under consideration the electron density is also considerably delocalized.

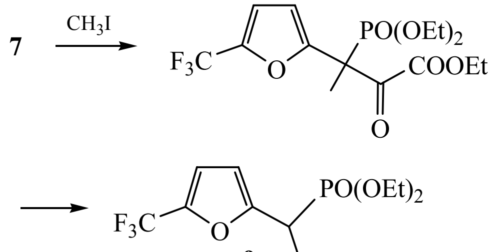
The treatment of the mixture formed after the above-described condensation by means of water extraction and subsequent acidifying showed that formal conversion of phosphonate **2** was only 38%. Consequently the condensation product is hydrolyzed with water to form the starting phosphonate. Yield of the acylation product with respect to the consumed phosphonate **2** was 74%. In the ^{19}F and ^{31}P NMR spectra in deuterochloroform two pairs of signals of the corresponding nuclei were observed at δ_{F} –64.16 and –64.22 ppm and δ_{P} 20.34 and 13.19 ppm in the 2 : 1 ratio. In the downfield part of the ^{1}H NMR spectrum intense signal of the enol OH group was observed at 10.47 ppm, and at 5.77 ppm a doublet of O=C–CHP fragment (J_{PH} 26.3 Hz) was present. Therefore in chloroform solution the acylation product is the equilibrium mixture of enol **8a** and ketone form **8b** in the 2 : 1 ratio. This fact was confirmed by the ^{13}C NMR data. Signals of the side chain carbon atoms of enol were found at 90.34 ppm (PC=, $^{1}J_{\mathrm{PC}}$ 179.6 Hz), 158.5 ppm (=CO, $^{2}J_{\mathrm{PC}}$ 26.4 Hz), and 162.32 ppm (C=O, $^{3}J_{\mathrm{PC}}$ 22.4 Hz). Large coupling constant of the signal of the carbonyl carbon atom shows that it is *trans*-located in relation to phosphorus. Signals of the side chain carbon atoms of ketone were observed at 47.49 ppm (PCH, $^{1}J_{\mathrm{PC}}$ 132.1 Hz), 189.65 ppm (C=O-ketone, $^{2}J_{\mathrm{PC}}$ 4.4 Hz), and 162.82 ppm (C=O, ester, $^{3}J_{\mathrm{PC}}$ 6.1 Hz) (Scheme 4).

Scheme 4.



Freshly prepared salt **7** was brought into alkylation with the excess of methyl iodide in dioxane. The reaction was carried out at 60°C for 10 h. The product isolated was a mixture of phosphonate **2** and diethyl 1-(5-trifluoromethylfur-2-yl)ethanephosphonate **9** in the 3 : 1 ratio. Structure of the latter was confirmed by the presence of signals of the methyl group protons at 1.58 ppm (J_{PH} 17.1 Hz, J_{HH} 7.4 Hz) and of the CHP fragment at 3.37 ppm (J_{PH} 23.7 Hz, J_{HH} 7.4 Hz). Signals of the corresponding carbon atoms were observed at 13.34 ppm ($^2J_{PC}$ 5.4 Hz) and 32.54 ppm ($^1J_{PC}$ 141.7 Hz). The signals of phosphorus and fluorine nuclei appeared at 25.18 ppm and –63.91 ppm respectively.

Heating of salt **7** evidently caused the elimination of the oxalyl residue. Simultaneously some part of salt succeeds to enter the reaction with methyl iodide. Alkylation in this case proceeds at the carbon atom. The reaction product is also labile. It decomposes with the elimination of the acyl fragment. Note that in contrast to the case of salt **3** no methylation at oxygen was found. Analogous cleavage of the alkylation product we previously observed in the case of the furylpyruvic acid derivative having no substituents in the furan ring [6].



9

All the attempts to carry out phosphorylation of salt **7** and oxalyl derivative **8** with diethyl chlorophosphate failed. Only compound **8** was always isolated from the reaction mixture.

Hence, the introduction of trifluoromethyl group in the furan ring strongly deactivates it with respect to the electrophilic substitution reactions. Phosphonate **2** does not enter chloromethylation even under the sufficiently rigid conditions. The methylene group near the phosphorus atom possesses sufficient CH-acidity to enter the Claisen reaction with ethyl formate and diethyl oxalate. The obtained sodium salts are considerably more stable than in the case of non-substituted phosphonates. In the DMSO solutions they exist as enols with *trans*-location of oxygen and phosphorus atoms in relation to the double bond. The formyl derivative exists in solutions only as enol. It is selectively alkylated and acylated at the oxygen. The phosphorylared furylpyruvate is a mixture of ketone and enol, and its anion is alkylated only at the carbon atom. The comparison with the previous data shows that trifluoromethyl derivative of (fur-2-yl)(diethoxyphosphoryl)acetaldehyde by its chemical properties resembles the compound with ethoxycarbonyl group in the furan ring. Unlike that trifluoromethyl derivative of (fur-2-yl)(diethoxyphosphoryl)pyruvic acid resembles the compounds having no acceptor substituents in the furan ring.

Potential biological activity of the compounds synthesized was evaluated with the help of PASS program [9]. Only the data with the probability more than 0.7 were selected. It occurred that trifluoromethylfuryl derivatives of the metane- and ethanephosphonic acids **2** and **9,** of phosphonoacetic aldehyde **4,** of the methyl ether and phosphate of its enol form **5, 6** and of the phosphonopyruvic acid **8** may be the potential cutinase inhibitors. Compounds **2, 3, 8** may show potential inhibiting activity with respect to acetylesterase. Potential inhibiting activity toward aspulvinone dimethylallyltransferase may be shown by phosphonoacetic aldehyde **4** and its methyl ether **5**. The latter is also potential inhibitor of feruloylesterase. Aldehyde **4** may occur also to be the antagonist of anatoxine receptors. Phosphonate **2** is regarded as the potential regulator of calcium exchange. Methyl ether and phosphate of the enol form of phosphonoacetic aldehyde **5** and **6** may possess insecticide activity. Hence the phosphorylated derivatives of trifluoromethylfuran may possess various physiological activity. They may be regarded as promising objects for pharmacological studies.

EXPERIMENTAL

^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were registered on a Bruker DPX-400 spectrometer (400.13 MHz ^{1}H, 376.43 MHz ^{19}F, 161.97 MHz ^{31}P, 100.16 MHz ^{13}C respectively). Spectra of sodium salts were obtained in DMSO-d_6, in the other cases $CDCl_3$ was used.

Diethyl (5-trifluoromethylfur-2-yl)methanephosphonate (2). A mixture of 5.3 g of 2-bromomethyl-5-trifluoromethylfuran and 4.5 mL of triethyl phosphite was heated under a vigorous stirring. The evolution of ethyl bromide began at 115°C. The temperature of the reaction mixture was gradually risen to 160°C when the complete liberation of bromide was achieved. The reaction mixture was stirred at this temperature for 2 min and then cooled. Total reaction time was 10 min. Distillation in a vacuum gave 5.1 g (78%) of phosphonate **2**, bp 96°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.29 t (6H, CH_3, J_{HH} 7.2 Hz), 3.25 d (2H, CH_2P, J_{PH} 21.2 Hz), 4.02 m (4H, CH_2OP, J_{HH} 7.2 Hz, J_{PH} 14.4 Hz), 6.33 br.s (1H, H^3-furan), 6.72 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.21 d (CH_3, $^3J_{PC}$ 5.8 Hz), 26.57 d (CH_2P, $^1J_{PC}$ 142.7 Hz), 62.52 d (CH_2OP, $^2J_{PC}$ 6.4 Hz), 109.14 d (C^3-furan, $^3J_{PC}$ 6.8 Hz), 112.78 (C^4-furan), 118.97 q (CF_3, $^1J_{FC}$ 265.1 Hz), 141.11 q (C^5-furan, $^2J_{FC}$ 42.6 Hz), 149.22 d (C^2-furan, $^2J_{PC}$ 8.6 Hz). ^{31}P NMR spectrum, δ_P, ppm: 21.53. ^{19}F NMR spectrum, δ_F, ppm: –64.17.

Reaction of phosphonate (2) with ethyl formate. To a solution of 2.3 g of phosphonate **2** and 1.3 mL of ethyl formate in 25 mL of toluene 0.3 g of sodium foil was added at stirring. The temperature of the reaction mixture gradually rose from 15 to 28°C and then decreased to the starting value. The dissolution of foil was complete in 3 h. The reaction mixture was stirred for 6 h and left overnight. On the next day it was diluted with 25 mL of petroleum ether, sodium salt was filtered off, washed with petroleum ether, and dried in the Fischer's pistol. Yield of the salt **3** 1.2 g, white crystals of mp 164°C. The filtrate was washed with water (3 × 15 mL), combined water layers were washed with 5 mL of ethyl acetate and acidified with concentrated hydrochloric acid to pH 2–3. The liberated oil was extracted with ethyl acetate (3 × 10 mL) and dried over sodium sulfate. After removing ethyl acetate 0.9 g of compound **4** was obtained as yellow crystals of mp 82–83°C. The removal of solvents from the remaining reaction mixture gave 0.3 g of phosphonate **2**. The conversion of starting phosphonate 87%, yield of condensation products calculated as sodium salt **3** 92%.

Sodium salt of (5-trifluoromethylfur-2-yl)(diethoxyphosphoryl)acetic aldehyde (3). ^{1}H NMR spectrum, δ, ppm: 1.12 t (6H, CH_3, J_{HH} 7.0 Hz, 3.75–3.86 m (4H, CH_2OP), 6.57 d (1H, H^3-furan, J_{HH} 3.6 Hz), 6.84 br.s (1H, H^4-furan), 8.67 d (1H, CHO, J_{PH} 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.63 d (CH_3, $^3J_{PC}$ 6.6 Hz), 59.77 d (CH_2OP, $^2J_{PC}$ 4.3 Hz), 79.16 d (P–C, $^1J_{PC}$ 200.7 Hz), 99.52 d (C^3-furan, $^3J_{PC}$ 8.8 Hz), 114.54 (C^4-furan), 121.07 q (CF_3, $^1J_{FC}$ 265.1 Hz), 131.60 q (C^5-furan, $^2J_{FC}$ 41.1 Hz), 160.35 d (C^2-furan, $^2J_{PC}$ 5.1 Hz), 177.80 d (CHO, $^2J_{PC}$ 18.3 Hz. ^{31}P NMR spectrum, δ_P, ppm: 29.62. ^{19}F NMR spectrum, δ_F, ppm: –60.91.

(5-Trifluoromethylfur-2-yl)(diethoxyphosphoryl)acetic aldehyde (4). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.18 t (6H, CH_3, J_{HH} 7.0 Hz), 3.94–4.03 m (4H, CH_2OP), 6.63 d (1H, H^3-furan, J_{HH} 3.6 Hz), 7.16 br.s (1H, H^4-furan), 7.50 d (1H, CHO, J_{PH} 10.0 Hz), 12.04 br.s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 16.68 d (CH_3, $^3J_{PC}$ 6.6 Hz), 59.77 d (CH_2OP, $^2J_{PC}$ 4.3 Hz), 79.16 d (P–C, $^1J_{PC}$ 200.7 Hz), 99.52 d (C^3-furan, $^3J_{PC}$ 8.8 Hz), 114.54 (C^4-furan), 121.07 q (CF_3, $^1J_{FC}$ 262.5 Hz), 131.60 q (C^5-furan, $^2J_{FC}$ 41.1 Hz), 160.33 d (C^2-furan, $^2J_{PC}$ 5.1 Hz), 177.80 d (CHO, $^2J_{PC}$ 18.3 Hz). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 19.69. ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –62.42. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: common signals: 1.33 m (6H, CH_3, J_{HH} 7.0 Hz), 4.05–4.20 m (4H, CH_2OP), 12.04 br.s (1H, OH); *E*-enol **4a**: 6.24 d (1H, H^3-furan, J_{HH} 3.6 Hz), 6.80 br.s (1H, H^4-furan), 7.68 d (1H, CHO, J_{PH} 10.4 Hz); *Z*-enol **4b**: 6.19 d (1H, H^3-furan, J_{HH} 3.6 Hz, 6.74 br.s (1H, H^4-furan), 7.87 d (1H, CHO, J_{PH} 38.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: common signal 16.00 d (CH_3, $^3J_{PC}$ 6.5 Hz), *E*-enol **4a**: 62.61 d (CH_2OP, $^2J_{PC}$ 5.3 Hz), 91.59 d (P–C, $^1J_{PC}$ 179.2 Hz), 106.83 (C^3-furan), 112.88 (C^4-furan), 119.33 q (CF_3, $^1J_{FC}$ 265.4 Hz), C^5-furan not found, 152.42 d (CHO, $^2J_{PC}$ 17.0 Hz), 163.99 (C^2-furan); *Z*-enol **4b**: 62.91 d (CH_2OP, $^2J_{PC}$ 4.3 Hz), 91.31 d (P–C, $^1J_{PC}$ 179.6 Hz), 105.28 (C^3-furan), 113.06 (C^4-furan), 119.13 q (CF_3, $^1J_{FC}$ 264.8 Hz), 131.66 q (C^5-furan, $^2J_{FC}$ 42.4 Hz), 151.27 d (CHO, $^2J_{PC}$ 17.0 Hz), 163.39 (C^2-furan). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 19.00 (**4a**), 20.56 (**4b**). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –63.93.

(5-Ethoxycarbonylfur-2-yl)(diethoxyphosphoryl)acetic aldehyde (4c), *E*-enol **form**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22 t (6H, CH_3, J_{HH} 7.2 Hz), 1.29 t (3H, CH_3-ester, J_{HH} 7.2 Hz), 3.97–4.07 m (4H, CH_2OP), 4.62 q (3H, CH_2OC, J_{HH} 7.2 Hz), 6.65 d (1H, H^3-furan, J_{HH} 3.6 Hz), 7.26 d (1H, H^4-furan, J_{HH} 3.6 Hz), 7.50 d (1H, CHO, J_{PH} 6.0 Hz), 12.03 br.s (1H, OH). ^{13}CNMR spectrum (DMSO-d_6), δ_C, ppm: 14.62 (CH_3-ester), 16.68 d (CH_3, $^3J_{PC}$ 6.6 Hz), 60.68 (CH_2O-ester), 61.89 d (CH_2OP, $^2J_{PC}$ 5.1 Hz), 94.32 d (P–C, $^1J_{PC}$ 199.5 Hz), 110.65 d (C^3-furan, $^3J_{PC}$ 6.5 Hz), 120.06 (C^4-furan), 141.74 (C^5-furan), 152.72 d (C^2-furan, $^2J_{PC}$ 5.8 Hz),158.33 (C=O), 159.88 d (CHO, $^2J_{PC}$ 20.0 Hz). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 17.94.

Diethyl *Z*-1-(5-trifluoromethylfur-2-yl)-2-methoxyethenephosphonate (5). To a solution of 1.4 g of salt **3** in 10 mL of dioxane 3 mL of methyl iodide was added, and the solution obtained was stirred for 8 h at

55–60°C. After cooling the reaction mixture to room temperature the precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in 15 mL of ethyl acetate, washed with 5 mL of water, and dried over sodium sulfate. After removing the solvent and keeping the residue in a vacuum 1.1 g (80%) of phosphonate **5** was obtained as a light brown viscous oil. ^{1}H NMR spectrum, δ, ppm: 1.33 t (6H, CH_3, J_{HH} 7.0 Hz), 3.97 s (3H, CH_3O), 4.07–4.19 m (4H, CH_2OP), 6.60 d (1H, H^{3}-furan, J_{HH} 3.2 Hz), 6.73 br.s (1H, H^{4}-furan), 7.37 d (1H, =CH–O, J_{PH} 32.4 Hz). ^{13}C NMR spectrum, δ_{C}, ppm: 16.21 d (CH_3, $^{3}J_{\mathrm{PC}}$ 6.6 Hz), 62.13 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 4.3 Hz), 62.71 (CH_3O), 97.83 d (P–C=, $^{1}J_{\mathrm{PC}}$ 187.4 Hz), 107.88 d (C^{3}-furan, $^{3}J_{\mathrm{PC}}$ 8.8 Hz), 113.29 (C^{4}-furan), 121.86 q (CF_3, $^{1}J_{\mathrm{FC}}$ 265.2 Hz), 139.50 q (C^{5}-furan, $^{2}J_{\mathrm{FC}}$ 42.6 Hz), 151.93 d (=CHO, $^{2}J_{\mathrm{PC}}$ 20.7 Hz), 161.25 br.s (C^{2}-furan). ^{31}P NMR spectrum, δ_{P}, ppm: 12.56. ^{19}F NMR spectrum, δ_{F}, ppm: –63.81.

Diethyl *E*-1-(5-trifluoromethylfur-2-yl)-2-(diethoxyphosphoryloxy)ethenephosphonate (6). To a solution of 0.7 g of phosphonate **4** in 10 mL of ethyl acetate 0.4 mL of triethylamine and 0.35 mL of diethyl chlorophosphate were added. The mixture obtained was stirred for 4 h at room temperature and left overnight. On the next day the reaction mixture was diluted with 10 mL of hexane, triethylamine hydrochloride was filtered off, the filtrate was evaporated to dryness, and the residue was kept in a vacuum to give 0.4 g (40%) of compound **6** as brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.27–1.30 m (12H, CH_3), 4.03–4.28 m (8H, CH_2OP), 6.72 d (1H, H^{3}-furan, J_{HH} 3.6 Hz), 6.87 br.d (1H, H^{4}-furan, J_{HH} 3.6 Hz), 7.50 d.d (1H, =CH–O, J_{PH} 10.6 Hz, $\mathrm{J}_{\mathrm{POH}}$ 6.6 Hz). ^{13}C NMR spectrum, δ_{C}, ppm: 15.92 d (CH_3, $^{3}J_{\mathrm{PC}}$ 6.3 Hz), 16.12 d (CH_3, $^{3}J_{\mathrm{PC}}$ 6.3 Hz), 62.76 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 5.6 Hz), 62.85 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 5.5 Hz), 65.36 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 5.9 Hz), 102.13 d (P–C=, $^{1}J_{\mathrm{PC}}$ 186.4 Hz), 111.78 d (C^{3}-furan, $^{3}J_{\mathrm{PC}}$ 3.7 Hz), 112.72 (C^{4}-furan), 119.02 q (CF_3, $^{1}J_{\mathrm{FC}}$ 265.4 Hz), 140.73 q (C^{5}-furan, $^{2}J_{\mathrm{FC}}$ 42.6 Hz), 148.10 d (C^{2}-furan, $^{2}J_{\mathrm{PC}}$ 3.9 Hz), 154.15 d (=CH–O, $^{2}J_{\mathrm{PC}}$ 21.8 Hz). ^{31}P NMR spectrum, δ_{P}, ppm: 13.65 (phosphonate), –5.59 (phosphate). ^{19}F NMR spectrum, δ_{F}, ppm: –64.21.

Reaction of phosphonate (2) with diethyl oxalate. *a.* To a solution of 2.2 g of phosphonate **2** and 1.6 mL of diethyl oxalate in 25 mL of toluene 0.25 g of freshly prepared sodium foil was added under vigorous stirring. The temperature of the reaction mixture gradually rose from 17 to 29°C and then decreased to the initial value. A complete dissolution of sodium was achieved in 4 h. The reaction mixture was left overnight and on the next day evaporated to dryness. The residue was treated with 30 mL of a mixture of petroleum ether and ethyl acetate (4 : 1), the crystals formed were filtered off and dried in the Fischer's pistol to give 1.1 g (55%) of light yellow crystals of sodium salt **7**, decomposition point 168–170°C. These crystals quickly become yellowish brown in air. ^{1}H NMR spectrum, δ, ppm: 1.07–1.21 t (9H, CH_3), 3.78–3.87 m (4H, CH_2OP), 3.99 q (2H, CH_2O, J_{HH} 7.2 Hz), 6.66 d (1H, H^{3}-furan, J_{HH} 3.6 Hz), 7.87 br.s (1H, H^{4}-furan). ^{13}C NMR spectrum, δ_{C}, ppm: 14.41 (CH_3), 16.52 d (CH_3, $^{3}J_{\mathrm{PC}}$ 6.5 Hz), 16.53 d (CH_3, $^{3}J_{\mathrm{PC}}$ 6.6 Hz), 59.26 (CH_2O), 59.86 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 4.0 Hz), 60.32 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 4.2 Hz), 74.68 d (P–C=, $^{1}J_{\mathrm{PC}}$ 201.1 Hz), 101.48 (C^{3}-furan, $^{3}J_{\mathrm{PC}}$ 7.7 Hz), 114.33 (C^{4}-furan), 120.87 q (CF_3, $^{1}J_{\mathrm{FC}}$ 262.7 Hz), 132.77 q (C^{5}-furan, $^{2}J_{\mathrm{FC}}$ 41.2 Hz), 159.78 br.s (C^{2}-furan), 169.20 (C=O), 176.96 d (=C-O, $^{2}J_{\mathrm{PC}}$ 18.2 Hz). ^{31}P NMR spectrum, δ_{P}, ppm: 25.82. ^{19}F NMR spectrum, δ_{F}, ppm: –61.19.

After removing the solvents and the excess diethyl oxalate, 0.8 g of phosphonate **2** was isolated from the filtrate. The conversion of the starting substance 64%.

b. To a solution of 2.6 g of phosphonate **2** and 1.6 mL of diethyl oxalate in 25 mL of toluene 0.25 g of freshly prepared sodium foil was added under vigorous stirring. The temperature of the reaction mixture gradually rose from 17°C to 28°C and then decreased to the initial value. Complete dissolution of sodium was achieved in 4 h. The reaction mixture was left for a night and then extracted with water (3 × 8 mL). The water extract was washed with 4 mL of ethyl acetate, acidified to pH 3, and then saturated with sodium chloride and the organic fraction formed was extracted with ethyl acetate. The extract obtained was dried over sodium sulfate, and then the solvent was removed. The residue was kept in a vacuum to give 1.0 (74%) of phosphonate **8** as a dark yellow syrup. ^{1}H NMR spectrum, δ, ppm: common signals: 1.29–1.40 m (9H, CH_3), 4.12–4.25 m (6H, CH_2OP), 4.37 q (6H, CH_2O, J_{HH} 7.0 Hz); *E*-enol **8a**: 6.31 br.s (1H, H^{3}-furan), 6.77 br.s (1H, H^{4}-furan), 12.04 br.s (1H, OH); ketone **8b**: 5.77 d (PCH, J_{PH} 26.3 Hz), 6.71 br.s (1H, H^{3}-furan), 6.80 br.s (1H, H^{4}-furan. ^{13}C NMR spectrum, δ_{C}, ppm: common signal 63.77 d (CH_2OP, $^{2}J_{\mathrm{PC}}$ 5.0 Hz), *E*-enol **8a**: 13.85 (CH_3), 15.92 d (CH_3,$^{3}J_{\mathrm{PC}}$ 6.6 Hz), 63.36 (CH_2O), 90.34 d (P–C, $^{1}J_{\mathrm{PC}}$ 179.1 Hz), 105.73 d (C^{3}-furan, $^{3}J_{\mathrm{PC}}$ 3.4 Hz), 112.88 (C^{4}-furan), 118.92 q (CF_3, $^{1}J_{\mathrm{FC}}$ 265.3 Hz), 141.23 q (C^{5}-furan, $^{2}J_{\mathrm{FC}}$ 42.4 Hz), 149.61 (C^2-furan, $^2J_{\mathrm{PC}}$ 8.7 Hz), 158.55 d (=C-O, $^2J_{\mathrm{PC}}$ 26.4 Hz), 162.32 d (C=O, $^3J_{\mathrm{PC}}$ 22.4 Hz); ketone **8b**: 13.61 (CH$_3$), 16.00 d (CH$_3$,$^3J_{\mathrm{PC}}$ 6.6 Hz), 47.49 d (PCH, $^1J_{\mathrm{PC}}$ 132.1 Hz), 63.58 (CH$_2$O), 111.73 d (C^3-furan, $^3J_{\mathrm{PC}}$ 5.6 Hz), 112.96 (C^4-furan), 116.20 q (CF$_3$, $^1J_{\mathrm{FC}}$ 250.5 Hz), 142.05 q (C^5-furan, $^2J_{\mathrm{FC}}$ 43.4 Hz), 145.91 d (C^2-furan, $^2J_{\mathrm{PC}}$ 8.2 Hz), 162.82 d (C=O-ester, $^3J_{\mathrm{PC}}$ 6.1 Hz), 183.65 d (C=O-ketone, $^2J_{\mathrm{PC}}$ 4.4 Hz). ^{31}P NMR spectrum, δ_{P}, ppm: 13.19 (**8b**), 20.34 (**8a**). ^{19}F NMR spectrum, δ_{F}, ppm: –64.16 (**8a**), –63.22 (**8b**).

After removing toluene and the excess diethyl oxalate from the toluene layer, 1.6 g of phosphonate **2** was obtained. The conversion of the starting substance 38%.

Reaction of sodium salt 7 with methyl iodide. To a solution of 1.5 g of freshly prepared salt **7** in 20 mL of dioxane 2 mL of methyl iodide was added, and the mixture obtained was stirred for 10 h at 60°C. On the next day the precipitate formed was filtered off, and dioxane was removed on a rotary evaporator. The residue was dissolved in 30 mL of ethyl acetate, the solution obtained was washed with 5 mL of water and dried with sodium sulfate. After removing the solvent 0.3 g of a mixture of phosphonate **2** and diethyl 1-(5-trifluoromethylfur-2-yl)ethanephosphonate **9** was obtained. According to NMR ^{1}H data ratio of these products was 2 : 1

Phosphonate 2. ^{1}H NMR spectrum, δ, ppm: 1.28 t (6H, CH$_3$, J_{HH} 7.2 Hz), 3.25 d (2H, CH$_2$P, J_{PH} 21.2 Hz), 4.02 m (4H, CH$_2$OP, J_{HH} 7.2 Hz, J_{PH} 14.4 Hz), 6.36 br.s (1H, H^3-furan), 6.75 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_{C}, ppm: 16.26 d (CH$_3$, $^3J_{\mathrm{PC}}$ 5.5 Hz), 26.73 d (CH$_2$P, $^1J_{\mathrm{PC}}$ 142.9 Hz), 62.56 d (CH$_2$OP, $^2J_{\mathrm{PC}}$ 6.3 Hz), 109.17 d (C^3-furan, $^3J_{\mathrm{PC}}$ 6.9 Hz), 112.81 (C^4-furan), 118.99 q (CF$_3$, $^1J_{\mathrm{FC}}$ 266.1 Hz), 140.78 q (C^5-furan, $^2J_{\mathrm{FC}}$ 40.6 Hz), 149.22 d (C^2-furan, $^2J_{\mathrm{PC}}$ 8.9 Hz). ^{31}P NMR spectrum, δ_{P}, ppm: 21.55. ^{19}F NMR spectrum, δ_{F}, ppm: –64.12.

Diethyl 1-(5-trifluoromethylfur-2-yl)ethanephosphonate 9. ^{1}H NMR spectrum, δ, ppm: 1.31 t (6H, CH$_3$, J_{HH} 7.2 Hz), 1.58 d.d (3H, CH$_3$, J_{HH} 7.4 Hz, J_{PH} 17.4 Hz), 3.37 d.q (1H, CHP, J_{HH} 7.4 Hz, J_{PH} 23.0 Hz), 4.12 m (4H, CH$_2$OP, J_{HH} 7.2 Hz, J_{PH} 14.4 Hz), 6.34 t (1H, H^3-furan, J_{HH}= J_{PH}=3.6 Hz), 6.70 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_{C}, ppm: 13.54 d (CH$_3$-ethane, $^2J_{\mathrm{PC}}$ 5.4 Hz), 15.92 d (CH$_3$, $^3J_{\mathrm{PC}}$ 6.9 Hz), 32.54 d (CHP, $^1J_{\mathrm{PC}}$ 141.7 Hz), 62.62 d (CH$_2$OP, $^2J_{\mathrm{PC}}$ 6.3 Hz), 107.96 d (C^3-furan, $^3J_{\mathrm{PC}}$ 6.8 Hz), 112.67 (C^4-furan), 118.99 q (CF$_3$, $^1J_{\mathrm{FC}}$ 266.1 Hz), 140.78 q (C^5-furan, $^2J_{\mathrm{FC}}$ 40.6 Hz), 148.25 d (C^2-furan, $^2J_{\mathrm{PC}}$ 7.1 Hz). ^{31}P NMR spectrum, δ_{P}, ppm: 25.19. ^{19}F NMR spectrum, δ_{F}, ppm: –64.06.

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