REACTIONS OF β-AMINOVINYL BROMODIFLUOROMETHYL KETONES WITH ALKYL PHOSPHITES: PERKOW VERSUS ARBUZOV

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Dedicated to Professor Oldřich Paleta on the occasion of his 70th birthday in recognition of his outstanding contributions to the area of organofluorine chemistry.

New bromodifluoromethyl enaminones **1a**–**1f** and γ-bromo-β-morpholinopropenyl fluoromethyl ketones **2a**, **2b** were synthesized. *N*-Substituted bromodifluoromethyl enaminones **1a**–**1d** do not react with triethyl or diethyl phosphites, whereas *N*-acylated enaminones **1e**, **1f** gave difluorodienyl phosphates **4a**, **4b** as Perkow rearrangement products. Fluoroketone **2a** reacts easily with triethyl phosphite according to the Arbuzov protocol and a perspective building block – trifluoromethyl-containing phosphonate **7a** is formed.

Keywords: Fluorine; Enaminones; Perkow reaction; Phosphates; Arbuzov reaction; Phosphonates; Fluorinated ketones; Enol phosphates.

It is well established that the introduction of fluorine atoms or organofluorine groups into organic molecules often changes their physical and chemical properties[1]. Many new agrochemicals (nearly 28% in 2002) and drugs (currently more than 18%) contain at least one fluorine atom[2]. On the other hand, the introduction of the organophosphorus groups into organic molecules often leads to the appearance of biological activity[3]. A combination of the two features (fluorine and phosphorous atoms) in one molecule is a useful methodology of searching for new effective inhibitors of enzyme systems[4]. One of convenient methods for synthesis of fluorophosphorus compounds is the phosphorylation of fluorine-containing building blocks.

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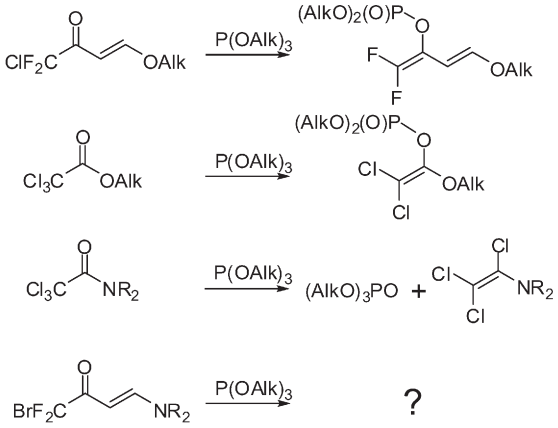
β-Alkoxy-α,β-unsaturated fluorine-containing ketones are readily accessible compounds, which are widely used in the fluoroorganic synthesis[5]. At the same time, only a few examples of the addition of phosphites to the β-ethoxyvinyl trifluoromethyl ketones are known. Thus, [1+4] cycloaddition of triethyl phosphite with (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one resulted in an oxaphosphole[6]; an addition of diethyl phosphite to the enone afforded a mixture of *E*- and *Z*-adducts[7]; and the reaction of tris(trimethylsilyl) phosphite with enones gave a mixture of 1,2- and 1,4-adducts[8].

The reactions of β-alkoxyvinyl chlorodifluoromethyl ketones with triethyl phosphite were recently investigated and various dienyl phosphates were obtained as the products of the Perkow reaction[9]. The β-alkoxyvinyl trihalomethyl ketones are the vinylogs of the esters of trihaloacetic acid, which also react with phosphites yielding useful products of the Perkow reaction[10]. At the same time, trichloroacetamides give triethyl phosphate and (trichlorovinyl)amines as the major products in the reaction with triethyl phosphite[10]. Taking into account that β-aminovinyl trihalomethyl ketones are the vinylogs of the amides of trihaloacetic acid, it is very difficult to predict the results of the reaction of the enaminones with phosphites (Scheme 1).



Alk = Me, Et; R = Alk, Ar

SCHEME 1

In order to predict a potential reactivity of β-aminovinyl trihalomethyl ketones, the electron structure of this class of compounds should be considered. The presence of both electron-donor and electron-withdrawing groups and the occurrence of six π-electrons make the structure of enaminones similar to heteroaromatic substances[11]. The analysis of literature data has shown the absence of information on reactions of phosphites and heteroaromatic compounds or enaminones containing the bromodifluoromethyl group. Continuing our investigations, we present in this work the most recent results of our research on the reactivity of β-aminovinyl bromodifluoromethyl ketones in the reaction with triethyl phosphite as well as direction of the reaction (Perkow rearrangement and/or Arbuzov reaction).

RESULTS AND DISCUSSION

Taking into account that bromide is a better leaving group than chloride, we chose bromodifluoromethyl-containing enaminones as objects in this research instead of chlorodifluoromethyl-containing ones. In order to study scope and limitations of the reactions between phosphites and bromodifluoromethyl enaminones, two series of β-aminovinyl ketones with general formulae **1** and **2** were synthesized (Fig. 1). In the series of enaminones **1** we modified substituents on the nitrogen atom in order to change gradu-

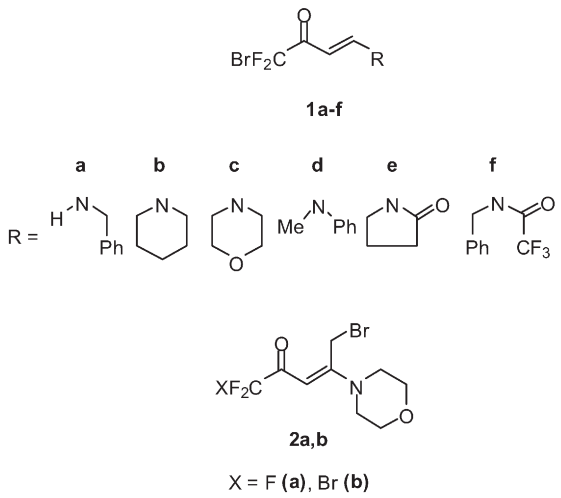
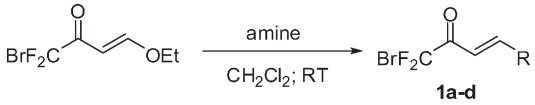


FIG. 1
Two synthesized series of β-aminovinyl ketones **1** and **2**

ally its basicity (high for **1a**–**1c**, medium for **1d** and low for **1e**, **1f**). We also included enaminones **2** bearing bromine atom at γ-position to the carbonyl group.

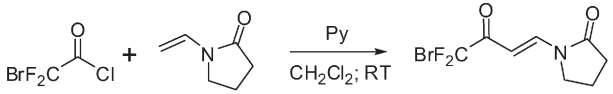
Compounds **1a**–**1d** were easily obtained by the reaction of bromodifluoromethyl β-ethoxyvinyl ketone[12] (prepared by the same method as its chlorodifluoromethyl analog[13]) with the corresponding amines[14] in high yields (Scheme 2).



R = BnNH (a), $(CH_2)_5N$ (b), $O(CH_2)_4NN$ (c), Ph(Me)N (d)

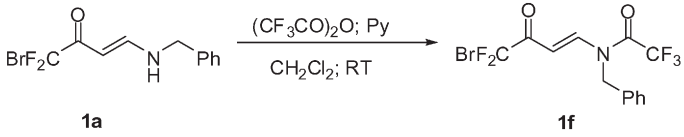
SCHEME 2

In contrast to compounds **1a**–**1d**, enaminone **1e** cannot be synthesized from the corresponding enone because of very low nucleophilicity of the nitrogen atom in pyrrolidone. Therefore, enaminone **1e** was obtained by an alternative method based on bromodifluoroacetylation of *N*-vinylpyrrolidone, similarly to the previously published trifluoroacetylation[15] (Scheme 3).



SCHEME 3

Compound **1g** was obtained by trifluoroacetylation of *N*-benzylenaminone **1a** under similar conditions as was previously published for chiral trifluoromethyl enaminone[16] (Scheme 4).

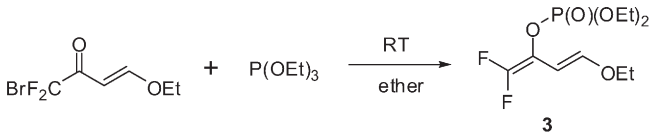


SCHEME 4

The structure of enaminones **1a**–**1f** was proved by NMR spectroscopy. It is worth mentioning that the C=C double bond of *N*,*N*-disubstituted enaminones **1b**–**1f** has exclusively the *E*-configuration, whereas *N*-monosubstituted enaminone **1a** shows an equilibrium between *E*- and *Z*-isomers

depending on the polarity of solvents, as is usual for polyfluoroalkylated enaminones[17]. We assume that enaminones **1e**, **1f** have *E*-*s*-*E*-conformation on the basis of X-ray data for *N*-trifluoroacetylated enaminones published recently[18].

Analogously to (chlorodifluoromethyl)enones[9], bromodifluoromethyl β-ethoxyvinyl ketone reacts with triethyl phosphite also under very mild conditions and the corresponding dienyl phosphate **3** is formed in good yield by the Perkow reaction (Scheme 5). NMR spectral characteristics of dienyl phosphate **3** coincide with the data for the same compound published previously[9].

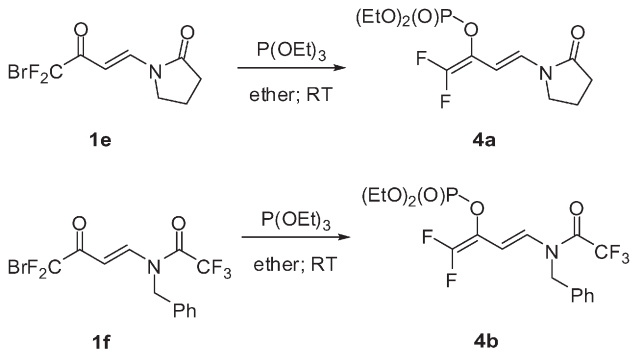


SCHEME 5

It is found that the reactivity of bromodifluoromethyl enaminones **1a**–**1d** (with the nitrogen atom of strong or medium basicity for **1a**–**1c** and **1d**, respectively) in the reaction with triethyl phosphite is very different from difluorohalomethyl-containing β-ethoxyvinyl ketones. All our attempts to react enaminones **1a**–**1d** with phosphites failed although various reaction conditions were used (the process was monitored by ^{31}P and ^{19}F NMR spectroscopy of the reaction mixtures). Enaminones **1a**–**1d** did not react with triethyl phosphite in various solvents (ether, dioxane) and at varied temperatures (20–100 °C) for several days. Also the Michaelis–Becker reaction between enaminone **1c** and diethyl phosphite in the presence of NEt_3 in THF or dioxane under reflux failed. In ^{19}F NMR spectra of the above-mentioned reaction mixtures, characteristic signals of neither the Perkow nor Arbuzov products were observed: two doublets in the region from –90 to –110 ppm (difluorodienyl phosphate)[9] or doublet at –110 ppm ($RCOCF_2P(O)(OEt)_2$ group)[19].

In the case of enaminones **1e**, **1f** (with nitrogen atom of low basicity), the reaction with triethyl phosphite occurs and difluorodienyl phosphates **4a**, **4b** (products of the Perkow rearrangement) are formed under mild conditions (20 °C/12 h) in high yields, as shown by the ^{19}F and ^{31}P NMR spectra of the reaction mixtures (Scheme 6). The spectral and physicochemical properties of phosphates **4a**, **4b** are very close to those of their alkoxy analogs synthesized previously[9]. Their instability under the conditions of column chromatography led to low yields of the products. However, in

contrast to the alkoxy analogs[9], we observed in ^{1}H and ^{19}F NMR spectra of the products **4a**, **4b** additional set of signals of olefinic hydrogen and fluorine atoms with the integration intensity about 20–25% close to major products. This can be explained by either asymmetric substitution on the nitrogen atom or restricted rotation around the C–N bond between the dienyl and amide functions[14,17,20]. In Experimental we have listed the spectral data only for major isomers of compounds **4a**, **4b**.

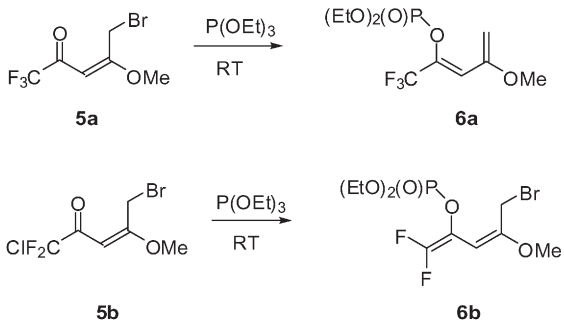


1e **4a**

1f **4b**

SCHEME 6

The recently published results[9] demonstrate that fluorinated γ-bromo-β-alkoxy-a,β-unsaturated ketones **5a**, **5b** react with triethyl phosphite forming the corresponding dienyl phosphates **6a**, **6b**. The direction of the reaction strongly depends on the nature of enones **5** (Scheme7).

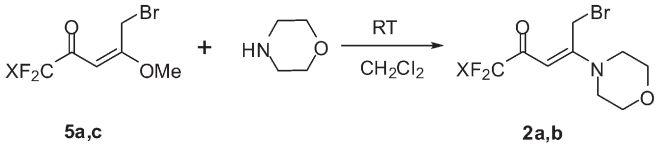


5a **6a**

5b **6b**

SCHEME 7

We believe[9] that the dienyl phosphates **3** and **6** are formed via cyclic intermediate oxaphosphole, the formation of which does not take place in the reaction of enaminones **1a**–**1d** with triethyl phosphite. Taking this into account the study of the reactivity of enaminones **2** (amino analogs of enones **5**) is of interest. The starting enaminones **2a**, **2b** were synthesized from the corresponding enones **5a** and **5c** in high yields (Scheme 8). The latter was obtained by the same method as enones **5a**, **5b** [21].

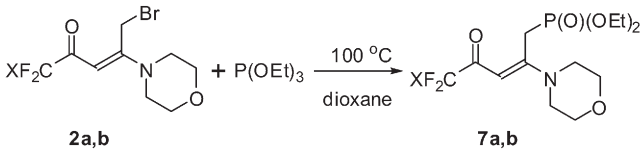


5a,c **2a,b**

X = F (**5a**, **2a**), Br (**5c**, **2b**)

SCHEME 8

It was found that enaminone **2a** reacts with triethyl phosphite in ether at 20 °C for 21 days affording trifluoromethyl-containing phosphonate **7a** in high yield as the product of the Arbuzov reaction. The use of dioxane as a solvent and the increase in the reaction temperature up to 100 °C decrease the reaction time without any change of the yield and quality of product **7a** (Scheme 9). In contrast to **2a** enaminone **2b** reacts with triethyl phosphite very slowly in ether at 20 °C (a conversion after 2 weeks by ^{19}F NMR spectroscopy was only about 5%) and the formation of phosphonate **7b** was also observed by ^{31}P NMR spectroscopy of the reaction mixture (a weak characteristic signal of phosphonate group at 26 ppm appeared, that complied with corresponding data of **7a**). Unfortunately, our attempts to decrease the reaction time and to improve the yield of phosphonate **7b** by an increase in reaction temperature failed and a complex mixture of products was obtained.



2a,b **7a,b**

X = F (**2a**, **7a**), Br (**2b**, **7b**)

SCHEME 9

The structure of phosphonate **7a** was elucidated by NMR spectroscopy. Thus in ^{31}P NMR spectrum of compound **7a** a characteristic phosphonate signal appeared at about 26 ppm in ^{13}C NMR spectra the characteristic doublet of methylene group linked to phosphorus atom is observed at 48 ppm with $^{1}J_{CP}$ = 132 Hz; at the same time the signal of the trifluoromethyl group almost does not change. We believe that the trifluoromethyl containing phosphonate **7a** is a perspective building block for organic chemistry, especially for heterocyclizations and olefin synthesis.

CONCLUSION

New bromodifluoromethyl enaminones **1a**–**1f** and γ-bromo-β-morpholinopropenyl fluoromethyl ketones **2a**, **2b** were synthesized. First examples of the reactions of fluorinated enaminones with alkyl phosphites are presented. The scope and limitations of the reaction of phosphites with different fluorine-containing enaminones have been investigated. Phosphorylation of *N*-substituted bromodifluoromethyl-containing enaminones **1a**–**1d** did not take place, whereas *N*-acylated enaminones **1e**, **1f** gave fluorine-containing dienyl phosphates **4a**, **4b** as a result of the Perkow rearrangement. γ-Bromo-β-morpholino-α,β-unsaturated trifluoromethyl ketone **2a** reacts with triethyl phosphite forming fluorine-containing phosphonate **7a** as a result of the Arbuzov reaction. The synthesized fluorine-containing compounds are of interest for synthesis due to the formation of highly functionalized organophosphorus compounds such as 1,3-dienyl phosphates **3**, **4a**, **4b**, and phosphonate **7a**.

EXPERIMENTAL

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a Bruker DRX-500 instrument. Chemical shifts (δ) are given in ppm relative to TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F), or 85% phosphoric acid (^{31}P); coupling constants (*J*) are given in Hz. Column chromatography was performed on silica gel 60 (Merck). Merck Silica Gel F_{254} plates were used for TLC and visualization was effected with UV light (254 nm). Melting points were measured in the open capillary; the values are uncorrected. Diethyl ether and dioxane were dried with sodium and benzophenone. Dichloromethane was dried with P_2O_5. The reactions with phosphites were performed under argon using the Schlenk technique. $P(OEt)_3$ was commercially available from Aldrich. Compounds 1-bromo-4-ethoxy-1,1-difluorobut-3-en-2-one[9] and 5-bromo-1,1,1-trifluoro-4-methoxypent-3-en-2-one[21] (**5a**) were prepared according to the published procedures.

Enaminones **1a**–**1d** and **2a**, **2b**. General Procedure

A solution of the corresponding amine (5 mmol) in dichloromethane (10 ml) was added dropwise to a solution of bromodifluoromethyl-containing enone (5 mmol) in dichloro-

methane (10 ml) under stirring at 0 °C. The mixture was stirred at room temperature for 10 h to complete the reaction. After evaporation of solvent, the residue was crystallized from hexane.

4-(Benzylamino)-1-bromo-1,1-difluorobut-3-en-2-one (**1a**). From bromodifluoromethyl-containing enone (1.15 g, 5 mmol), product **1a** (1.32 g, 91%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 10.35 br s, 1 H (NH); 7.10–7.55 m, 6 H (ArH; =CH-N); 5.40 d, 1 H, ^3J = 6.1 (=CH-C); 4.50 d, 2 H, ^3J = 5.1 (CH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –60.2 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 180.7 t, $^2J_{CF}$ = 24.5; 158.1; 136.2; 129.1; 128.4; 127.6; 115.5 t, $^1J_{CF}$ = 319.6; 85.6; 53.3. For $C_{11}H_{10}BrF_2NO$ calculated: 45.54% C, 3.47% H, 4.83% N; found: 45.63% C, 3.48% H, 4.82% N.

(E)-1-Bromo-1,1-difluoro-4-(piperidin-1-yl)but-3-en-2-one (**1b**). From bromodifluoromethyl-containing enone (1.15 g, 5 mmol), product **1b** (1.18 g, 88%) was obtained as light yellow needle. M.p. 57–59 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.80 d, 1 H, ^3J = 12.1 (=CH-N); 5.32 d, 1 H, ^3J = 12.1 (=CH-C); 3.46 m, 2 H (CH_2-N); 3.35 m, 2 H (CH_2-N); 1.69 m, 6 H (CH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –60.9 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 180.0 t, $^2J_{CF}$ = 23.6; 135.4; 116.3 t, $^1J_{CF}$ = 320.8; 84.5; 55.9; 47.0; 26.5; 25.0; 23.7. For $C_9H_{12}BrF_2NO$ calculated: 40.32% C, 4.51% H, 5.22% N; found: 40.40% C, 4.52% H, 5.22% N.

(E)-1-Bromo-1,1-difluoro-4-(morpholin-4-yl)but-3-en-2-one (**1c**). From bromodifluoromethyl-containing enone (1.15 g, 5 mmol), product **1c** (1.19 g, 88%) was obtained as yellow powder. M.p. 72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.81 d, 1 H, ^3J = 12.7 (=CH-N); 5.36 d, 1 H, ^3J = 12.7 (=CH-C); 3.73–3.80 m, 4 H (OCH_2); 3.49–3.55 m, 2 H (NCH_2); 3.37–3.43 m, 2 H (NCH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –61.7 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 180.3 t, $^2J_{CF}$ = 24.3; 155.4; 115.8 t, $^1J_{CF}$ = 320.8; 85.3; 66.8; 65.6; 53.8; 46.2. For $C_7H_{10}BrF_2NO_2$ calculated: 35.58% C, 3.73% H, 5.19% N; found: 35.65% C, 3.73% H, 5.19% N.

(E)-1-Bromo-1,1-difluoro-4-(N-methylanilino)but-3-en-2-one (**1d**). From bromodifluoromethyl-containing enone (1.15 g, 5 mmol), product **1d** (1.29 g, 89%) was obtained as yellow powder. M.p. 54 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.20 d, 1 H, ^3J = 12.7 (=CH-N); 7.40 m, 2 H (ArH); 7.26 t, 1 H, ^3J = 7.1 (ArH); 7.20 d, 2 H, ^3J = 7.6 (ArH); 5.60 d, 1 H, ^3J = 12.7 (=CH-C); 3.41 s, 3 H (CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): –61.7 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 180.5 t, $^2J_{CF}$ = 24.6; 153.3; 145.9; 129.8; 126.3; 121.0; 115.7 t, $^1J_{CF}$ = 319.3; 89.9; 37.7. For $C_{11}H_{10}BrF_2NO_2$ calculated: 45.54% C, 3.47% H, 4.83% N; found: 45.58% C, 3.48% H, 4.82% N.

(E)-5-Bromo-1,1,1-trifluoro-4-(morpholin-4-yl)pent-3-en-2-one (**2a**). From trifluoromethyl-containing enone (1.48 g, 6 mmol), product **2a** (1.63 g, 90%) was obtained as yellow powder. M.p. 74–76 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.38 s, 1 H (=CH-C); 4.86 br s, 2 H (CH_2Br); 3.84 m, 4 H (OCH_2); 3.57 br m, 4 H (NCH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –77.6 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 176.3 q, $^2J_{CF}$ = 31.4; 163.5; 117.4 q, $^1J_{CF}$ = 292.3; 87.6; 66.1; 47.3; 22.6. For $C_9H_{11}BrF_3NO_2$ calculated: 35.78% C, 3.67% H, 4.64% N; found: 35.81% C, 3.60% H, 4.64% N.

(E)-1,5-Dibromo-1,1-difluoro-4-(morpholin-4-yl)pent-3-en-2-one (**2b**). From bromodifluoromethyl-containing enone (1.85 g, 6 mmol), product **2b** (1.9 g, 89%) was obtained as yellow powder. M.p. 37–39 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.36 s, 1 H (=CH-C); 4.84 br s, 2 H (CH_2Br); 3.82 m, 4 H (OCH_2); 3.55 br m, 4 H (NCH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –60.84 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 178.7 t, $^2J_{CF}$ = 25.8; 163.6; 115.9 t, $^1J_{CF}$ = 321.6; 86.3; 66.1; 47.3; 22.6. For $C_9H_{11}Br_2F_2NO_2$ calculated: 29.78% C, 3.05% H, 3.86% N; found: 29.83% C, 3.05% H, 3.86% N.

1-[(*E*)-4-Bromo-4,4-difluoro-3-oxobut-1-en-1-yl]pyrrolidin-2-one (**1e**)

A solution of bromodifluoroacetyl chloride acid (2 g, 10.34 mmol) in dichloromethane (10 ml) was added dropwise to a mixture of *N*-vinylpyrrolidone (1.26 g, 11.38 mmol) and pyridine (1.06 g, 13.45 mmol) in dichloromethane (15 ml) under stirring at 0–4 °C. The mixture was stirred at 0 °C for 10 h to complete the reaction. Then dichloromethane (20 ml) was added, the reaction mixture was washed with water (5 × 30 ml), organic layer was separated and dried with anhydrous $MgSO_4$. After evaporation of solvent the product was crystallized from hexane to afford product **1e** (2.13 g, 77%) as light yellow powder. M.p. 73 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.35 d, 1 H, ^3J = 14.1 (=CH-N); 5.77 d, 1 H, ^3J = 14.1 (=CH-C); 3.64–3.70 m, 2 H (CH_2); 2.56–3.62 m, 2 H (CH_2); 2.19–2.27 m, 2 H (CH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –64.0 s. ^{13}C NMR ($CDCl_3$, 125 MHz): 181.0 t, $^2J_{CF}$ = 26.2; 174.6; 141.9; 114.4 t, $^1J_{CF}$ = 320.0; 97.9; 45.1; 30.8; 17.4. For $C_8H_8BrF_2NO_2$ calculated: 35.85% C, 3.01% H, 5.23% N; found: 35.81% C, 3.01% H, 5.24% N.

N-Benzyl-*N*-[(*E*)-4-bromo-4,4-difluoro-3-oxobut-1-en-1-yl]-2,2,2-trifluoroacetamide (**1f**)

Trifluoroacetic anhydride (1.74 g, 8.27 mmol) was added dropwise to a cooled (ice bath) solution of **1a** (2 g, 6.89 mmol) and pyridine (0.66 g, 8.27 mmol) in dichloromethane (15 ml) under stirring and in the argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for 4 h. Then the reaction mixture was washed with water (2 × 10 ml), organic layer was separated and dried with anhydrous $MgSO_4$. Evaporation an only the solvent gave the product **1f** (2.4 g, 90%) as oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.33 d, 1 H, ^3J = 13.6 (=CH-N); 7.32–7.42 m, 3 H (ArH); 7.20 d, 2 H, ^3J = 6.5 (ArH); 6.15 d, 1 H, ^3J = 13.6 (=CH-C); 5.07 s, 2 H (CH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): –65.3 s, 2 F (CF_2Br); –68.17 br s, 3 F (CF_3). ^{13}C NMR ($CDCl_3$, 125 MHz): 180.1 t, $^2J_{CF}$ = 27.3; 158.5; 157.2 q, $^2J_{CF}$ = 37.6; 143.2; 129.3; 128.54; 126.55; 115.7 q, $^1J_{CF}$ = 288.1; 113.7 t, $^1J_{CF}$ = 320.1; 103.0; 48.9. For $C_{13}H_9BrF_5NO_2$ calculated: 40.44% C, 2.35% H, 3.63% N; found: 40.52% C, 2.35% H, 3.62% N.

(*E*)-4-Ethoxy-1,1-difluorobuta-1,3-dien-2-yl Diethyl Phosphate (**3**)

A solution of triethyl phosphite (0.95 ml, 5.5 mmol) in diethyl ether (10 ml) was added dropwise to a solution of enone (1.15 g, 5 mmol) in diethyl ether (10 ml) at –30 °C under stirring in the argon atmosphere. After the addition had been finished, the temperature of the reaction mixture was arisen to room temperature. The end of the reaction was determined by ^{31}P and ^{19}F NMR spectra. Reaction mixture was washed with 5% solution $NaHCO_3$ (2 × 3 ml) and dried with anhydrous $MgSO_4$. The solvent was removed in vacuum and phosphate **3** of 90% purity (1.15 g, 73%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 6.78 d, 1 H, ^3J = 12.7 (=CH-O); 5.29 dd, 1 H, ^3J = 12.7, ^4J = 3.3 (=CH-C); 4.07–4.26 m, 6 H (3 OCH_2); 1.27–1.40 m, 9 H (3 CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): –101.11 d, 1 F, $^2J_{FF}$ = 61.2; –113.46 d, 1 F, $^2J_{FF}$ = 61.2. ^{31}P NMR ($CDCl_3$, 202 MHz): 0.46 m.

Phosphates **4**. General Procedure

A solution of triethyl phosphite (0.95 ml, 5.5 mmol) in diethyl ether (10 ml) was added dropwise to a solution of corresponding enaminone (5 mmol) in diethyl ether (30 ml) under stirring at 0 °C in argon. Then the temperature of the reaction mixture was raised to room

temperature. The end of the reaction was determined by TLC, ^{31}P and/or ^{19}F NMR spectra. The reaction mixture was washed with 5% solution of $NaHCO_3$ (2 × 3 ml) and dried with anhydrous $MgSO_4$. The solvent was removed in vacuum and the product was obtained as slightly impure brown oil in almost quantitative yield. The product was purified by column chromatography (eluent ethyl acetate).

[(E)-1,1-Difluoro-4-(2-oxopyrrolidin-1-yl)buta-1,3-dien-2-yl] diethyl phosphate (**4a**) (major isomer). By column chromatography, product **4a** (0.6 g, 37%) was obtained as yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 7.05 d, 1 H, ^3J = 14.2 (=CH-O); 5.13 d, 1 H, ^3J = 14.2 (=CH-C); 3.75–3.85 m, 4 H ($OC\mathbf{H}_2CH_3$); 3.27–3.33 m, 2 H (CH_2); 2.18–2.25 m, 2 H (CH_2); 1.84–1.91 m, 2 H (CH_2); 0.99–1.07 m, 6 H ($OCH_2C\mathbf{H}_3$). ^{19}F NMR ($CDCl_3$, 470 MHz): –98.5 dm, 1 F, $^2J_{FF}$ = 53.6; –111.12 dm, 1 F, $^2J_{FF}$ = 53.6. ^{31}P NMR ($CDCl_3$, 202 MHz): 0.22 m. ^{13}C NMR ($CDCl_3$, 125 MHz): 173.1; 153.3 ddd, $^1J_{CF}$ = 288.7, $^1J_{CF}$ = 286.9, $^3J_{CP}$ = 6.5; 124.2; 112.4 ddd, $^2J_{CF}$ = 43.7, $^2J_{CF}$ = 19.6, $^2J_{CP}$ = 8.5; 98.1; 64.7 d, $^2J_{CP}$ = 6.1; 44.8; 30.7; 17.1; 15.7 d, $^3J_{CP}$ = 6.1. For $C_{13}H_{20}F_2NO_4P$ calculated: 48.30% C, 6.24% H, 4.33% N; found: 48.30% C, 6.24% H, 4.34% N.

(E)-4-(N-Benzyl-2,2,2-trifluoroacetamido)-1,1-difluorobuta-1,3-dien-2-yl diethyl phosphate (**4b**) (major isomer). By column chromatography, product **4b** (0.89 g, 40%) was obtained as yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 7.09–7.35 m, 6 H (=CH-N, Ar-H); 5.68 d, 1 H, ^3J = 13.4 (=CH-C); 4.96 s, 2 H (-CH_2-Ar); 4.10–4.20 m, 4 H ($OC\mathbf{H}_2CH_3$); 1.25–1.35 m, 6 H (OCH_2-$C\mathbf{H}_3$). ^{19}F NMR ($CDCl_3$, 470 MHz): –68.9 s, 3 F (CF_3); –94.8 dd, 1 F, $^2J_{FF}$ = 45.1, $^4J_{FP}$ = 6.2 (F-C=C); –108.41 dd, 1 F, $^2J_{FF}$ = 45.1, $^4J_{FP}$ = 9.1 (F-C=C). ^{31}P NMR ($CDCl_3$, 202 MHz): 0.58 m. ^{13}C NMR ($CDCl_3$, 125 MHz): 156.1 q, $^2J_{CF}$ = 37.7; 153.8 br dd, $^1J_{CF}$ = ~290; 134.4; 129.0; 127.9; 126.6; 125.5; 116.2 q, $^1J_{CF}$ = 288.3; 111.6 ddd, $^2J_{CF}$ = 43.3, $^2J_{CF}$ = 20.1, $^2J_{CP}$ = 8.7; 103.9; 65.2 d, $^2J_{CP}$ = 5.5; 48.5; 15.8 d, ^2J = 5.5. For $C_{18}H_{21}F_5NO_4P$ calculated: 48.99% C, 4.80% H, 3.17% N; found: 49.08% C, 4.79% H, 3.18% N.

(*E*)-1,5-Dibromo-1,1-difluoro-4-methoxypent-3-en-2-one (**5c**)

Bromine (2.24 ml, 43.66 mmol) was added dropwise to a solution of enone (10 g, 43.66 mmol) in dichloromethane (50 ml) at 0 °C with stirring. After 1 h, pyridine (3.45 ml, 43.66 mmol) was added. The cooling bath was removed and the reaction mixture was stirred for 2 h. Then the reaction mixture was washed with water (2 × 10 ml), organic layer was separated and dried with anhydrous $MgSO_4$ and the solvent was evaporated. The residue was distilled in vacuum. The product (10.3 g, 76.5%) was obtained as yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 5.75 s, 1 H (=CH-C); 4.47 s, 2 H (CH_2Br); 3.88 s, 3 H (OCH_3) ^{19}F NMR ($CDCl_3$, 470 MHz): –64.0 s. For $C_6H_6Br_2F_2O_2$ calculated: 23.40% C, 1.96% H; found: 23.39% C, 1.96% H.

Diethyl [(*E*)-5,5,5-Trifluoro-2-morpholin-4-yl-4-oxopent-2-en-1-yl] Phosphonate (**7a**)

Method A. Triethyl phosphite (0.66 ml, 3.81 mmol) was added to a solution of enaminone **2a** (1 g, 3.31 mmol) in dry ether (10 ml) under stirring in argon. The reaction mixture was stirred at room temperature for 21 days. The end of the reaction was determined by ^{19}F and ^{31}P NMR spectra. The solvent was removed in vacuum. The product was purified by column chromatography (eluent ethyl acetate, then methanol).

Method B. The same as method *A* but with dioxane as the solvent and the reaction mixture was stirred at 100 °C for 72 h.

By procedure *A*, from 1 g of enaminone **2a**, phosphonate **7a** was obtained as brown oil (0.88 g, 74%). By procedure *B*, from 1 g enaminone **2a**, phosphonate **7a** was obtained as

brown oil (0.85 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): 5.42 s, 1 H (=CH-C); 4.00–4.28 m, 6 H ($OC\mathbf{H}_2CH_3$); 3.79 m, 4 H (OCH_2); 3.61 br m, 4 H (NCH_2); 1.20–1.41 m, 6 H ($C\text{-}CH_2\text{-}P$, $OCH_2C\mathbf{H}_3$). ^{19}F NMR ($CDCl_3$, 470 MHz): –77.7 s. ^{31}P NMR ($CDCl_3$, 202 MHz): 26.05 m. ^{13}C NMR ($CDCl_3$, 125 MHz): 176.12 q, $^2J_{CF}$ = 31.6; 161.15 d, $^2J_{CP}$ = 7.6; 117.15 q, $^1J_{CF}$ = 292.1; 88.11; 66.25; 63.0 d, ^2J = 6.5; 47.94 d, $^1J_{CP}$ = 132.4; 16.2 d, $^3J_{CP}$ = 6.5. For $C_{13}H_{21}F_3NO_5P$ calculated: 43.46% C, 5.89% H, 3.90% N; found: 43.54% C, 5.89% H, 3.89% N.

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