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Synthesis of new polyhalogenoalkyl-containing phosphonates with an enaminone core and their use in the preparation of fluorinated heterocycles

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ABSTRACT

A number of polyhalogenoalkyl-containing phosphonates with an enaminone core were synthesized from readily available β-alkoxyvinyl polyhalogenoalkyl ketones by successive bromination, amination, and Arbuzov reaction. The new phosphonates were used for the syntheses of five- and six-membered heterocycles bearing both trifluoromethyl and methylenephosphonate groups.

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The chemistry of fluorinated organo phosphates and phosphonates has numerous attractive features. Phosphate esters are important due to the participation of phosphate-containing molecules in biological processes including signaling pathways, information storage, and energy transfer.[1] As a result, they have been a topic of interest for many years, with applications mainly directed toward bioorganic and medicinal chemistry. The development of new prodrugs among phosph(on)ates and bisphosph(on)ates is of interest to many medicinal chemists.[2] The interest in fluorine substitution of organic groups attached to phosphorus stems from the possible effect of such substitution on the physical, chemical, and biological properties of the resulting phosphonates.[3] In general, incorporating fluorine as either a bioisosteric replacement for hydrogen or an isoelectronic replacement for a hydroxy group has profound consequences on metabolic degradation, lipophilicity, hydrogen bonding, and the reactivity of organic molecules. Fluoro-containing phosphonates are important considering their unique properties, whilst the development of useful methods for the synthesis of fluoro-containing phosphonates is of interest for the synthesis of potentially bioactive substances.[4]

β-Alkoxy- and β-aminovinyl polyfluoroalkyl ketones are readily accessible building blocks for the preparation of fluorinated heterocycles, amino acids, etc.[5] However, there are only a few communications on the reactions of fluorinated enones and enaminones with phosphites.[6,7]

As a part of our research program we have studied the reactions of (β-alkoxy, amino)vinyl chloro(bromo)difluoromethyl ketones and triethyl phosphite.[6d,7] It was found that the reactivity of chloro(bromo)difluoromethyl-containing β-alkoxy enones and similar enaminones was very different in reactions with phosphites. β-Alkoxy enones reacted with triethyl phosphite at room temperature via the Perkow reaction to yield difluoro-containing dienyl phosphates.[6d] In contrast to β-alkoxy enones the reactivity of enaminones in reactions with phosphites depends strongly on the basicity of the nitrogen atom. Enaminones containing a nitrogen with high or medium basicity did not react with phosphites under various conditions. At the same time, enaminones with a nitrogen of low basicity reacted with triethyl phosphite under mild conditions via Perkow rearrangement to give difluorodienyl phosphates.[7] Also, the reactivity of γ-bromo-β-(alkoxy, amino)vinyl polyhalogenomethyl ketones with phosphites depends strongly on the nature of the β-substituent. γ-Bromo-substituted β-alkoxyenones afforded polyhalogenomethyl-containing dienyl phosphates[6d] (Perkow route), while γ-bromo-β-morpholinovinyl trifluoromethyl ketone reacted with triethyl phosphite exclusively via the Arbuzov protocol to yield a trifluoromethyl-containing phosphonate (Scheme 1).[7]

Herein we report our results on the scope and limitations of the Arbuzov reaction of various γ-bromo-β-aminovinyl polyhalogenomethyl ketones with triethyl phosphite. We also demonstrate the utility of polyfluoroalkyl-containing phosphonates as precursors for the synthesis of five- and six-membered heterocycles and a 1,3-diketone bearing both trifluoromethyl and methylenephosphonate

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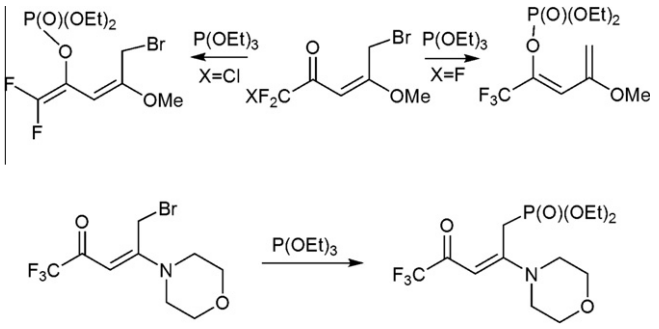


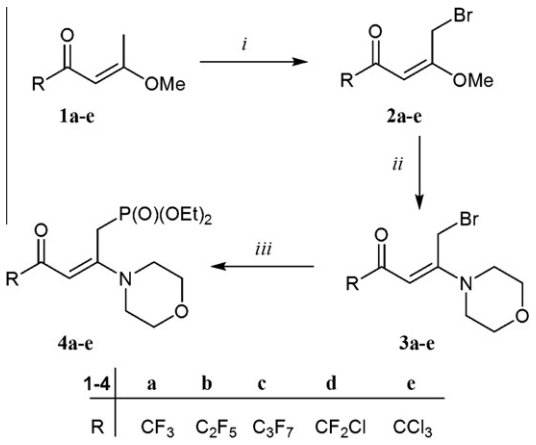
Scheme 1. Reactions of γ-bromo-β-(alkoxy, amino)vinyl polyhalogenomethyl ketones with triethylphosphite.

groups. These products are potential precursors for Horner–Wadsworth–Emmons reaction.[8]

Polyhalogenoalkyl-containing phosphonates were synthesized using the strategy presented in Scheme 2. Compounds **2a**–**e** were obtained by bromination of the corresponding polyhalogenoalkyl-containing enones **1a**–**e**, as published previously.[6d,9] This method is a general procedure for preparing γ-bromo-polyhalogenoalkyl-containing enones **2** in high yields (80–93%). Enaminones **3a**–**e** were synthesized by reaction of polyhalogenoalkyl ketones **2a**–**e** with morpholine at 25 °C for eight hours.[7] It is worth mentioning that various secondary aliphatic amines could be used for the synthesis of enaminones such as **3**, but morpholine provided better yields and led to easier isolation of the corresponding enaminones.

Phosphonates **4a**–**e** were obtained via Arbuzov reaction of enaminones **3** with triethyl phosphite by continuous heating in 1,4-dioxane. We found that the presence of the longer chain perfluoroalkyl groups in enaminones **3b**,**c** led to slightly higher yields in shorter reaction times. It is interesting that in spite of the presence of two possible reaction centers in compounds **3d**,**e**, we observed exclusively nucleophilic substitution of bromine furnishing trihalogenomethyl-containing phosphonates **4d**,**e** in high yields. Similar inactivity of chlorine in trichloromethyl and chlorodifluoromethyl groups in reactions with phosphites was noted previously.[7] The ratio of reagents, reaction times, yields, and conditions are summarized in Table 1.

To our knowledge, only one compound of similar structure was previously prepared by trichloroacetylation of *N*-methylenamines bearing a phosphonate group in 33% yield.[10] Our methodology



Scheme 2. Synthesis of polyhalogenoalkyl-containing phosphonates **4**. Reagents and conditions: (i) Br_2, CH_2Cl_2, 25 °C, 1 h; pyridine, 0 °C, 1 h, 80–93%; (ii) morpholine, CH_2Cl_2, 0→25 °C, 8 h, 59–85%; (iii) $P(OEt)_3$, 1,4-dioxane, 50–100 °C, 72–120 h, 70–85%.

for the synthesis of enaminones containing both polyhalogenoalkyl and methylenephosphonate groups is efficient and successful on varying both the polyhalogenoalkyl and amino group. For instance, bis-enaminone **5** was synthesized from piperazine and two equivalents of enone **2a**, and then converted successfully into the corresponding bisphosphonate **6** (Scheme 3).

Compounds **2**–**6** were fully characterized by ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectroscopy and by elemental analysis.[11] Exceptions were the ^{13}C NMR spectra of enaminones **5** and **6** because of poor solubility and the presence of broad signals.

We and others have demonstrated the wide possibilities of using fluorinated enones and enaminones in heterocyclization reactions.[5,12] The novel compounds **4** represent precursors for the synthesis of various heterocycles bearing both polyhalogenoalkyl and methylenephosphonate groups. We used phosphonate **4a** as a model compound for investigating the scope and limitations of the utility of this type of phosphonate for the synthesis of five- and six-membered heterocyclic systems (Scheme 4).

It was found that phosphonate **4a** reacted with hydrazine hydrate under mild conditions to furnish pyrazole **7** in high yield and purity without the need for any additional purification. In contrast, the reaction of enaminone **4a** with hydroxylamine in water afforded isoxazolinol **8** in a low isolated yield. The synthesis of six-membered heterocycles from phosphonate **4a** and (thio)urea proceeded to give oxy- and thiopyrimidines **9** and **10** in low yields. We examined various standard heterocyclization conditions, but only in the case of aqueous methanol with HCl at rt did we obtain pyrimidines **9** and **10** after preparative HPLC purification. The heterocycles were fully characterized by ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectroscopy and by elemental analysis. We observed two tautomeric forms in the NMR spectra of compound **9**. Similar behavior of trifluoromethyl-containing 2-substituted pyrimidines was described earlier.[13]

Unfortunately, the corresponding substituted pyrimidines were not obtained by the reaction of phosphonate **4a** with guanidine or amidines under standard conditions, although the disappearance of the enaminone signal at −78 ppm was evident from ^{19}F NMR spectroscopy. We observed an increase in the intensity of the singlet at −85 ppm characteristic for hydrates of trifluoromethyl ketones. The hydrolysis of enaminone **4a** takes place in acidic aqueous medium and the methylenephosphonate-containing trifluoromethyl diketone **11** was formed, presumably according to the poor results obtained during the pyrimidine synthesis.

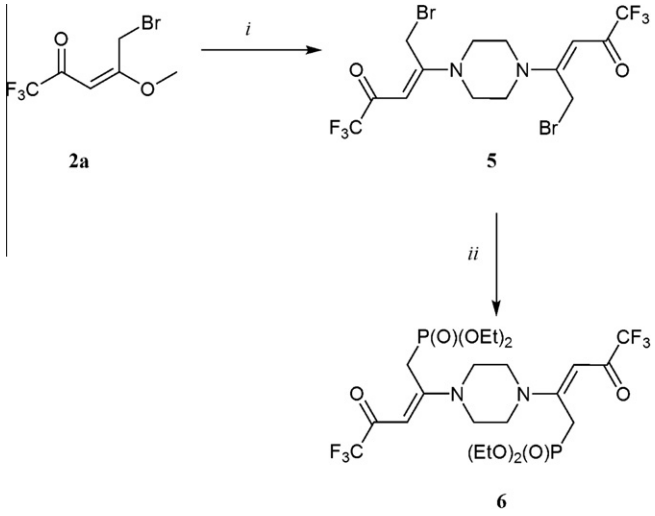
We synthesized diketone **11** via hydrolysis of enaminone **4a** in the presence of hydrochloric acid to confirm our assumption (Scheme 5). Diketone **11** did not react with (thio)urea, guanidine, or amidines under various condensation conditions (in aqueous methanol and ethanol, aqueous 1,4-dioxane, toluene, at 30–110 °C and in the presence of hydrochloric or toluenesulfonic acids).

Compound **11** was isolated in hydrate form according to NMR spectra and elemental analysis. As expected, diketone **11** formed complex equilibria mixtures of various tautomers and hydrate forms (Scheme 6) depending on the nature of the solvents. The spectral data were complicated by the possible formation of intramolecular enol hydrogen bonds with keto- or phosphonate groups. Thus, in the ^{19}F NMR spectrum of diketone **11** we observed, in $CDCl_3$, the dominance of two signals at −77.0 and −87.5 ppm in a 5:1 ratio, and in methanol, mainly two hydrate forms with signals at −83.9 and −87.9 ppm in a 3:1 ratio were observed. Only in dry DMSO-d_6 did compound **11** exists as nearly one isomer which allowed us to prove its structure as **11d**—the hydrate form of diketophosphonate **11**.

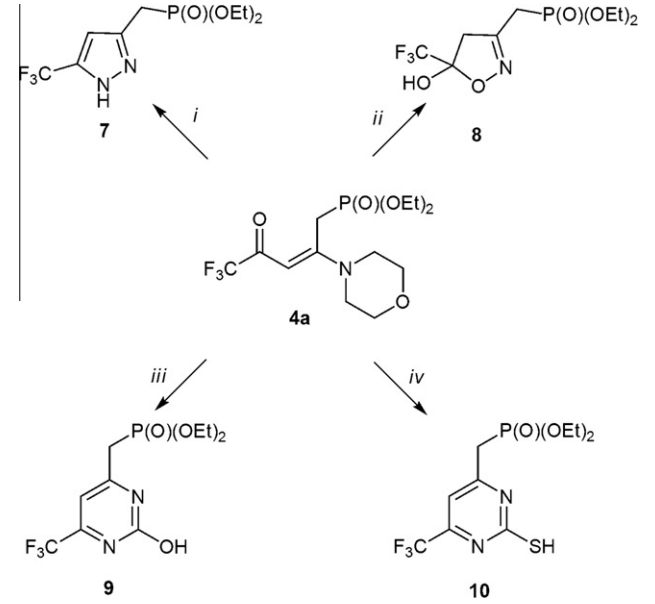
It should be noted that diketophosphonate **11** was reported previously but without any synthetic or characteristic data and was used as the starting material for the synthesis of fluorinated hydroxy phosphonic acid via reduction with Baker's yeast.[14]

Table 1
Reaction conditions for the synthesis of phosphonates **4a–e**, **6**

Substrate	Ratio of **3** (**5**):$P(OEt)_3$	Temperature (°C)	Product	Time (h)	Yield (%)
3a	1:1.2	100	**4a**	72	74
3b	1:1.2	100	**4b**	72	84
3c	1:1.2	100	**4c**	72	87
3d	1:0.8	50	**4d**	96	58
3e	1:0.8	50	**4e**	96	46
5	1:2.2	100	**6**	96	72

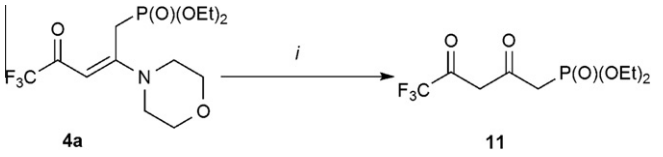


Scheme 3. Synthesis of fluorinated bisphosphonate **6**. Reagents and conditions: (i) piperazine, CH_2Cl_2, 0→25 °C, 8 h, 86%; (ii) $P(OEt)_3$, 1,4-dioxane, 100 °C, 120 h, 68%.

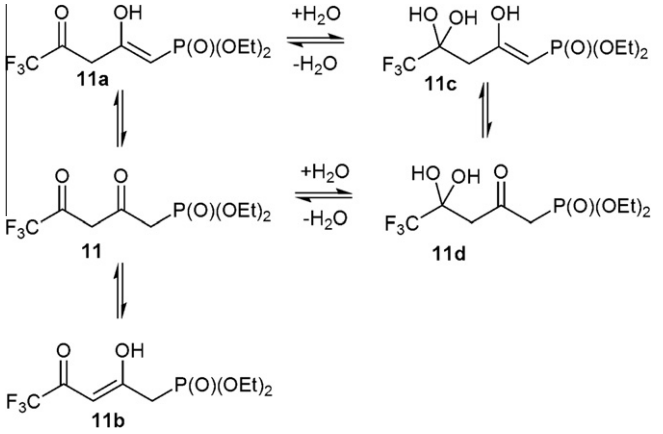


Scheme 4. Synthesis of five- and six-membered heterocycles **7–10** bearing both trifluoromethyl and methylene phosphonate groups. Reagents and conditions: (i) $N_2H_4{\cdot}H_2O$, CH_2Cl_2, 0→25 °C 12 h, 73%; (ii) $NH_2OH{\cdot}HCl$, $NaHCO_3$, methanol–water, rt, 3 h, 27%; (iii, iv) (thio)urea, HCl, methanol–water, rt, 144 h, 21–23%.

In conclusion, we have investigated the scope and limitations of the reactions of various γ-bromo-β-aminovinyl polyhalogenoalkyl ketones with triethyl phosphite. This reaction represents a method to synthesize fluorinated phosphonates in moderate to high yields. No side reactions/products were observed during the course of the reaction. Using diethyl (2*E*)-5,5,5-trifluoro-2-morpholin-4-yl-4-oxopent-2-enylphosphonate (**4a**), we have demonstrated the utility of this class of phosphonates for the synthesis of heterocycles bearing both polyhalogenoalkyl and methylenephosphonate groups.



Scheme 5. Synthesis of diketone **11**. Reagents and conditions: (i) MeOH, concd HCl, rt, 15 h, 53%.



Scheme 6. Tautomeric and hydrate forms of diketophosphonate **11**.

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Supplementary data

Supplementary data (experimental procedures, characterization and spectroscopic data for all obtained compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.123.

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11. *General procedure for the preparation of compounds* **1a–e**: A solution of the corresponding acyl chloride (86 mmol) in dry CH_2Cl_2 (40 ml) was added dropwise to a solution of 2-methoxypropene (7.13 g, 99 mmol) and pyridine (8.85 g, 112 mmol) in dry CH_2Cl_2 (80 ml) at 0 °C. The mixture was stirred at 0 °C for 4 h until the reaction was complete. CH_2Cl_2 (150 ml) was added and the mixture was washed with H_2O (3 × 50 ml), a 5% solution of HCl (3 × 50 ml), and H_2O (1 × 50 ml). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Distillation afforded compounds **1a–e** as colorless oils.
General procedure for the preparation of compounds **2a–e**: A solution of elemental Br_2 (22.38 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a solution of the corresponding enone (22.38 mmol) in dry CH_2Cl_2 (80 ml) at 20–25 °C. The mixture was stirred at rt for 1 h and pyridine (22.38 mmol) was added dropwise with stirring at 0 °C. The temperature was increased to rt and the reaction mixture was stirred for 5 h. The solvent was removed in vacuum and the residue was distilled to yield **2a–e**.
General procedure for the preparation of compounds **3a–e**: A solution of morpholine (5 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of halogenoalkyl-containing enone **2** (5 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at room temperature for 10 h. After evaporation of the solvent, the residue was crystallized from a mixture of hexane–Et_2O to give **3a–e**.
General procedure for the preparation of compounds **4a–c**: Triethyl phosphite (1.7 mmol) was added to a solution of the corresponding enaminone **3** (1.3 mmol) in dry 1,4-dioxane (10 ml) under an argon atmosphere. The reaction mixture was stirred at 100 °C for 72 h. The extent of reaction was determined by ^{19}F and ^{31}P NMR spectroscopy. The solvent was removed in vacuum and the residue was purified by column chromatography [eluent EtOAc–hexane (1:1), then MeOH].
General procedure for the preparation of compounds **4d,e**: Triethyl phosphite (1.14 mmol) was added to a solution of the corresponding enaminone **3** (1.42 mmol) in dry 1,4-dioxane (15 ml) under an argon atmosphere. The reaction mixture was stirred at 50 °C for 120 h. The solvent was removed in vacuum and the residue was purified by column chromatography [eluent EtOAc–hexane (1:1), then MeOH].
Preparation of compound **7**: Hydrazine hydrate (151 mg, 2.78 mmol) was added dropwise to a solution of phosphonate **4a** (1 g, 2.78 mmol) in CH_2Cl_2 (15 ml) with stirring at 0 °C. The mixture was stirred at rt for 12 h then washed with H_2O (2 × 3 ml) and dried over Na_2SO_4. After evaporation of the solvent, pure pyrazole **7** was obtained as a yellow oil.
Preparation of compound **8**: $NaHCO_3$ (152 mg, 1.81 mmol) was added gradually to a solution of enaminone **4a** (500 mg, 1.39 mmol) and hydroxylamine hydrochloride (126 mg, 1.81 mmol) in H_2O (8 ml) and MeOH (3 ml) with stirring at rt. The reaction mixture was stirred for 3 h at rt and extracted with Et_2O (3 × 10 ml). The combined organic layer was dried over Na_2SO_4. After evaporation of the solvent, pure diethyl (5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl)methylphosphonate (**8**) was obtained as a yellow oil.
General procedure for the preparation of compounds **9** *and* **10**: Concentrated HCl (1 ml) was added to a solution of enaminone **4a** (1.08 g, 3 mmol) and (thio)urea (4 mmol) in 50% aqueous MeOH (30 ml). The reaction mixture was stirred for 6 days and evaporated under reduced pressure. The residue was chromatographed using a Combiflash Companion chromatograph (eluent EtOAc–MeOH, gradient from 0% to 30% of MeOH in EtOAc, RediSep® Normal-phase Silica Flash Columns).
Preparation of compound **11**: Enaminone **4a** (230 mg, 0.64 mmol) was dissolved in MeOH (7 ml), concentrated HCl (0.3 ml) was added, and the reaction mixture was stirred overnight. The MeOH was evaporated in vacuum, the residue was dissolved in Et_2O (20 ml), and the solution was washed with H_2O (4 ml). The organic layer was separated, dried over Na_2SO_4, and the solvent was evaporated under vacuum.
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