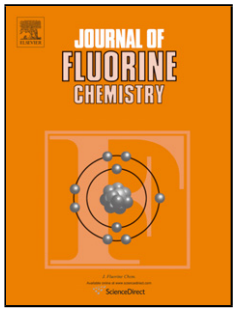
Journal Pre-proof



Uncommon fluorination of enones with xenon difluoride

Igor I. Gerus, Yury I. Zhuk, Liliya M. Kacharova, Gerd-Volker Röschenthaler, Elena N. Shaitanova, Alexandr E. Sorochinskii, Sergey I. Vdovenko, Jacek Wojcik

PII: S0022-1139(19)30345-8

DOI: https://doi.org/10.1016/j.jfluchem.2019.109413

Reference: FLUOR 109413

To appear in: *Journal of Fluorine Chemistry*

Received Date: 3 October 2019

Revised Date: 5 November 2019

Accepted Date: 6 November 2019

Please cite this article as: Gerus II, Zhuk YI, Kacharova LM, Röschenthaler G-Volker, Shaitanova EN, Sorochinskii AE, Vdovenko SI, Wojcik J, Uncommon fluorination of enones with xenon difluoride, *Journal of Fluorine Chemistry* (2019), doi: https://doi.org/10.1016/j.jfluchem.2019.109413

Uncommon fluorination of enones with xenon difluoride

Igor I. Gerus*[1], Yury I. Zhuk[1], Liliya M. Kacharova[1,2], Gerd-Volker Röschenthaler[3], Elena N. Shaitanova[1], Alexandr E. Sorochinskii[1], Sergey I. Vdovenko[1], Jacek Wojcik[4]

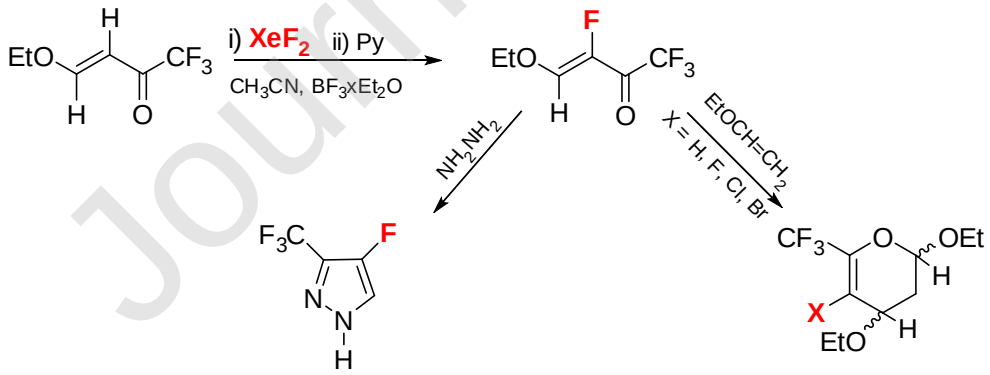
[1] V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Science, Murmanska Str. 1, Kiev 02094, Ukraine

[2] University of Minnesota Duluth Advanced Materials Center, 102 HCAMS, 1038 University Drive 55812, Duluth, MN USA

[3] Jacobs University Bremen gGmbH, Life Sciences and Chemistry, Campus Ring 1, 28759 Bremen, Germany

[4] Institute of Biochemistry and Biophysics Polish Academy of Sciences, ul. Pawińskiego 5a, 02-106 Warszawa, Poland

Graphical abstract



Highlights

- The fluorination of readily available β-alkoxy-enones using the commercial reagent XeF_2 and $BF_3 \cdot Et_2O$ as catalyst gives the *vic*-difluoro ketones
- α-Fluoro-β-alkoxy-enones can be obtained as *Z*-isomers under farther dehydrofluorination
- The synthesis is based on fluorination by XeF_2
- The chemical evaluation of synthesized α-fluoro-β-alkoxy-enones was investigated
- New fluorinated dihydropyranes were obtained which are perspective precursors for fluorocontaining hexoses

Abstract

Readily available β-alkoxyvinylpolyfluoroalkyl ketones react with XeF_2 to give the products of addition of two Fluorine atoms to the C=C double bond - vic-difluoro ketones, which can be easily converted to α-F enones. We demonstrated chemical evaluation of these compounds by formation of new fluorocontaining enaminones and pyrazoles. In order to obtain new precursors for bioactive compounds we performed [4+2] hetero Diels-Alder reaction and obtained dihydropyranes which are perspective starting materials for fluorinated carbohydrates.

Keywords: Halogenation; Enones; Heterocyclic compounds; XeF_2; [4+2] Cyclization; Fluorinated synthons

1. Introduction

The current interest to fluoroorganic compounds connected with its unique beneficial properties [1] used in pharmaceuticals [2-5], agrochemicals [6], medical imaging and as radio labels [7, 8]. There are two major processes for the synthesis of fluoroorganic compounds:

- Replacement of an atom or group by a fluorine atom
- Using a fluorinated synthon as a building block.

Of course, the second approach is more common and convenient. In our group, we work with readily available (E)-β-alkoxyvinylpolyfluoroalkyl ketones **A** - enones, that may be considered as a synthetic equivalent of 1,3-ketoaldehydes **B**) and are an useful precursors with fluoroalkyl groups, see Fig. 1 [9-14].

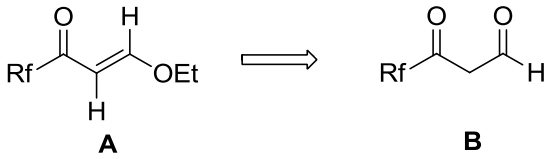
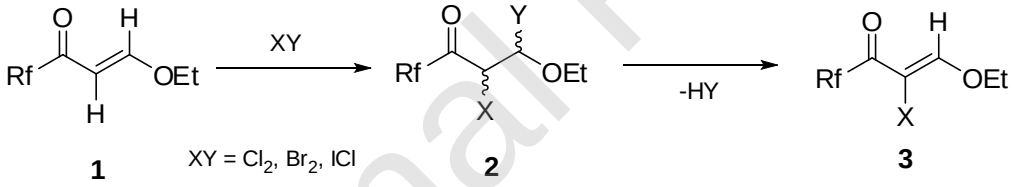


Fig. 1. Enones **A** are a synthetic equivalent of 1,3-ketoaldehydes **B**.

Although the first reactions of trifluoromethyl-containing enone **1** were published 30 years ago, but abiding interest to β-alkoxyvinylpolyhaloalkyl ketones compounds is not reduced due to their high functionality and attractive reactivity. We have modified this useful synthon by adding one more reaction center to obtain a series of α-halogen enones that generally have reactivity similar to starting enone **1** (Scheme 1) [15, 16].



Scheme 1. Halogenation of β-alkoxyvinylpolyhaloalkyl ketones **1**.

The presence of a halogen atom at the α-position gives more reaction opportunities for α-halogeno enones **3**, which are obviously impossible for enone **1**. Only α-Br, Cl, I derivatives [15-17] were synthesized, the literature contains no reports about the synthesis of α-F enones **3** (X=F). There are few reports about α-fluoro-β-alkoxyvinyl ketones showing that synthetic routes are unique for each compound. For example, 3-fluoro-4-methoxybut-3-en-2-one was obtained as a result of a rearrangement of gem-chlorofluorocyclopropanes under basic

conditions. 5-Fluorodioxinones were synthesized from readily available 1,3-dioxin-4-ones using molecular fluorine followed by treatment with an organic base in yields of 5% and 10%, respectively [18]. Introduction of the fluorine into α-position of enones **1** is difficult. It could be achieved by using molecular fluorine or other electrophilic fluorinating reagents. Reaction with molecular Fluorine is complicated and suffers difficulties of handling, therefore the development of new methods for the introduction of fluorine remains important. We have been studying the fluorination of β-alkoxyenones **1** with different fluoroalkyl groups using commercially available reagents such as: NFSI, Selectfluor®, XeF_2 with the aim to obtain α-fluoroenones and study their reactivity, as well.

2. Results and discussion

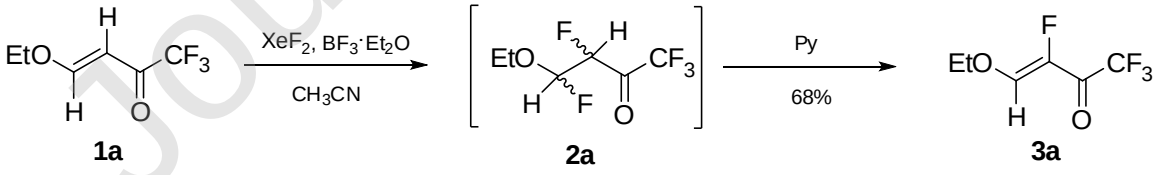
2.1. Synthesis of α-F enones

Elecrophilic halogenation of olefins is widely used for the synthesis of a variety useful vinyl halide building blocks and fluorine containing compounds, as well [19, 20]. Notable, fluorination of olefins is not convenient because of the high likelihood of polymerization. In order to achieve α-fluoroenones we used polyfluoroalkyl enones **1** as our starting materials which are push-pull compounds with highly polarized C=C double bond.

Our goal was to develop a convenient method for direct fluorination of enones **1**, as we previously have reported for the halogenation of enones **1** with Br_2, Cl_2 [15,16]. It could be easily achieved by using commercially available reagents: NFSI, Selectfluor® and XeF_2. We started our fluorination studies reacting enone **1a** with Selectfluor® in CH_2Cl_2 at room temperature. But this reagent as well, as NFSI in CH_3CN (the temperature was increased in some cases to 80 °C) did not lead to the respective difluorides or products with α-F-vinyl group. ^{19}F NMR data showed only the starting compound **1a** was recovered from the reaction mixtures.

Next, we investigated the reaction of trifluoromethyl enone **1a** with xenon difluoride. XeF_2 was first described in 1962 [21] and since then it has received wide attention as an "easy to handle" reagent for introduction of fluorine in to organic molecules instead of aggressive elemental fluorine [22]. Reactions of aliphatic alkenes with XeF_2 have been reported, especially with phenylalkenes [23]. Generally, complex reaction mixtures were formed containing, among others, germinal difluorides, along with lower amount of vicinal difluorides. As exceptions, individual examples showed formation of vicinal difluorides in high yields [24]. It is known that in the absence of catalyst reactions with XeF_2 are going slow or even not observed and depend on substituents on the C=C double bond and nature of the solvent [25].

We studied the reaction of enone **1a** with the XeF_2 in different conditions to achieve an efficient fluorination method. Various solvents (CH_3CN, CH_2Cl_2) were tested. We used HF, CF_3COOH as catalysts but did not receive the corresponding products. We choose $BF_3{\cdot}Et_2O$ as a catalyst because it was frequently used in fluorination reaction of alkenes and dienes [26], and it was effective. But the addition of a small amount of $BF_3{\cdot}Et_2O$ to the mixture of enone **1a** and XeF_2 in CH_2Cl_2 resulted a violent reaction with evolution of Xe gas and rapid reaction mixture heating. The complex mixture of products containing the corresponding difluoro ketone **2a** was obtained (by ^{19}F NMR) (Scheme 2).



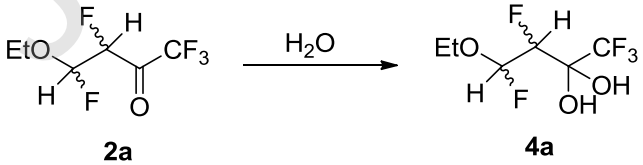
1a **2a** **3a**

Scheme 2. The fluorination of enone **1a** with XeF_2.

The reaction conditions were modified by optimizing the temperature (starting with −10 °C with a slow increase to room temperature), by using acetonitrile

instead of CH_2Cl_2 and addition of XeF_2 in small portions (to keep the temperature range from −10 to −5 °C). Under the optimized reaction conditions enone **1a** gives vic-difluoro ketones **2a** as a major products with 100% conversion. We also investigated the product formation and their conversion in the reaction mixture by integration of signals ratio to internal standard using ^{19}F NMR spectroscopy (the results are summarized in Table 1). Thus, to the mixture of enone **1a** in acetonitrile catalytic amount of $BF_3{\cdot}Et_2O$ and XeF_2 were added in portions at −10 °C. Each portion (0.25 eq.) was added after the end of gas evolution. In the ^{19}F NMR spectra two sets of dual signals at: −133.2 and −136.2 ppm (doublet of multiplets, EtOCHF, $^2J_{FH}$ ~62 Hz), and −210.7 and −213.1 ppm (doublet of multiplets, OC−CHF, $^2J_{FH}$ ~50 Hz) were observed corresponding to two diastereomeric vic-difluoroketones **2a** in a 55% to 45% ratio. The formation of the diastereomeric mixture is a result of both syn- and anti-addition of fluorine to the C=C double bond of (E)-enone **1a**. In comparison, the halogenation of enone **1a** with chlorine gives predominantly syn-adducts in a 80:20 ratio. Bromination gives anti-adducts in a 80:20 ratio, respectively [15].

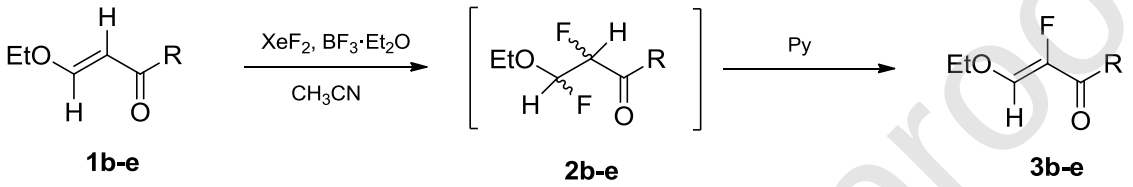
The ketones **2a** are rather unstable for being isolated in pure form in contrast to similar dibromo and dichloro ketones (which are more stable and can be isolated by vacuum distillation). Addition of one equivalent of water to difluoroketones **2a** gave hydrates **4a** with 100% conversion. Structure of hydrates **4a** was determined by ^{19}F NMR data: CF_3 groups have characteristic assignment at −82.68 and −84.51 ppm, respectively (Table 1, Entry 5) (Scheme 3) [27].



2a **4a**

Scheme 3. Formation of hydrates **4a**.

During the water work up and vacuum distillation of difluoroketons **2a** the partial HF elimination was observed with formation of the β-alkoxy-α-fluorovinyl trifluoromethyl ketone **3a** (Scheme 2). The elimination of HF is more effective in the presence of the base. Some bases (NEt_3, DBU, Py, and Hunig base) were tested. We found that pyridine is the most suitable base for HF elimination (Table 1, Entry 6) and under the protocol α-fluoroenone **3a** was obtained in gram quantity with 68% yield.



R = CF_2H (**b**); CF_2Cl (**c**); C_2F_5 (**d**); C_3F_7 (**e**)

Scheme 4. Fluorination of enones **1b-e** with XeF_2.

We applied the optimized procedure of the fluorination with XeF_2 to enones **1b-e** bearing different fluorocontaining groups (Scheme 4). The formation of corresponding ketones **2b-e** was detected by ^{19}F NMR without their isolation. Thus, the α-fluoropolyfluoromethyl-containing enone **3b** was isolated with 71% yield, and **3c** with 70%, respectively. Whereas enones **3d,e** were synthesized with low purity and low yield. Despite the formation of the diastereomeric mixture of intermediate difluoroketones **2** the final α-F-enones **3a-c** were obtained as a single Z-isomers regarding NMR data. Thus, α-fluorine of enone **3a** has characteristic coupling constant $^3J_{HF}$ = 19 Hz. We assigned the Z-configuration of the C=C double bond (trans-position between ethoxy and trifluoroacetyl groups) with two broad signals (with ratio 3:1) at −73.0 and −161.2 ppm (with a half-width 0.6 and 1.0 ppm) of CF_3 and =CF fragments in ^{19}F NMR, respectively. It is a result of restricted rotation around formally C−C single bond in the heterodiene system O=C–C=C.

Using NMR data of compound **3a** at low temperature (−22.3 °C) we assigned the separate signals of =CF and CF_3 groups of Z- and E-conformers which confirms our hypothesis (Fig. 2). At the same time the comparison of FTIR spectra (in CCl_4) of the previously studied enone **1a** [28] and α-fluoro containing enone **3a** demonstrates that **3a** also has three stereoisomeric structures. Characteristic vibrations of the carbonyl(C=O) and carbon-carbon double bond (C=C) for all three isomers were confirmed by FTIR data: E-s-Z-s-cis [ν(C=O) 1719 cm^{-1}, ν(C=C) 1594 cm^{-1}], E-s-E-s-cis [ν(C=O) 1714 cm^{-1}, ν(C=C) 1614 cm^{-1}] and E-s-E-s-trans [ν(C=O) 1698 cm^{-1}, ν(C=C) 1638 cm^{-1}]. Nevertheless, the ratio of isomers **1a** and α-fluoroenone **3a** is significantly different: cf. 4% (E-s-E-s-trans), 39% (E-s-E-s-cis), 57% (E-s-Z-s-cis) for **1a** and 36% (E-s-E-s-trans), 55% (E-s-E-s-cis), 9% (E-s-Z-s-cis) for **3a**. In the ^{19}F NMR spectra of α-fluoroenones **3b-g** all fluorine signals are also broad just like in enone **3a**. It is worth to mention that in the NMR data of the corresponding α-Cl- and α-Br-enones with CF_3-group, the broad signals of the CF_3-group were not observed, because of the bulkier chlorine and bromine atoms the rotation around C−C single bond is restricted.

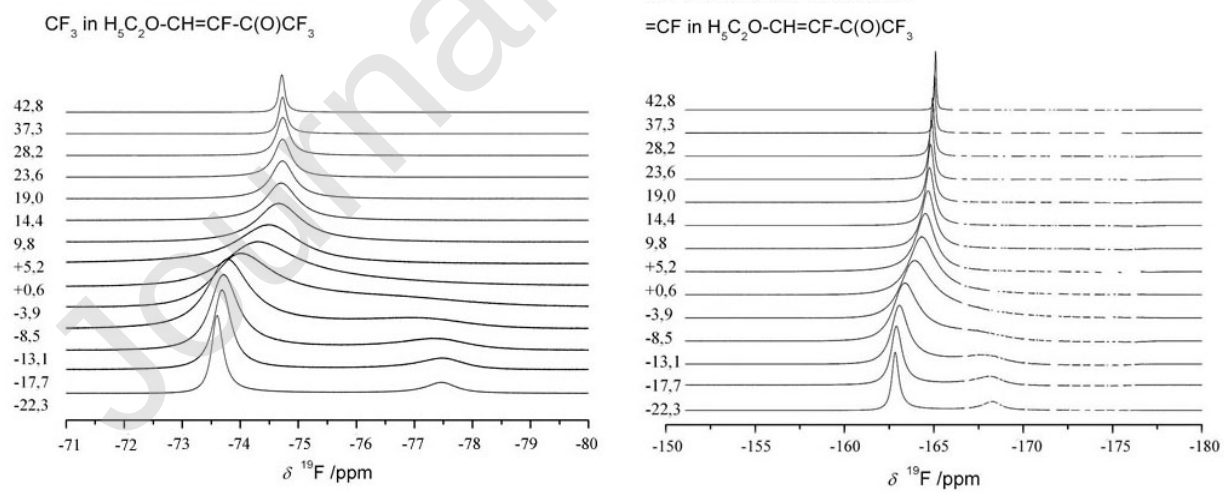
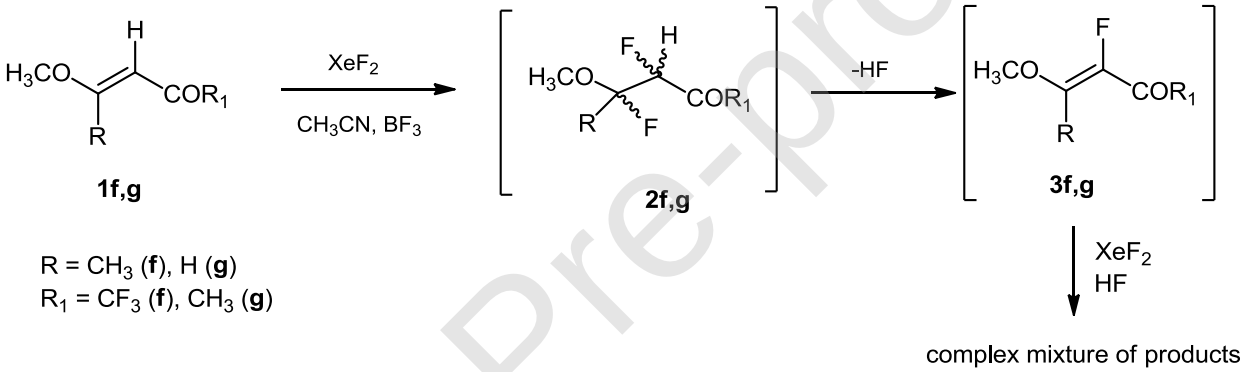


Fig. 2. Low temperature ^{19}F NMR spectra of 4-ethoxy-1,1,1,3-tetrafluorobut-3-en-2-one **3a**.

We observed the differences in the reaction of XeF_2 with trifluoromethylenone **1f**, containing a CH_3 group in β-position under the same reaction conditions. The reaction was started at −20 °C and ^{19}F NMR analysis of the reaction mixture showed very complex mixture of products. Obviously, difluoroketones **2f** are more unstable compared to all investigated difluoroketones **2a-e**, and partially HF elimination took place without base and gave the complex mixture of fluorinated products. About 17% of starting enone **1f** was left unreacted (Scheme 5).

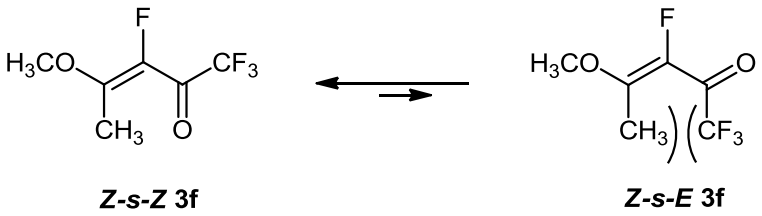


Scheme 5. Reaction of enones **1f,g** with XeF_2.

Since enones **3f,g** are involved into subsequent fluorination with XeF_2 and following HF release, the addition of base to the reaction mixture leads to formation of a complex mixture of products. The results of ^{19}F NMR study show that the reaction mixture contains compounds with CH_2F-group (product of fluorination of methyl group), as well as products with $CHF_2C{=}O$ fragment in their structures. Unfortunately, the corresponding products were detected only by NMR.

In contrast to enones **3a-c** the signals of $-CF_3$ and =CF groups of enone **3f** are sharp in ^{19}F NMR. This is a result of the rotation restriction between bulky methyl group at β-position and trifluoromethyl group, when rotation around single C=C−C=O bond is not possible. So, the most stable structure for α-fluoro-β-

methylenone **3f** is Z-s-Z configuration which confirms with F-F coupling constant 20 MHz (Fig. 3).



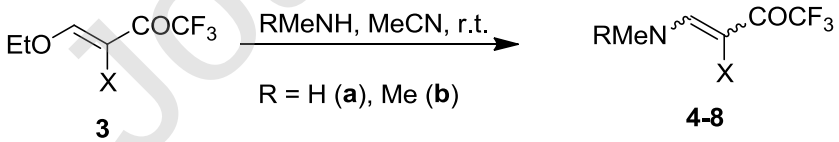
***Z-s-Z* 3f** ***Z-s-E* 3f**

Fig. 3. Two conformers of α-fluoro-β-methylenone **3f**

Both the polyfluoroalkyl chain length and the electrononegativity decrease of the C(=O)R acyl group lead to spontaneous HF elimination which gives complicated mixtures of products.

2.2. Synthesis of α-halogen containing enaminones

Previously we showed that α-halogen ketones **3** (where R=Cl, Br, I) easily react with methyl- or dimethylamines and give corresponding α-halogen enaminones [15]. As was mentioned above, there are three stereoisomeric forms of enone **3a**, each form having different reactivity. Detailed investigation of the stereochemistry of α-fluorine-β-N,N-dimethylaminovinyl trifluoromethyl ketones (Scheme 6) was done earlier [29, 30] and kinetic study of reaction of **3a** with amines is in progress and the results will be published later.



3 **4-8**

X = H (**4**), F (**5**), Cl (**6**), Br (**7**), I (**8**)

Scheme 6. Synthesis of α-halogen-containing enaminones **4-8**.

The presence of halogen atom in α-position of enone **3** leads to a number of significant changes in the stereochemistry of enaminones **5-7** in comparison to unsubstituted enaminon **4** (trans-position between amino and trifluoroacetyl groups). N,N-Dimethyl enaminones α-H, Cl, Br exist predominantly in a Z-configuration (trans-position between the trifluoroacetyl and amino groups) which was determined directly by IR and NMR spectra. Since the relatively small size difference between hydrogen and fluorine α-F enaminone **5b** also gives two conformers of Z-isomer: Z-s-Z and Z-s-E in equilibrium as α-H enaminone **4b** [13-15,29,30].

In order to evaluate the effect of α-substituents (H, F, Cl, Br) in N-monomethyl enaminones on their spatial forms, we synthesized α-F-substituted N-Me enaminone **5a**. Based on ^{19}F and ^{1}H NMR data enaminone **5a** exists as a mixture of 4 conformers (Fig. 4). The ratio of conformers slightly depends on the nature of the solvent: less polar ($CDCl_3$) or polar (DMSO-d_6). Two conformers have $^{4}J_{FF}$ = 5.7 Hz (Z-s-E and Z-s-Z), the other two (E-s-Z, E-s-E) have J_{FF} about 17 Hz. In the ^{1}H NMR spectra we observed different shifts for conformers with hydrogen bonding between C=O···HN-groups and with unbound NH group.

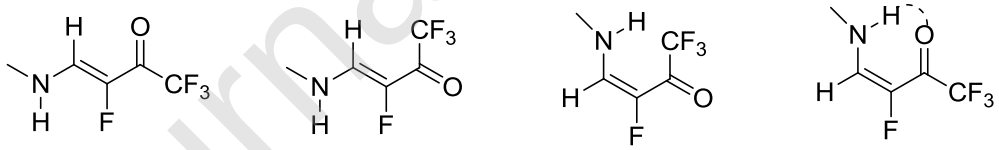
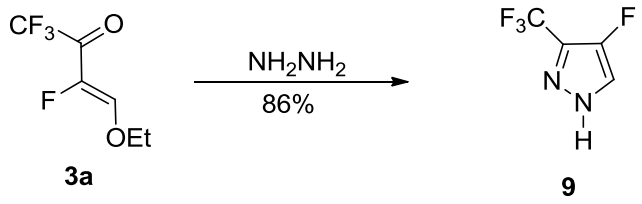


Fig. 4. Possible conformers of enaminone **5a**.

2.3. Synthesis of fluoro containing pyrazole and dihydropyranes

Pyrazoles attract biochemical community because some of them have a pesticide activity [31, 32]. Also 4-fluoropyrazole is a part of bioavailable Hsp90 inhibitors which displays a good efficacy in a melanoma A2058 tumor model [33].

However, the number of convenient methods to these compounds is limited mostly due to the difficulty of introducing a fluorine atom into heterocycles. That is why the synthesis of pyrazoles with different fluoro-containing groups is still of great interest, and new methods for preparing pyrazoles are required [34]. Thus, the condensation of α-fluoro-β-ethoxytrifluoromethyl enone **3a** with $N_2H_4 \cdot H_2O$ gives F- and CF_3-substituted pyrazole **9** with a high yield (Scheme 7).



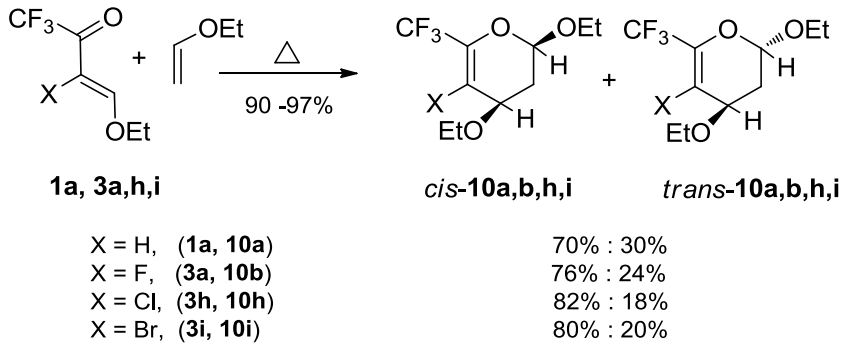
3a **9**

Scheme 7. Synthesis of pyrazole **9**.

Fluorinated carbohydrates play an important role in organic chemistry. They increase the bioavailability of drugs. In this context, the carbohydrate units are good components for synthesis of bioactive analogs. One of the most suitable methods to obtain dihydropyrans is [4+2] hetero Diels-Alder reaction [35-38]. Dihydropyrans are a key intermediates in the synthesis of carbohydrates [39,40] which are the part of bioactive compounds with antitumor activity [40], also they are a fragments of macrolides antibiotics and a cardiac glycoside digitoxin [41]. The synthesis of carbohydrates which contain not only trifluoromethyl group but also Halogen atom is a very attractive way of developing new routes to bioactive compounds.

With the aim to obtain new fluorinated dihydropyranes and to compare the reactivity of trifluoromethyl enone **1a** with α-halogeno-substituted enones **3a,h,i** [4+2] Diels-Alder approach was used. The first reaction with enone **1a**, as a precursor for the dihydropyrans synthesis, was performed at similar conditions

more than 30 years ago [37,38]. α-Halogenoenones **3** react with vinyl ether and give the corresponding dihydropyrans **10** in a very good yields (Scheme 8).



Scheme 8. [4+2] Hetero Diels-Alder reaction of enones with vinyl ether.

[4+2] Hetero Diels-Alder reaction of enones **1a** and **3a,h,i** with vinyl ethers and a small amount of hydroquinone was run at 80 °C for 24-30 hrs and 2,4-disubstituted-5-(hydrogen,halogen)-6-(trifluoromethyl)-3,4-dihydro-2H-pyranes **10** were obtained [38]. α-Halogen enones contain some insignificant amount of acid after prolonged storing. Therefore freshly distilled enone was used or a small amount of Et_3N was added to prevent the polymerization of the vinyl ether. In the cycloaddition we observed a stereoselective reaction for enone **1a** and for **3a,h,i**. Unsubstituted enone **1a** gave a mixture of diastereomeric adducts **10a** in a 70:30 ratio with δ_F = –73.51 and –73.45 respectively. The diastereoselectivity of cycloadditions was estimated by ^1H and ^{19}F NMR data of the crude product mixtures. Using literature data (both chemical shifts of characteristic protons and constants, and CF_3 group shifts) for adducts **10a** we assigned the cis-configuration for predominant diastereomers **10b,h,i** [36,40]. The diastereomeric ratio is 76:24 for **10b** (X = F), 82:18 for **10h** (X = Cl), 80:20 for **10i** (X = Br).

3. Conclusions

The fluorination of readily available polyfluoroalkyl enones **1** using XeF_2 and $BF_3 \cdot Et_2O$ as a catalyst, gives the vic-difluoro ketones. α-Fluoroenones **3** can be

obtained as a Z-isomers under further dehydrofluorination with pyridine as a base. The yield of α-fluoroenones **3** strongly depends from the nature of R_fCO group or substituents in β-position of enone **1**. New fluoro containing enaminones **4,5** and pyrazole **9** were obtained from α-fluoroenones **3**. Also α-fluoroenones **3** are a useful dienophiles in [4+2] hetero Diels-Alder cycloaddition and it is a convenient route to synthesis of fluorinated hexose.

4. Experimental

4.1. General

All reagents were commercially available and used as received. Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Merck, Fluka, and Enamine. Melting points are uncorrected. Characterization of intermediates and final compounds was done by ^{1}H, ^{13}C, ^{19}F NMR and IR spectroscopies. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on Varian VXR at 300 MHz, Varian Unity Plus at 400 MHz and Bruker DRX-500 at 25 °C. Low temperature NMR spectra of enone **3a** were recorded on Varian Unity Plus at 500 MHz. Chemical shifts are reported in ppm from TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR), coupling constants are in Hz. Multiplicity is: (s) for singlet, (br.s) for broad singlet, (d) for doublet, (t) for triplet, (q) for quartet, (dd) for doublet of doublets, and (m) for multiplet. Infrared spectra were recorded on a Bruker Vertex 70 FTIR spectrometer with KBr beamsplitter and RT-DLaTGS detector at ambient temperature (20±1 °C). The progress of reactions was monitored by using TLC (silica gel 60 F254, Merck). The purification by column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm).

4.2. Experimental procedures

4.2.1. General procedure for α-fluoroenones (**3a-c**) synthesis

To a 50 mL round-bottom flask under argon 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **1a** (8.2 g, 48.8 mmol) in dry acetonitrile (20 mL) and $BF_3 \cdot Et_2O$ (50 mg) were added. To the stirring solution the xenon difluoride (8.42 g, 49.8 mmol) was added in portions to keep the reaction temperature at -10 to -5°C. After the completion of the gas evolution the pyridine (3.86 g, 49.8 mmol) was added at 0°C. Reaction mixture was poured in 50 mL of dichloromethane and washed with 30 mL of 5% water solution of citric acid and 2×30 mL of H_2O. Organic layer was separated and dried with sodium sulfate. Dry solution was filtered and the solvent was removed under reduced pressure. The residue was purified by vacuum distillation (10 mm Hg) to give **3a**.

4.2.1.1. 4-Ethoxy-1,1,1,3-tetrafluorobut-3-en-2-one (**3a**). Pale yellow oil, yield 68% (6.17 g), bp = 62 °C (10 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (t, 3H, J = 7.1 Hz, CH_3), 4.26 (q, 2H, J = 7.1 Hz, CH_2), 7.24 (d, J = 19.2 Hz, 1H, OCH=); ^{19}F NMR (376 MHz, $CDCl_3$): δ –73.49 (br. s, 3F, CF_3), –162.08 (br. s, 1F, =CF); ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.1, 73.2, 116.1 (qd, $^1J_{CF}$ = 289.2 Hz, $^3J_{CF}$ = 2.0 Hz, CF_3), 140.3 (d, $^1J_{CF}$ = 244.4 Hz, =CF), 148.9, 172.8 (dq, $^2J_{CF}$ = 37.0 Hz, $^2J_{CF}$ = 23.0 Hz, CO). Anal.calcd. for $C_6H_6F_4O_2$: C, 38.72; H, 3.25; found: C, 38.45; H, 3.32.

4.2.1.2. 4-Ethoxy-1,1,3-trifluorobut-3-en-2-one (**3b**). Pale yellow oil, yield 68% (2.7 g), bp = 75 °C (10 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (t, 3H, J = 7.1 Hz, CH_3), 4.26 (q, 2H, J = 7.1 Hz, CH_2), 6.03 (t, $^2J_{HF}$ = 56.3 Hz, CHF_2), 7.3 (d, $^3J_{HF}$ = 20 Hz, 1H, OCH=); ^{19}F NMR (376 MHz, $CDCl_3$): –123.41 (br. s, 2F, CF_2H), –161.33 (br. s, 1F, =CF) Anal. calcd. for $C_6H_7F_3O_2$: C, 42.87; H, 4.20; found: C, 42.98; H, 4.27;

4.2.1.3. 1-Chloro-4-ethoxy-1,1,3-trifluorobut-3-en-2-one (**3c**). Pale yellow oil, yield 70% (3.9 g), bp = 74° C (0.5 mm.Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (t,

3H, J = 7.1 Hz, CH_3), 4.29 (q, 2H, J = 7.1 Hz, CH_2), 7.31 (d, $^3J_{HF}$ = 19 Hz, 1H, OCH=); ^{19}F NMR (376 MHz, $CDCl_3$): δ –63.46 (br. s, 2F, CF_2Cl), –160.45 (br. s, 1F, =CF). Anal. calcd. for $C_6H_6ClF_3O_2$: C, 35.58; H, 2.89; found: C, 35.42; H, 3.02.

4.2.2 General procedure for enamonones (**4-8**) synthesis [15]

4.2.2.1. 1,1,1,3-Tetrafluoro-4-(methylamino)but-3-en-2-one (**5a**) crystals, yield 85%, (0.96 g), mp = 83-85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (m, 3H), 5.58 (br. s, 0.16H, NH), 5.86 (br. s, 0.7H, NH), 7.20 (dd, 0.68H, $^3J_{HH}$ = 13.7 Hz, $^3J_{HF}$ = 23.3 Hz, OCH=), 7.32 (dd, 0.32H, $^3J_{HH}$ = 10.7 Hz, $^3J_{HF}$ = 13.5 Hz, OCH=), 8.79 (br. s, 0.14H, NH); ^{19}F NMR (376 MHz, $CDCl_3$, {H}): δ –69.28 (br. m, 0.04F), –69.79 (br. d, $^4J_{FF}$ = 6.3 Hz, 1.95F, CF_3), –75.49 (d, 0.55F, $^4J_{FF}$ = 16.9 Hz, CF_3), –75.68 (br. d, 0.46F, $^4J_{FF}$ = 16.3 Hz, CF_3), –169.14 (q, 0.64F, $^4J_{FF}$ = 6.5 Hz, =CF), –170.79 (br. m, 0.04F, =CF), –179.08 (q, 0.18F, $^4J_{FF}$ = 16.5 Hz, =CF), –186.64 (q, 0.14F, $^4J_{FF}$ = 17.0 Hz, =CF). Anal. calcd. for $C_5H_5F_4NO$: C, 35.10; H, 2.95; N, 8.19; found: C, 35.42; H, 3.01; N, 8.01.

4.2.2.2 4-(Dimethylamino)-1,1,1,3-tetrafluorobut-3-en-2-one (**5b**) [29]

Pale yellow oil, yield 76% (0.8 g), bp = 71°C (1 mm).

4.2.3 4-Fluoro-3-(trifluoromethyl)-1H-pyrazole (**9**)

To the stirred solution of H_2SO_4 (1.32 g, 13.43 mmol) in toluene (5 mL) the hydrazine hydrate (134.5 mg, 2.69 mmol) and 4-ethoxy-1,1,1,3-tetrafluorobut-3-en-2-one (**3a**) (500 mg, 2.69 mmol) were added at 0 °C. The mixture was heated and stirred for 24 h at 80 °C. Then the reaction mixture was cooled to rt and treated with aq. KOH solution (0.84 g, 15 mmol). CH_2Cl_2 (20 mL) was added and the organic layer was separated and washed with water (2x15 mL). The solvent was evaporated under reduced pressure and residue was crystallized from hexane to give 355.9 mg of **9**. Pale yellow crystals, yield 86%, mp = 89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (br. d, 1H, $^3J_{HF}$ = 4.4 Hz, CH), 10.87 (br. s. 1H, NH); ^{19}F

NMR (376 MHz, $CDCl_3$, {H}): –62.02 (d, 3F, J_{FF} = 6.6 Hz, CF_3), –174.60 (q, 1F, $^4J_{FF}$ = 6.6 Hz, CF); ^{13}C NMR (126 MHz, $CDCl_3$): δ 116.5 (d, $^2J_{CF}$ = 25.6 Hz, CH), 119.9 (qd, $^1J_{CF}$ = 268.6 Hz, $^3J_{CF}$ = 3.4 Hz, CF_3), 128.6 10/2(qq, $^2J_{CF}$ = 38.8 Hz, $^2J_{CF}$ = 10.2 Hz, C-CF_3), 145.7 (br. d, ^1J = 254.6 Hz, CF). Anal. calcd. for $C_4H_2F_4N_2$: C, 31.18; H, 1.31; N, 18.18; found: C, 31.38; H, 1.61; N, 18.16.

4.2.4. General procedure for dihydropyranes (**10**) synthesis

The mixture of enone **3** (2.5 mmol), ethylvinyl ether (7.5 mmol), trimethylamine (0.15 mmol) and hydrohinone (0.15 mmol) was heated in closed pressure tube for 24 h at 70 °C in argon atmosphere. The reaction was monitored by GLC. Then the reaction mixture was cooled to rt and hexane (25 mL) was added. The solution was filtered and the filtrate was evaporated under reduced pressure.

4.2.4.1. 2,4-Diethoxy-5-fluoro-6-(trifluoromethyl)-3,4-dihydro-2H-pyran (**10b**)

Colorless oil, yield of crude product 78% (0.5 g), yield after column chromatography 65% (0.42 g) (eluents Hexane : EtOAc 6:1), major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (t, J = 7 Hz, 6H, $2CH_3$), 2.14 (m, 1H, CH_2), 2.28 (m, 1H, CH_2), 3.59 (m, 1H, CH_2), 3.65 (m, 2H, OCH_2), 3.84 (m, 1H, CH_2), 4.14 (br.t. 1H, J = 7.2 Hz, CH), 5.12 (s, 1H, CH); ^{19}F NMR (376 MHz, $CDCl_3$, {H}): –68.01 (d, J_{FF} = 23.7 Hz, 3F, CF_3), – 147.10 (qt, J_{FF} = 23.6 and 4.2 Hz, 1F, CF); minor diastereomer ^{19}F NMR (376 MHz, $CDCl_3$, {H}): – 68.10 (d, J_{FF} = 22.9 Hz, 3F, CF_3), – 149.39 (qt, J_{FF} = 23.3 and 3.7 Hz, 1F, CF);

4.2.4.2. 5-Chloro-2,4-diethoxy-6-(trifluoromethyl)-3,4-dihydro-2H-pyran (**10h**)

Yield of crude product 97% (0.66 g), yield after distillation 67% (0.46 g), bp = 84 °C (0.5 mm.Hg); major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.0 Hz, 3H, CH_3) 1.26 (t, J = 7.0 Hz, 3H, CH_3), 2.26 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 3.65 (m, 3H, OCH_2), 4.01 (m, 1H, CH), 5.21 (dd, ^{1}J = 3.0 Hz, ^{2}J = 4.5 Hz, 1H, CH); ^{19}F NMR (282 MHz, $CDCl_3$): –66.96 (s, 3F, CF_3); minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.0 Hz, 3H, CH_3) 1.26 (t, J = 7.0 Hz,

3H, CH_3), 2.10 (m, 1H, CH_2), 2.22 (m, 1H, CH_2), 3.91 (m, 3H, OCH_2), 3.99 (m, 1H, CH), 5.11 (dd, ^1J = 2.3 Hz, ^2J = 7.8 Hz, 1H, CH); ^{19}F NMR (282 MHz, $CDCl_3$): –67.14 (s, 3F, CF_3).

4.2.4.3. 5-Bromo-2,4-diethoxy-6-(trifluoromethyl)-3,4-dihydro-2H-pyran (**13i**)

Yield of crude product 93% (0.74 g), yield after distillation 60% (0.48 g), bp = 94 °C (0.5 mm.Hg); major diastereomer: ^1H NMR (400 MHz, $CDCl_3$): 1.24 (m, 6H, $2CH_3$), 2.11 (m, 1H, CH_2), 2.28 (m, 1H, CH_2), 3.63 (m, 3H, OCH_2), 3.88 (m, 1H, OCH_2), 4.04 (m, 1H, CH), 5.24 (m, 1H, CH); ^{19}F NMR (282 MHz, $CDCl_3$): –66.80 (s, 3F, CF_3); minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$): 1.24 (m, 6H, $2CH_3$), 2.11 (m, 1H, CH_2), 2.28 (m, 1H, CH_2), 3.66 (m, 3H, OCH_2), 3.88 (m, 1H, OCH_2), 4.04 (m, 1H, CH), 5.12 (m, 1H, CH); ^{19}F NMR (282 MHz, $CDCl_3$): –66.97 (s, 3F, CF_3).

Acknowledgments Financial support by the Deutsche Forschungsgemeinschaft Grant 436 UKR 113/101/0 is gratefully acknowledged.

References

1. T. Liang, C.N. Neumann, T. Ritter, Introduction of fluorine and fluorine-containing functional groups. Angew. Chem. Int. Ed Engl, 52 (2013) 8214-8264.
2. I. Ojima, Use of fluorine in the medicinal chemistry and chemical biology of bioactive compounds--a case study on fluorinated taxane anticancer agents. Chembiochem, 5 (2004) 628-35.
3. D. O'Hagan, Understanding organofluorine chemistry. An introduction to the C–F bond. Chem. Soc. Rev. 37 (2008) 308-319.
4. S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry. Chem. Soc. Rev, 37 (2008) 320-330.
5. K.L. Kirk, Selective fluorination in drug design and development: an overview of biochemical rationales, Curr Top Med Chem. 6 (2006) 1447-56.
6. P. Jeschke, The unique role of fluorine in the design of active ingredients for modern crop protection, Chembiochem 5 (2004) 571-89.
7. S.M. Ametamey, M. Honer, P.A. Schubiger, Molecular imaging with PET. Chem Rev. 108 (2008) 1501-1516.
8. R. Littich, P.J.H. Scott, Novel strategies for fluorine-18 radiochemistry, Angew. Chem. Int. Ed. 49 (2010) 6821-6824.
9. I.I. Gerus, N.A. Tolmachova, S.I. Vdovenko, R. Fröhlich, A Convenient Synthesis and Chemical Properties of 3-Acylamino-6-poly-fluoroalkyl-2H-pyran-2-ones. Synthesis 08 (2005) 1269-1278.
10. I.S. Kondratov, I.I. Gerus, V.P. Kukhar, O.V. Manoilenko, New synthetic approach to mevalonate and mevaldate fluoroanalogues. Tetrahedron: Asymmetry. 18 (2007) 1918-1925.
11. S.I. Vdovenko, I.I. Gerus, V.P. Kukhar, Solvent effects on the infrared spectra of beta-alkoxyvinyl methyl ketones I. Carbonyl and vinyl stretching vibrations. Spectrochim Acta A Mol Biomol Spectrosc, 71 (2008) 779-85.
12. I.I. Gerus, M.G. Gorbunova, V.P. Kukhar, β-Ethoxyvinyl polyfluoroalkyl ketones — versatile synthones in fluoroorganic chemistry. J. Fluorine Chem. 69 (1994) 195-198.
13. I.I. Gerus, R. V. Mironets, E. N. Shaitanova, V.P. Kukhar, Synthesis of new β-trifluoromethyl containing GABA and β-fluoromethyl containing N-benzylpyrrolidinones. J. Fluorine Chem. 131 (2010) 224-228.
14. M.G. Gorbunova, I.I. Gerus, V.P. Kukhar, Synthesis and Properties of β-Ethoxyvinyl Polyfluoroalkyl Ketones. Synthesis 5 (2000) 738-742.
15. I.I. Gerus, L.M. Kacharova, S.I. Vdovenko, Halogenation of β-Alkoxyvinyl Polyhaloalkyl Ketones: A Convenient Route for the Synthesis of α-Chloro- or α-Bromo-β-alkoxyvinyl Polyhaloalkyl Ketones. Synthesis 03 (2001) 0431-0436.
16. L.A Kacharova,. A.D Kacharov, I. I. Gerus, Synthesis and Properties of α-Iodo-β-ethoxyvinyl Trifluoromethyl Ketone. J. Fluorine Chem. 111 (2001) 29-31.
17. L.M. Kacharova, I.I. Gerus, A.D. Kacharov, Reaction of α-halogen substituted β-ethoxyvinyl trifluoromethyl ketones with 2-aminopyridine: new route to trifluoroacetyl-containing heterocycles. J. Fluorine Chem. 117 (2002) 193-197.
18. T. Iwaoka, T. Murohashi, M. Sato, C. Kaneko, Synthesis of 5-Fluoro-1,3-dioxin-4-ones: Novel Alternatives to α-Fluorinated Acyl Ketenes. Synthesis 10 (1992) 977-981.
19. G.S. Lal, G.P. Pez, R.G. Syvret, Electrophilic NF Fluorinating Agents. Chem. Rev. 96 (1996) 1737-1756.

20. X. Yang, T. Wu, R.J. Phipps, F.D. Toste, Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. Chem. Rev. 115 (2) (2015) 826-870.
21. H.H. Claassen, H. Selig, J.G. Malm, Xenon Tetrafluoride. J. Am. Chem. Soc. 84 (18) (1962) 3593-3593.
22. K.K. Laali, Advances in Organic Synthesis: Modern Organofluorine Chemistry Synthetic Aspects. Vol 2. (2006) DOI: 10.2174/97816080519841060201.
23. M. Constantinou, F. I. Aigbirhio, R. G. Smith, C. A. Ramsden, V. W. Pike, Xenon Difluoride Exchanges Fluoride under Mild Conditions: A Simple Preparation of [^{18}F]Xenon Difluoride for PET and Mechanistic Studies. J. Am. Chem. Soc. 123 (2001) 1780–1781.
24. N. Vasdev, B. E. Pointner, R. Chirakal, G. J. Schrobilgen, On The Preparation of Fluorine-18 Labelled XeF_2 and Chemical Exchange between Fluoride Ion and XeF_2. J. Am. Chem. Soc. 124 (2002) 12863–12868.
25. R. Chirakal, G. Firnau, G.G. J. Schrobilgen, J. McKay, E.S. Guarnett, The synthesis of [^{18}F]xenon difluoride from [^{18}F]fluorine gas. Int. J. Appl. Radiat. Isot. 35 (1984) 401-404.
26. S. Sood, G. Firnau, E. S. Garnett, Radiofluorination with xenon difluoride: a new high yield synthesis of [^{18}F[2-fluoro-2-deoxy-D-glucose. Int. J. Appl. Radiat. Isot. 34 (1983) 743-745.
27. I.S. Kondratov, I.I. Gerus, A.D. Kacharov, M.G. Gorbunova, V.P. Kukhar, R. Frölich, New derivatives of trifluoroacetyl acetaldehyde and trifluoroaldol. J. Fluorine. Chem. 126 (2005) 541-548.
28. S.I. Vdovenko, I.I. Gerus, N.V. Lutenko, V.P. Kukhar, J. Wójcik, J. Spatial structure of β-substituted alkoxyvinyl trifluoromethyl ketones. J Mol Struct. 840 (2007) 125-132
29. S.I. Vdovenko, I.I. Gerus, M. Pagacz-Kostrzewa, M. Wierzejewska, Y.I. Zhuk, V.P. Kukhar. Special feature of kinetics of ZcE isomerization of β-N-methylaminovinyl trifluoromethyl ketone in Ar matrix exposed to UV radiation and spontaneous E⇌Z isomerization of α-methyl-β-N-methylaminovinyl trifluoromethyl ketone. Spectrochim. Acta Part A, 199 (2018) 130-140.
30. S.I. Vdovenko, I.I. Gerus, Y.I. Zhuk, V.P. Kukhar, G.V. Röschenthaler. The conformational analysis of push-pull enaminones using Fourier transform IR and NMR spectroscopy, and quantum chemical calculations. V. alpha-Methyl-, fluorine-beta-N,N-dimethylaminovinyl trifluoromethyl ketones. Spectrochim Acta Part A. 131 (2014) 94-101.
31. K. Gunjima. Substituted pyrazole-containing compounds and their use as pesticides, B. SE, Editor. BASF SE WO2013/164295.
32. P. Jeschke, Latest generation of halogen-containing pesticides. Pest Management Science 73 (2017) 1053-1066.
33. L. Zehnder, Optimization of Potent, Selective, and Orally Bioavailable Pyrrolodinopyrimidine-Containing Inhibitors of Heat Shock Protein 90. Identification of Development Candidate 2-Amino-4-{4-chloro-2-[2-(4-fluoro-1H-pyrazol-1-yl)ethoxy]-6-methylphenyl}-N-(2,2-difluoropropyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide. J. Med. Chem. 54(9) (2011) 3368-3385.
34. J. C. Sloop, C. L. Bumgardner, W. D. Loehle, Synthesis of fluorinated heterocycles. J. Fluorine Chem. 118 (2002) 135-147.

35. A. Kirschning, M. Jesberger, K.-U. Schöning. Concepts for the Total Synthesis of Deoxy Sugars. Synthesis 04 (2001) 0507-0540.
36. C.M. Hayman, D.S. Larsen, S. Brooker, A Facile Synthesis of 2,6-Dideoxy 6,6,6-Trifluorinated Carbohydrate Analogues. Aust. J. Chem. 51 (1998) 545-554.
37. M. Hojo, R. Masuda, E. Okada, A Convenient Synthetic Route to Functionalized 5-Trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2H-pyrans: Hetero-Diels-Alder Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers with Electron-Rich Alkenes. Synthesis, (04) (1990) 347-350.
38. N. Ota, Y. Kamitori, D. Shibata, E. Okada, Hetero Diels-Alder reaction of β-trifluoroacetylated vinyl ethers with vinyl ethers to access fluorine-containing dihydropyran deravatives- a molecular orbital calculation study. Heterocycles 80 (2010) 329-338.
39. P. Czodrowski, A. Mallinger, D. Wienke,C. Esdar, O. Pöschke, M. Busch, F. Rohdich, S.A. Eccles, M. Ortiz-Ruiz, R. Schneider, F.I. Raynaud, P.A. Clarke, D. Musil, D. Schwarz, T. Dale, K. Urbahns, J. Blagg, K. Schiemann, Structure-Based Optimization of Potent, Selective, and Orally Bioavailable CDK8 Inhibitors Discovered by High-Throughput Screening. J. Med. Chem. 59 (2016) 9337-9349.
40. C.M. Hayman, L. R. Hanton, D. S. Larsen, J. M. Guthrie A stereoselective synthesis of 2,6-Dideoxy-6,6,6-trifluoro-arabino-hexoses via an asymmetric Diels-Alder strategy. Aust. J. Chem. 52 (1999) 921-927.
41. M. Zhou, G.A. O'Doherty, De novo Approach to 2-Deoxy-β-glycosides: asymmetric syntheses of digoxose and digitoxin J. Org. Chem. 72 (2007) 2485-2493.

Table 1. Products ratio in the reaction of enone **1a** with XeF_2 by ^{19}F NMR data.

Entry	Reagents	Ratio of the products (%)[a]			
		1a	**2a**	**3a**	**4a**
1	Starting point[b]	100	-	-	-
2	0.25 eq XeF_2	74	11	15	
3	0.5 eq XeF_2	45	19	28	
4	1 eq XeF_2	10	80	10	
5	1eq H_2O				100
6	1 eq Py			100	

[a] by ^{19}F NMR, as internal standard 1 equivalents of C_6F_6 was used;
[b] 50 mg (0.27 mmol) **1a**, 4 mg $BF_3 \cdot Et_2O$ in CH_3CN 1mL.