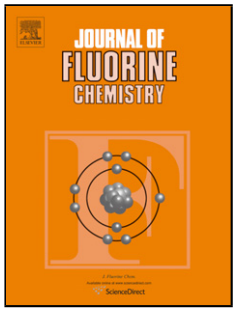


Title: Metal free electrophilic fluoro-cyclization of unsaturated N-hydroxy- and N-acetoxyamides with N-F reagents

Author: Lyudmila F. Lourie Yurii A. Serguchev Anton V. Bentya Maxim V. Ponomarenko Eduard B. Rusanov Michail V. Vovk Andrey A. Fokin Nikolai V. Ignat'ev

PII: S0022-1139(15)00117-7
DOI: http://dx.doi.org/doi:10.1016/j.jfluchem.2015.04.011
Reference: FLUOR 8549

To appear in: *FLUOR*

Received date: 25-1-2015
Revised date: 9-4-2015
Accepted date: 14-4-2015

Please cite this article as: L.F. Lourie, Y.A. Serguchev, A.V. Bentya, M.V. Ponomarenko, E.B. Rusanov, M.V. Vovk, A.A. Fokin, N.V. Ignat'ev, Metal free electrophilic fluoro-cyclization of unsaturated N-hydroxy- and N-acetoxyamides with N-F reagents, *Journal of Fluorine Chemistry* (2015), http://dx.doi.org/10.1016/j.jfluchem.2015.04.011

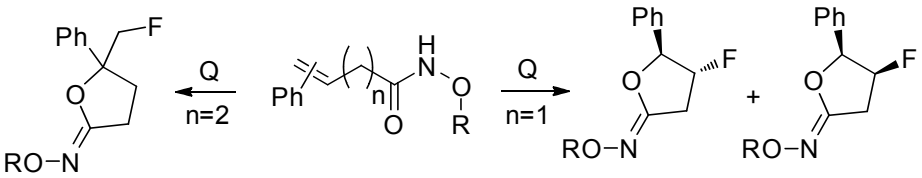
Highlights

1. Metal-free electrophilic fluoro-cyclizations of the unsaturated *N*-hydroxy- and *N*-acetoxyamides leads to cyclic imidates

2. The stereoselectivity of fluoro-cyclization depends on the fluorinating reagent and solvent

3. F-TEDA-FAP provides better stereoselectivity

Graphical Abstract



Q = F-TEDA-BF_4 or F-TEDA-FAP R = H, $C(O)CH_3$

Graphical Abstract (synopsis)

Metal-free electrophilic fluoro-cyclizations unsaturated *N*-hydroxy- and *N*-acetoxyamides under action of the 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate) (F-TEDA-BF_4) and F-TEDA-FAP (FAP = $[(C_2F_5)_3PF_3]^-$) were studied in organic solvents and ionic liquid 1-ethyl-3-methylimidazolium triflate.

Metal free electrophilic fluoro-cyclization of unsaturated N-hydroxy- and N-acetoxyamides with N-F reagents

Lyudmila F. Lourie[a], Yurii A. Serguchev[a*], Anton V. Bentya[a], Maxim V. Ponomarenko[a,b], Eduard B. Rusanov[a], Michail V. Vovk[a], Andrey A. Fokin[c], Nikolai V. Ignat'ev[d*]

[a]Institute of Organic Chemistry, National Academy of Sciences of Ukraine,5 Murmanskaya Str.,02094 Kiev, Ukraine; serguch@gmail.com
[b]School of Engineering and Science, Jacobs University Bremen gGmbH, Campus Ring 1, 28759 Bremen, Germany
[c]Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy 37,03056 Kiev, Ukraine
[d]Merck KGaA, PM-APR-FT, Frankfurter Str. 250, D-64271 Darmstadt, Germany; nikolai.ignatiev@merckgroup.com; ignatiev@web.de

Dedicated to Professor Veronique Gouverneur of Oxford University, winner of the 2015 ACS Award for Creative Work in Fluorine Chemistry

Keywords: Electrophilic fluoro-cyclization; Cyclic imidates; F-TEDA-FAP; Stereoselectivity

Abstract

Metal-free electrophilic fluoro-cyclizations of the respective unsaturated *N*-hydroxy- and *N*-acetoxy-amides under action of the 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4; trade name Selectfluor^{TM}) and F-TEDA-FAP (FAP = $[(C_2F_5)_3PF_3]^-$) were carried out in organic solvents and ionic liquid 1-ethyl-3-methylimidazolium triflate. The fluoro-cyclization of *trans*-N-acetoxy-4-phenylbut-3-enamide (**1**), *trans*-N-hydroxy-4-phenylbut-3-enamide (**2**), N-hydroxy-4-phenylpent-4-enamide (**3**) and N-acetoxy-4-phenylpent-4-enamide (**4**) results in the formation of cyclic imidates. The influence of the nature of fluorinating reagent and solvent on the stereoselectivity of fluoro-cyclization is discussed.

1. Introduction

Organofluorine compounds are of interest for development of new agrochemicals and pharmaceuticals. Introduction of fluorine or fluorinated moieties often positively influences the properties of biologically active substances. By this reason, the development of convenient protocols to prepare the fluorinated compounds is of great importance [1-5]. In particular, the fluorinated heterocyclic building blocks are on demand.

Electrophilic halo-cyclization of unsaturated carboxylic acids and their derivatives with chlorine, bromine, iodine or halo-reagents as electrophiles is a useful methodology for preparation of a variety of functionalized lactons, lactams, oxazolines and cyclic amides, which are valuable synthones for natural products syntheses [6-8]. The electrophilic cyclization of unsaturated *N*-hydroxy- and *N*-oxyamides (hydroxamic acids and *O*-acyl hydroxamates) displays a straightforward protocol for the preparation of various *β*-lactam

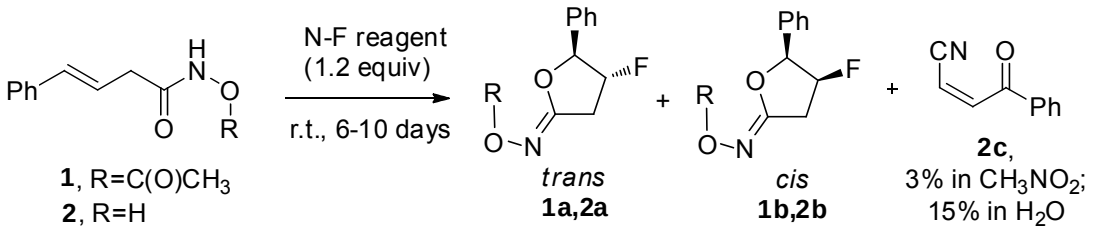
antibiotic analogues and antibacterial remedies [9-15]. The important entity in the structure of these compounds is the *β*-lactam moiety. Such kind of *β*-lactams were prepared by the electrophilic cyclization of *β,γ*-unsaturated hydroxamic acids and *O*-acyl hydroxamates with bromine [16-18] or *N*-bromosuccinimide [19, 20]. The cyclic imidates are formed as a major product in the reaction of *γ*-phenyl-*β*,*γ*-unsaturated hydroxamates with bis(collidine)bromine(I) hexafluorophosphate [21]. However, the use of organoselenium reagents instead of bromine for cyclization of *β,γ*-unsaturated hydroxamic acids resulted in the formation of *N*-hydroxy γ-lactams or/and cyclic imidates depending on the substituents attached to the double bond [22]. These results show that the course of cyclization is strongly depended on the nature of electrophilic reagents and reaction conditions. To our best knowledge, the metal-free electrophilic fluoro-cyclization of unsaturated hydroxyamides is not described in the literature.

The fluoro-cyclization of N-arylpent-4-enamides to 5-fluoromethyl-substituted *γ*-lactams in aqueous media under action of $AgNO_3$ and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4, Selectfluor^{TM}) was recently reported [23]. Reaction proceeds presumably through the radical mechanism where F-TEDA-BF_4 serves as fluorine source to generate *in situ* the silver fluoride species acting as fluorinating reagent [23]. Iron(II)-catalyzed fluoroamination of functionalized hydroxylamines in the presence of Et_3N-HF was also described [24]. This reaction proceeds stepwise and includes the ring closure followed by addition of fluorine to intermediately generated cyclic carbocations.

Herein we present the results on the metal-free electrophilic fluoro-cyclization of unsaturated *N*-hydroxy- and *N*-acetoxyamides induced by F-TEDA-BF_4 and a new fluorinating reagent F-TEDA-FAP, where FAP is $[(C_2F_5)_3PF_3]^-$ [25]. The fluorination of *trans*-*N*-acetoxy-4-phenylbut-3-enamide (**1**), *trans*-*N*-hydroxy-4-phenylbut-3-enamide (**2**), *N*-hydroxy-4-phenylpent-4-enamide (**3**), *N*-acetoxy-4-phenylpent-4-enamide (**4**), *N*-acetoxy-*trans*-2-methylcinnamamide (**5**) was carried out in organic solvents and ionic liquid 1-ethyl-3-methylimidazolium triflate ([emim][CF_3SO_3]).

2. Results and discussion

The fluoro-cyclization of *trans*-*N*-acetoxy amide **1** and *trans*-*N*-hydroxy amide **2** with F-TEDA-BF_4 in water, organic solvents (nitromethane and acetonitrile), and ionic liquid [emim][CF_3SO_3] resulted in the formation of corresponding fluorinated *trans*-(**1a**) and *cis*-(**1b**) *N*-acetoxyimidates, and *trans*-(**2a**) and *cis*-(**2b**) *N*-hydroxyimidates in moderate yields (Scheme 1 and Table 1). The reactions proceeded very slowly (within 6 to 10 days) at room temperature. Our attempts to accelerate the reactions by heating have failed, presumably due to the lability of the starting compounds.



1, R=C(O)CH$_3$
2, R=H

trans **1a,2a**

cis **1b,2b**

2c, 3% in CH_3NO_2; 15% in H_2O

Scheme 1. Formation of *trans*-(**1a**) and *cis*-(**1b**) *N*-acetoxyimidates, and *trans*-(**2a**) and *cis*-(**2b**) *N*-hydroxyimidates.

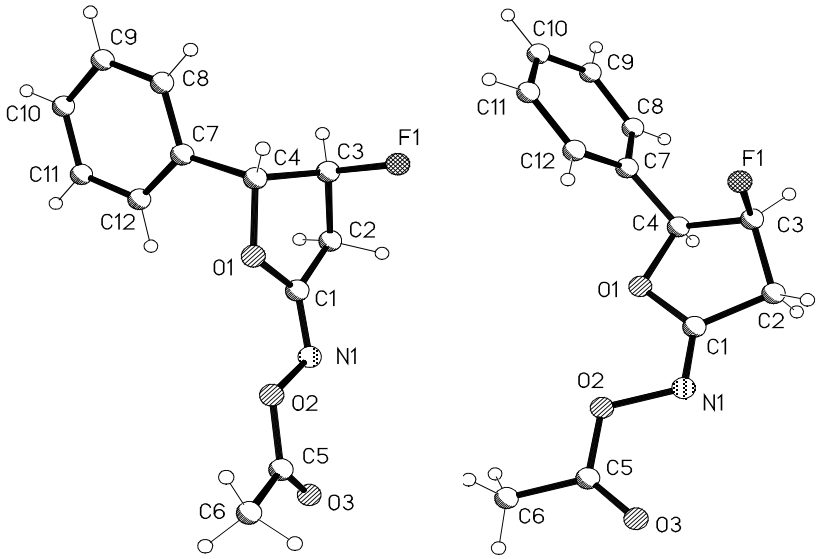
Table 1. Fluorocyclization of *trans*-N-acetoxy-(**1**) and *trans*-N-hydroxy-4-phenylbut-3-enamide (**2**).

Entry	N–F reagent	Sub-strate	Base or salt	Solvent	Yield (**a+b**) %	*Trans/cis* by ^{19}FNMR
1	F-TEDA-BF$_4$	**1**	–	CH_3NO_2	69	1.3
2	F-TEDA-BF$_4$	**1**	–	CH_3CN	68	1.3
3	F-TEDA-BF$_4$	**1**	–	[emim][CF_3SO_3]	30	1.3
4	F-TEDA-BF$_4$	**1**	K_2CO_3[a]	CH_3NO_2	53	1.0
5	F-TEDA-FAP	**1**	-	CH_3NO_2	53	0.6
6	F-TEDA-BF$_4$	**1**	KFAP[b]	CH_3NO_2	55	0.6
7	F-TEDA-BF$_4$	**2**	–	CH_3NO_2	48	0.6
8	F-TEDA-BF$_4$	**2**	KFAP[b]	CH_3NO_2	40	0.8
9	F-TEDA-BF$_4$	**2**	–	H_2O	64	1.7

[a] 1 equiv., [b] 2 equiv.

The reaction of **1** and **2** with F-TEDA-BF$_4$ likely occurs *via* addition of fluorine to double bond resulting in the formation of carbo-cationic intermediate that undergoes 5-*endo*-cyclization into *trans*-(**1a**) and *cis*-(**1b**) *N*-acetoxyimidates, and *trans*-(**2a**) and *cis*-(**2b**) *N*-hydroxyimidates (Scheme 1). The reason for *O*-cyclization is presumably higher nucleophilicity of carbonyl oxygen in comparison to amide's nitrogen bearing hydroxy or acetoxy group (Milliken charges: δ_O = -0.728, δ_N = -0.062 for compound **1** and δ_O = -0.748, δ_N = -0.013 in the case of compound **2**). Products of nucleophilic oxygen-attack, but not nitrogen-attack, were described for the intramolecular halo-cyclization of unsaturated amides, which had no electron-withdrawing group attached to the nitrogen [6].

The fluoro-cyclization of *trans*-N-acetoxy-4-phenylbut-3-enamide (**1**, R = C(O)CH$_3$) with F-TEDA-BF$_4$ in organic solvents (nitromethane, acetonitrile), as well as in [emim][CF_3SO_3], resulted in the formation of *trans*-isomer **1a** as the main product. The diastereomeric ratio of **1a**/**1b** (1.3) doesn't depend on the reaction media used (Table 1, entries 1-3). The configuration of the products **1a,b** was confirmed by X-ray analysis, where in both *trans*- and *cis*-diastereomers *syn*-position of the acetoxy group to the ring oxygen was proven (Fig. 1).



1a **1b**

Fig. 1. Molecular structures of *trans*-*N*-acetoxyimidate **1a** and *cis*-*N*-acetoxyimidate **1b** (CCDC 1043973 and 1043974).

Attempt to prepare fluorinated lactam by means of fluoro-cyclization of **1** by adding of base, which was usually used in halo-cyclizations of amides [6,16-18] to facilitate the *N*-cyclization, failed. The fluoro-cyclization of **1** in presence of K_2CO_3 proceeded non-stereoselectively giving fluoroimidates **1a** and **1b**, the products of *O*-cyclization, in molar ratio 1:1 (Table 1, entry 4).

We also tested the fluoro-cyclization of **1** with the new N–F reagent F-TEDA-FAP (FAP = tris(pentafluoroethyl)trifluorophosphate) that was recently synthesized through the anion exchange between F-TEDA-BF_4 and KFAP salt in acetonitrile [25]. F-TEDA-FAP possess better solubility in organic solvents in comparison to F-TEDA-BF_4. Surprisingly, the fluoro-cyclization of **1** with F-TEDA-FAP changed the stereoselectivity relatively to that with F-TEDA-BF_4. Preferable formation of *cis*-fluoro-*N*-hydroxyimidate **1b** was observed in this case (Table 1, entry 5). Probably, FAP anion only weakly coordinates to the carbocationic center that drives fast intramolecular *O*-cyclization towards the *cis*-isomer. We also found similar stereoselectivity when the fluorocyclization of **1** was conducted with F-TEDA-BF_4 and KFAP salt in the ratio 1:2 (*in situ* generation of F-TEDA-FAP). This may have preparative applications (Table 1, entries 5 and 6) for carbocationic stereo-selective cyclizations.

The diastereomeric ratio of the products **2a,b** depends on the solvent used. *N*-hydroxy amide **2** reacts with F-TEDA-BF_4 in nitromethane leading to the preferable formation of *cis*-fluoro-*N*-hydroxyimidate **2b** (Table 1, entry 7). Almost the same result was obtained when KFAP was added to the reaction mixture (Table 1, entry 8). Apparently, both $[BF_4]^-$ and FAP-anion interact with acidic proton of the N-O-H group ($[BF_4]^-$ more efficiently). That enlarges the electron density on carbonyl oxygen facilitating rush cyclisation after addition of

fluorine to double bond. In both cases (Table 1, entry 7 and 8) the *cis*-isomer **2b** is preferably formed. However, the predominant formation of *trans*-fluoro-*N*-hydroxyimidate **2a** was observed when reaction was carried out in water (Table 1, entry 9) presumably due to the strong solvation of the reaction center. It looks that reaction proceeds in this case stepwise: addition of F and cyclization via intermediate formation of carbocation which has time (slow kinetic) to assume energetically more favored configuration leading to the formation of *trans*-isomer. In both reactions, in nitromethane as well as in water, the **2c** was isolated as a by-product. The formation of the unsaturated nitrile **2c** was observed earlier in electrophilic bromo-cyclization of γ-phenyl-β,γ-unsaturated hydroxamates [21].

Computational simulation [26] shows that in the case of electrophilic fluoro-cyclization of **2** the *syn*-conformation of the fluorinated products **2a,b** is stabilized additionally by the intramolecular O···HO hydrogen bonding with energy gain of *ca.* 6.0 kcal·mol^{-1} (Fig. 2). The computational results are well in agreement with *syn*-conformation of the products **2a,b** determined by NMR spectra, where multiplicities and chemical shifts of the characteristic signals are similar to the NMR spectra of the products **1a,b**.

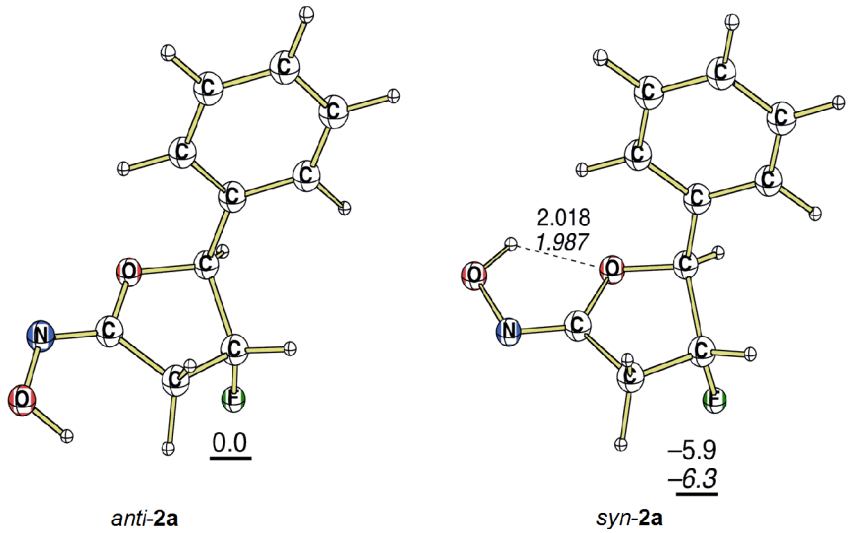
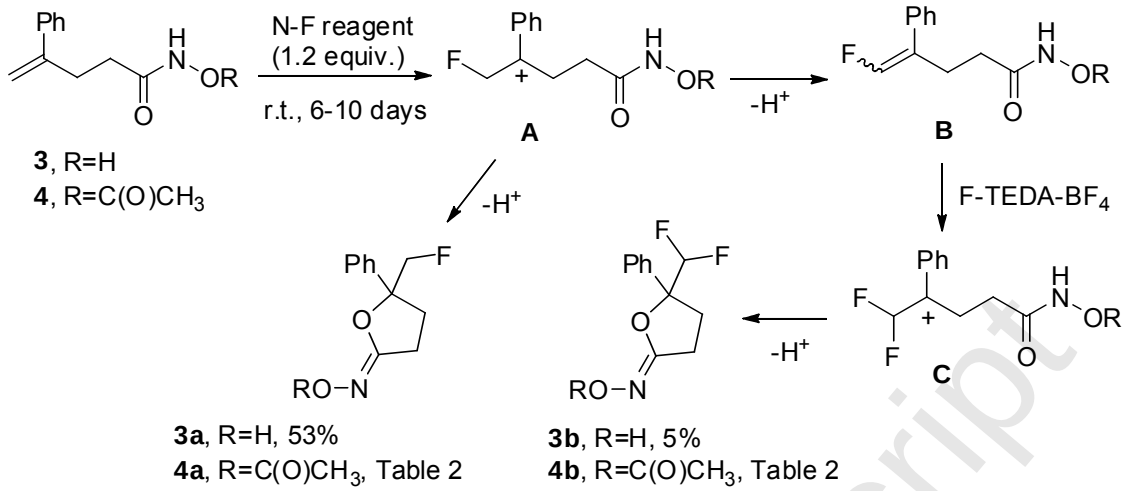


Fig. 2. The M06-2X/cc-pVDZ and MP2/cc-pVDZ relative energies (kcal·mol^{-1}) of *syn*- and *anti*-**2a**.

The fluoro-cyclization of *N*-hydroxy amide **3**, which contains a terminal double bond, with F-TEDA-BF_4 in nitromethane results in the formation of fluoromethyl-*N*-hydroxyimidate **3a** and difluoromethyl-*N*-hydroxyimidate **3b** in 53% and 5% isolated yields, correspondingly (Scheme 2).



Scheme 2. Fluoro-cyclization of *N*-hydroxy-4-phenylpent-4-enamide (**3**) and *N*-acetoxy-4-phenylpent-4-enamide (**4**).

This reaction likely occurs *via* intermediately formed carbocation **A** that undergoes cyclization to fluoromethyl-N-hydroxyimidate **3a** and besides is deprotonated to fluoroalkene **B** with the base released from F-TEDA-BF_4. The follow-up electrophilic fluorination of **B** leads to difluoroimidate **3b** through carbocation **C** stabilized by conjugation with Ph-group. Similar mechanism was proposed for electrophilic fluorocyclization of unsaturated carboxylic acids and alkenols with F-TEDA-BF_4 [27, 28].

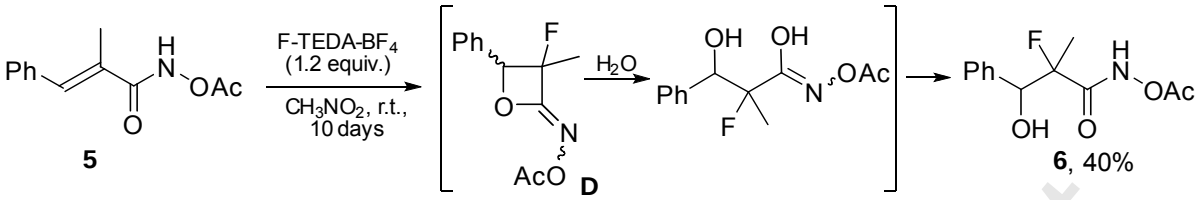
The fluorocyclization of N-acetoxy amide **4** with F-TEDA-BF_4 in nitromethane proceeds similarly to that for amide **3** and results in the formation of monofluorinated (**4a**) and difluorinated (**4b**) imidates with the ratio of *ca.* 4.9 estimated by ^{19}F-NMR data (Scheme 2, Table 2).

Table 2. Fluorocyclization of N-acetoxy-4-phenylpent-4-enamide (**4**).

Entry	N–F Reagent	Time, days	Solvent	Isolated yields, % **4a**	**4b**	Ratio **a/b**
1	F-TEDA-BF_4	6	CH_3NO_2	49	10	4.9
2	F-TEDA-BF_4	10	[emim][CF_3SO_3]	24	19	1.3
3	F-TEDA-FAP	6	CH_3NO_2	51	–	–

When changing nitrometane to [emim][CF_3SO_3] the amount of *gem*-difluorinated compound **4b** increases (the ratio of **4a/4b** is 1.3; Table 2, entry 2) due to additional stabilization of the carbocation **A** through its coordination with CF_3SO_3-anion. The latter retards the cyclization and facilitates the deprotonation to the carbocation **B**. (Table 2, entry 2). On the contrary, weakly coordinating anion [$(C_2F_5)_3PF_3$] of F-TEDA-FAP does not contribute to the

stabilization of **A** that results exclusively in fast intramolecular cyclization to **4a** (Table 2, entry 3).



Scheme 3. Fluorination of N-acetoxy-*trans*-2-methylcinnamamide (**5**).

Our attempts to build the fluorinated four-membered cycle through the reaction of N-acetoxy-*trans*-2-methylcinnamamide (**5**) with F-TEDA-BF_4 in nitromethane were unsuccessful. Only the open-chain fluorinated compound **6** was isolated in 40% yield after quenching the reaction mixture with water (Scheme 3). Presumably, intermediately formed labile four-membered fluorinated oxetane **D** undergoes rapid hydrolysis to the N-acetoxy-3-phenyl-3-hydroxy-2-fluoro-2-methylpropioamide **6**.

3. Conclusion

The fluorocyclization of *trans*-N-acetoxy-4-phenylbut-3-enamide (**1**) and *trans*-N-hydroxy-4-phenylbut-3-enamide (**2**) with N-F reagents (F-TEDA-BF_4 and F-TEDA-FAP) results in the formation of diastereomeric mixtures of fluorinated N-acetoxy- and N-hydroxy-imidates. The use of F-TEDA-FAP instead F-TEDA-BF_4 reverses the diastereoselectivity in favour of the *cis*-fluoro-N-acetoxyimidate **1b** formation. *Syn*-configurations of fluorinated N-acetoxyimidates **1a** and **1b** were confirmed by X-ray analysis.

The fluorocyclization of the N-hydroxy-(**3**) and N-acetoxy-4-phenylpent-4-enamides (**4**) with terminal double bond under action of F-TEDA-BF_4 in nitromethane proceeds with the formation of monofluorinated (**3a,4a**) and *gem*-difluorinated (**3b,4b**) imidates. The use of the F-TEDA-FAP reagent instead of F-TEDA-BF_4 in nitromethane results in the formation of the monofluorinated product **4a** exclusively.

4. Experimental section

Analytical Instruments.

The NMR spectra were recorded on spectrometers Varian VXR-300 [^{1}H (300 MHz), ^{13}C (75.5 MHz), ^{19}F (282.2 MHz)], Varian UNITY plus 400 [^{1}H (399.9 MHz), ^{13}C (100.5 MHz), ^{19}F (376 MHz)] and Bruker Avance DRX-500 [^{1}H (500 MHz), ^{13}C (125.7 MHz)] using $CDCl_3$ as a solvent and TMS or CCl_3F as internal standards. Mass spectra were measured on a Thermo Finnigan LCQ Advantage LC/mass detector instrument.

Chemicals.

Unsaturated *N*-acetoxy- and *N*-hydroxy-amides **1**, **2**, **3**, **4**, and **5** were synthesized according to known procedures [21,29].

Typical fluoro-cyclization protocol in nitromethane. The dry nitromethane (10 ml) and F-TEDA-BF_4 or F-TEDA-FAP (1.8mmol, 1.2 equiv) were placed into a three-necked flask equipped with a reflux condenser. Argon gas was passed through the reaction mixture for 20 min. After addition of the corresponding substrate (1.5 mmol) the mixture was stirred at ambient temperature until the reaction was completed (monitoring by TLC). Then, water (25 ml) was added to reaction mixture and the product was extracted with dichloromethane (3×15 ml). Organic phase was washed two times with water, dried with $MgSO_4$ and filtered. After evaporation of the solvent the product was purified by column chromatography on silica gel with eluent: n-hexane/ethyl acetate (3:2).

Products characterization:

(4R,5S,Z)-4-fluoro-5-phenyldihydrofuran-2(3H)-one O-acetyl oxime (1a)

White crystals, m.p. 134-135°C;^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (m, 3H), 7.26 (m, 2H), 5.87 (d, $^3J_{HF}$ = 20.5 Hz), 5.21 (d, $^2J_{HF}$ = 52.5 Hz), 3.11 (m, 2H), 2.20 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.6, 162.3, 134.0 (d, ^3J = 9.5 Hz), 128.8, 124.3, 93.9 (d, ^1J = 187.0 Hz), 90.1 (d, ^2J = 25.3 Hz), 32.3 (d, ^2J = 23.9 Hz), 18.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ –172.0 (m, *J* = 52.5, 29.3, 20.3 Hz); LC/MS: *m/z* 260 $(M+Na)^+$, 238 $(M+H)^+$, 196 $(M+H\text{-}OAc)^+$; Anal. Calcd. for $C_{12}H_{12}FNO_3$: C, 60.76; H, 5.10; N, 5.90. Found: C, 60.71; H, 5.02; N, 5.87.

X-ray Structure (see Supporting Information) determination for **1a.**

Crystal data: $C_{12}H_{12}FNO_3$, M 237.23, orthorhomic, space group $P2_12_12_1$,*a*= 8.6617(9), *b* = 10.0279(11), *c* = 13.3467(16) Å, V = 1159.3(2)Å^3, Z = 4, d_c = 1.359 g·cm^{-3}, μ = 0.108 mm^{-1}, F(000) = 496, crystal size ca. 0.09 × 0.20 × 0.40 mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and φ scans mode. The intensity data were collected within the range of 2.54 ≤θ≤ 26.32° using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 6481 reflections were collected (2322 unique reflections, R_{merg} = 0.039). The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package [29]. All hydrogen atoms were refined as 'riding' model. In the refinement 2322 reflections were used. Convergence was obtained at R1 = 0.0771 and wR2 = 0.1131 for all reflection and R1 = 0.0454 and wR2 = 0.0983, GOF = 1.097 for 1631 observed reflections with I ≥2σ(I), 159 parameters; the largest and minimal peaks in the final difference map 0.16 and –0.18 e/Å^3,

weighting scheme is as follows: $\omega = 1/[\sigma^2(Fo^2) + (0.0492P)^2]$, where $P = (Fo^2 + 2Fc^2)/3$), Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 1043973.

(4S,5S,Z)-4-fluoro-5-phenyldihydrofuran-2(3H)-one O-acetyl oxime (1b)

White crystals, m.p. 104-105°C;^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (m, 5H), 5.57 (dd, $^3J_{HF}$ = 26.5 Hz, $J_{HH'}$ = 2.4 Hz, 1H), 5.33 (dm, $^2J_{HF}$ = 52.1 Hz, 1H), 3.28 (A-part, J_{AB} = 18.0 Hz, $^3J_{HF}$ = 22.1 Hz, 1H), 3.22 (B-part, J_{AB} = 18.0 Hz, $^3J_{HF}$ = 37.9 Hz, J_{HH} = 4.3 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 162.4, 131.7 (d,^3J = 3.7 Hz), 129.4, 128.6, 127.3, 90.1 (d, ^1J = 191.1 Hz), 89.0 (d, ^2J = 20.4 Hz), 35.6 (d, ^2J = 24.2 Hz), 19.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ –191.3 (m, J = 52.0, 37.7, 26.4, 22.5 Hz). LC/MS: *m/z* 260 $(M+Na)^+$, 238 $(M+H)^+$, 196 $(M+H\text{-}OAc)^+$; Anal. Calcd. for $C_{12}H_{12}FNO_3$: C, 60.76; H, 5.10; N, 5.90. Found: C, 60.73; H, 5.06; N, 5.86.

X-ray Structure (see Supporting Information) determination for **1b.**

Crystal data: $C_{12}H_{12}FNO_3$, M 237.23, monoclinic, space group $P2_1/c$, a= 12.5764(12), b = 7.5009(8), c = 12.2587(13) Å, β = 95.357(6)°, V = 1151.4(2)Å^3, Z = 4, d_c = 1.369 g·cm^{-3}, μ = 0.109 mm^{-1}, F(000) = 496, crystal size ca. 0.26 × 0.33 × 0.37 mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and φ scans mode. The intensity data were collected within the range of $1.63 \leq \theta \leq 26.00°$ using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 8960 reflections were collected (2150 unique reflections, R_{merg} = 0.0587). The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package [29]. All hydrogen atoms were refined isotropically. In the refinement 2150 reflections were used. Convergence was obtained at R1 = 0.0977 and wR2 = 0.2253 for all reflection and R1 = 0.0687 and wR2 = 0.2093, GOF = 1.04 for 1556 observed reflections with $I \geq 2\sigma(I)$, 202 parameters; the largest and minimal peaks in the final difference map 0.16 and –0.18 e/Å^3, weighting scheme is as follows: $\omega = 1/[\sigma^2(Fo^2) + (0.015P)^2]$, where $P = (Fo^2 + 2Fc^2)/3$), Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 1043974.

(4R,5S,Z)-4-fluoro-5-phenyldihydrofuran-2(3H)-one oxime (2a)

Colorless oil;^{1}H NMR (400 MHz, C_6D_6): δ6.57–7.25 (bs, 1H), 6.97 (m, 3H), 6.80 (m, 2H), 5.21 (d, $^3J_{HF}$ = 21.1 Hz, 1H), 4.32 (dm, $^2J_{HF}$ = 53.5 Hz, 1H), 2.13 (A-part, J_{AB} = 18.6 Hz, $^3J_{HF}$ = 23.1 Hz, 1H), 1.94 (B-part, J_{AB} = 18.6 Hz, $^3J_{HF}$ = 34.0 Hz, $^3J_{HH}$ = 5.1 Hz, 1H); ^{13}C NMR (126 MHz,

$CDCl_3$): δ 173.4 (C=N), 134.7 (d, *J* = 9.3 Hz), 128.8, 128.6, 124.4, 93.5 (d, *J* = 185.6 Hz), 85.2 (d, *J* = 26.2 Hz), 33.7 (d, *J* = 23.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$): δ –172.0 (m, *J* = 53.0 Hz); LC/MS: *m/z* 196 $(M+H)^+$; Anal. Calcd. for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; N, 7.18. Found: C, 61.49; H, 5.12; N, 7.13.

(4S,5S,Z)-4-fluoro-5-phenyldihydrofuran-2(3H)-one oxime (2b)

White crystals, m.p. 61-62 °C; ^{1}H NMR (400 MHz, C_6D_6): δ 6.90–7.20 (bs, 1H), 7.09 (m, 5H), 4.61 (d, $^3J_{HF}$ = 26.6 Hz, 1H), 4.30 (d, $^2J_{HF}$ = 53.0 Hz, 1H), 2.34 (A-part, J_{AB} = 18.6 Hz, $^3J_{HF}$ = 19.4 Hz, 1H), 2.00 (B-part m, J_{AB} = 18.6 Hz,$^3J_{HF}$ = 40.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3 (C=N), 131.8 (d, *J* = 4.2 Hz), 128.6, 128.1, 126.2, 89.6 (d, *J* = 188.1 Hz), 83.8 (d, *J* = 20.9 Hz), 36.8 (d, *J* = 25.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$): δ –190.5 (m, *J* = 53.0 Hz); LC/MS: *m/z* 196 $(M+H)^+$; Anal. Calcd. for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; N, 7.18. Found: C, 61.47; H, 5.12; N, 7.14.

The spectral data of the product **1c** are identical to described previously [21].

5-(fluoromethyl)-5-phenyldihydrofuran-2(3H)-one oxime (3a)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–8.20 (bs, 1H), 7.57–7.24 (m, 5H), 4.60 (A-part,dd, $^2J_{HF}$ = 48.0 Hz, $^2J_{AB}$ = 10.3 Hz, 1H), 4.51 (B-part,dd, $^2J_{HF}$ = 48.0 Hz, $^2J_{AB}$ = 10.3 Hz, 1H), 2.81 (m, *J* = 15.0, 6.1 Hz, 1H), 2.72 (m, 1H), 2.58 (m, *J* = 15.0, 7.1 Hz, 1H), 2.36 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 138.1 (d, ^3J = 5.0 Hz), 128.3, 128.1, 124.8, 90.5 (d, ^2J = 18.4 Hz), 86.0 (d, ^1J = 184.4 Hz), 30.8 (d, ^3J = 2.7 Hz), 25.7; ^{19}F NMR (376 MHz $CDCl_3$): δ–222.1 (t, *J* = 47.6 Hz); LC/MS: *m/z* 210 $(M+H)^+$, 191 $(M+H-F)^+$; Anal. Calcd. for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.08; H, 5.75; N, 6.61.

The difluorinated lactone **3b** was not separated from the reaction mixture in pure form and the formation of this compound was proved based upon the characteristic signals in NMR spectra. ^{1}H NMR (299.9 MHz, $CDCl_3$): δ5.79 (t, $^2J_{HF}$ = 55.9 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ–129.4 (A-part, J_{AB} = 283.0 Hz, $^2J_{FH}$ = 56.5 Hz, 1F, ABX), –130.9 (B-part, $^2J_{FF}$ = 283.0 Hz, $^2J_{FH}$ = 56.5 Hz, 1F, ABX).

5-(fluoromethyl)-5-phenyldihydrofuran-2(3H)-one O-acetyl oxime (4a)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.29 (m, 5H), 4.54 (A-part,dd, $^2J_{HF}$ = 48.0 Hz, $^2J_{AB}$ = 10.4 Hz, 1H), 4.47 (B-part,dd, $^2J_{HF}$ = 48.0 Hz, $^2J_{AB}$ = 10.4 Hz, 1H), 3.08 (m, 1H), 2.90–2.72 (m, 2H), 2.40 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 168.2, 138. (d, ^3J = 5.5 Hz), 128.7, 128.7, 125.1, 91.2 (d, ^2J = 18.2 Hz), 87.1 (d, ^1J = 184.8 Hz), 30.5 (d, *J* = 2.3 Hz), 26.3 (d, *J* = 2.1 Hz), 19.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ –222.1 (t, *J* = 47.5 Hz); LC/MS: *m/z* 252 $(M+H)^+$; Anal. Calcd. for $C_{13}H_{14}FNO_3$: C, 62.14; H, 5.62; N, 5.57. Found: C, 62.09; H, 5.58; N, 5.50.

5-(difluoromethyl)-5-phenyldihydrofuran-2(3H)-one O-acetyl oxime (4b)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57–7.34 (m, 5H), 5.80 (t, ^{2}J = 55.5 Hz, 1H), 3.08 (m, 1H), 2.95–2.85 (m, 1H), 2.77 (m, 1H), 2.46 (m, 1H), 2.16 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ173.8, 136.1 (t, ^{3}J = 3.6 Hz), 129.2, 128.7, 125.9, 115.0 (d, ^{1}J = 249.4 Hz), 89.6 (t, ^{2}J = 21.4 Hz), 28.3, 26.0, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ –129.8 (A-part, J_{AB} = 283.8 Hz, $^{2}J_{FH}$ = 55.0 Hz, 1F, ABX), –130.9 (B-part, $^{2}J_{FF}$ = 283.8 Hz, $^{2}J_{FH}$ = 55.0 Hz, 1F, ABX); LC/MS: *m/z* 270 $(M+H)^{+}$; Anal. Calcd. for $C_{13}H_{13}F_2NO_3$: C, 57.99; H, 4.87; N, 5.20. Found: C, 57.92; H, 4.83; N, 5.15.

N-acetoxy-2-fluoro-3-hydroxy-2-methyl-3-phenylpropanamide (6)

White crystals, m.p. 89-90°C;^{1}H NMR (500 MHz, CD_3CN):δ 10.28 (bs, 1H), 7.54–7.13 (m, 5H), 4.87 (d, ^{3}J = 24.8 Hz, 1H), 4.11 (bs, 1H), 2.17 (s, 3H), 1.28 (d, ^{3}J = 22.6 Hz, 3H); ^{13}C NMR (126 MHz, CD_3CN): δ 169.8 (d, ^{2}J = 23.1 Hz), 169.5, 139.4, 129.2, 129.0, 100.2 (d, ^{1}J = 192.1 Hz), 76.7 (d, ^{2}J = 18.9 Hz), 21.6 (d, ^{2}J = 22.6 Hz), 18.3; ^{19}F NMR (188 MHz, $CDCl_3$): δ –178.6 (quin, J = 23.2 Hz); LC/MS: *m/z* 278 $(M+Na)^{+}$, 238 $(M-OH)^{+}$, 196 $(M-OAc)^{+}$; Anal. Calcd. for $C_{12}H_{14}FNO_4$: C, 56.47; H, 5.53; N, 5.49. Found: C, 56.38; H, 5.50; N, 5.48.

Acknowledgement

Financial support from company Merck KGaA (Darmstadt, Germany) is gratefully acknowledged.

References.

[1] J.T. Welch, S. Eswarakrishman, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991.

[2] R.E. Banks, B.E. Smart, J.C. Tailow, Organofluorine Chemistry: Principle and Commercial Application, Plenum Press, New York, 1994.

[3] S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev., 37 (2008) 320-330.

[4] P. Kirsch, Modern Fluoroorganic Chemistry Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005.

[5] I. Ojima, Fluorine in Medicinal Chemistry and Chemical Biology, Wiley-Blackwell, 2009.

[6] S. Robin, G. Rousseau, Tetrahedron, 54 (1998) 13681-13736.

[7] S. Robin, G. Rousseau, Eur. J. Org. Chem., (2002) 3099-3114.

[8] A.I. Vas'kevich, N.M. Tsizorik, E.B. Rusanov, V.I. Stanitets, M.V. Vovk, Russ. J. Org. Chem., 47 (2011) 1146-1152.

[9] L. Bauer, O. Exner, Angew. Chem., Int. Ed., 13 (1974) 376-384.

[10] K.A. Fennell, U. Möllmann, M.J. Miller, J. Org. Chem., 73 (2008) 1018-1024.

[11] K.A. Fennell, M.J. Miller, Org. Lett., 9 (2007) 1683-1685.

[12] L.P. Tardibono, M.J. Miller, Org. Lett., 11 (2009) 1575-1578.

[13] K.D. Watson, S. Carosso, M.J. Miller, Org. Lett., 15 (2013) 358-361.
[14] M.J. Miller, G. Zhao, S. Vakulenko, S. Franzblau, U. Mollmann, Org. Biomol. Chem., 4 (2006) 4178-4185.
[15] C. Ji, R.E. Juarez-Hernandez, M.J. Miller, Future Med. Chem., 4 (2012) 297-313.
[16] G. Rajendra, M.J. Miller, Tetrahedron Lett., 26 (1985) 5385-5388.
[17] G. Rajendra, M.J. Miller, J. Org. Chem., 52 (1987) 4471-4477.
[18] G. Rajendra, M.J. Miller, Tetrahedron Lett., 28 (1987) 6257-6260.
[19] G.F. Miknis, R.M. Williams, J. Am. Chem. Soc., 115 (1993) 536-547.
[20] S.-S. Jew, K.-H. Cha, S.-D. Kang, Y.-H. Woo, H.-O. Kim, H.G. Park, Heterocycles, 50 (1999) 677-680.
[21] H. Trabulsi, G. Rousseau, Synthetic Communications, 41 (2011) 2123-2134.
[22] M. Tiecco, L. Testaferri, M. Tingoli, F. Marini, J. Chem. Soc., Chem. Commun., (1994) 221-222.
[23] Z. Li, L. Song, C. Li, J. Am. Chem. Soc., 135 (2013) 4640-4643.
[24] D.-F. Lu, G.-S. Liu, C.-L. Zhu, B. Yuan, H. Xu, Org. Lett., 16 (2014) 2912-2915.
[25] N. Ignatiev, A. Atatran, B. Barthen, W. Frank, WO 2011/124307 A1.
[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, J., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09.
[27] Y.A. Serguchev, L.F. Lourie, M.V. Ponomarenko, E.B. Rusanov, N.V. Ignat'ev, Tetrahedron Lett., 52 (2011) 5166-5169.
[28] L.F. Lourie, Y.A. Serguchev, M.V. Ponomarenko, E.B. Rusanov, M.V. Vovk, N.V. Ignat'ev, Tetrahedron, 69 (2013) 833-838.
[29] G.M. Sheldrick, Acta Crystallographica Section A, 64 (2008) 112-122.