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Synthesis of 5-fluorovinyl derivatives of pyrimidines via Suzuki–Miyaura coupling and their 1,3-dipolar cycloaddition reactions with nitrones

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ABSTRACT

A simple two-step synthesis of a new class of fluorinated isoxazolidinyl derivatives of pyrimidine is described. The reactions proceed via the Suzuki–Miyaura coupling followed by highly regioselective 1,3-dipolar cycloaddition with nitrones. Removal of the pyrimidine protecting groups leads to a fluorinated isoxazolidine analogue of pseudouridine.

1. Introduction

1,3-Dipolar cycloadditions of nitrones to alkenes leading to isoxazolidines are especially important in organic chemistry [1]. Numerous uses of isoxazolidines have been reported in total synthesis, often based on their ability to be transformed into polyfunctional amines including aminoalcohols, aminoketones and esters [2]. In recent years much attention has been paid to heterocyclic nucleosides having an isoxazolidine moiety instead of a ribofuranose ring. The synthesis of modified isoxazolidine nucleosides using nitrones and *N*-vinyl nucleobases as dipolarophiles is the most convenient and simplest method [3]. Some of these nucleosides have been found to show high cytostatic activity [4]. To the best of our knowledge only a few papers have reported on the synthesis of isoxazolidine and isoxazole analogues of C-nucleosides. These compounds were obtained from the 1,3-dipolar cycloadditions of nitrones based on a pyrimidine ring with the appropriate dipolarophiles [5].

Fluorinated analogues of biologically important compounds have aroused much interest because of their unique properties which are important for medicinal chemistry and biochemistry [6]. Although there is a growing interest in the development of new methods for the introduction of a fluorine atom or fluorinated groups to molecules, only a few reports have been published on the reactions of fluoroalkenes with nitrones [7].

2. Results and discussion

In the course of our work on fluorovinyl derivatives of nucleic acid bases [8], in this paper we would like to report our results on the palladium-catalysed Suzuki–Miyaura cross-coupling of fluoroalkenes with pyrimidine derivatives and on the use of the products as dipolarophiles in 1,3-dipolar cycloadditions with nitrones. A new class of fluorinated isoxazolidine derivatives was synthesised and furthermore, as a result of non-standard hydrolysis of protecting groups, a fluorinated isoxazolidine derivative of pseudouridine was obtained. The classical route to fluorovinylpyrimidines involves palladium-catalysed cross-coupling reactions of perfluoroalkenylzinc reagents with halogenopyrimidines in Negishi reactions [9]. Pentafluoropropenylpyrimidines can also be alternatively obtained by lithiation of bromopyrimidines at positions C-5 or C-6 followed by Michael type addition–elimination reactions with hexafluoropropene (HFP) [8a,10]. Unfortunately, the organozinc method is characterised by unsatisfactory yields, while the lithiated pyrimidines only react with HFP, which is strongly activated electrophile due to the electron withdrawing CF_3 group.

Coupling reactions of the previously described 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidines **4–6** [11] with the appropriate olefins in the presence of $Pd(PPh_3)_4$ and KOH took place smoothly in THF at 65–70 °C to give compounds **7–9** but in unsatisfactory yields. The use of $AsPh_3$ as an external ligand has considerably

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Table 1
5-Fluorovinyl derivatives of pyrimidines via Suzuki–Miyaura coupling reactions.

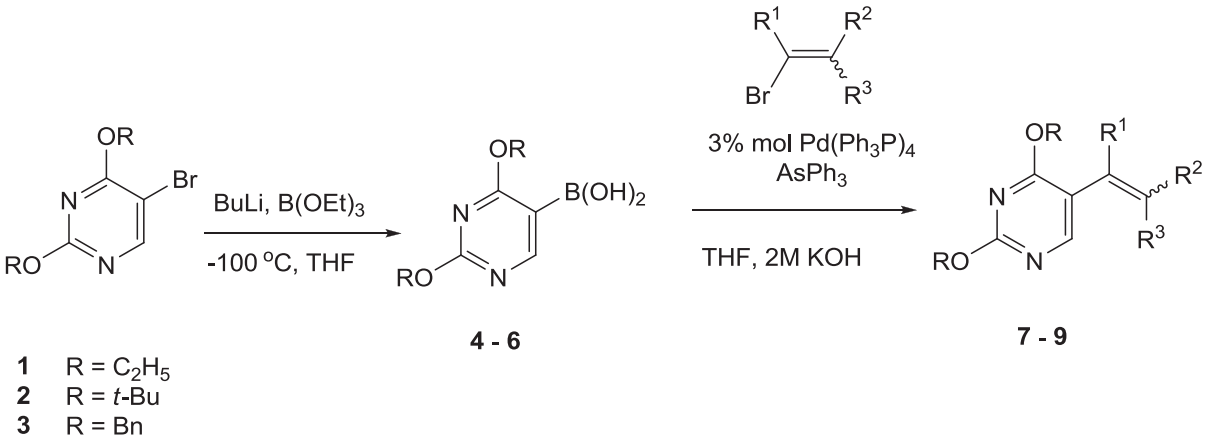
Entry	Product	R	R^1	R^2	R^3	Yield (%)[a]
1	**7a**	C_2H_5	F	F	F	65 (49)
2	**7b**	*t*-Bu	F	F	F	45
3	**8a**	C_2H_5	F	CF_3	F	68 (34)
4	**8b**	*t*-Bu	F	CF_3	F	40
5	**8c**	CH_2Ph	F	CF_3	F	71 (47)
6	**9a**	C_2H_5	CF_3	H	H	61 (17)
7	**9b**	*t*-Bu	CF_3	H	H	40
8	**10**	C_2H_5	CF_3	F	F	0

[a] Isolated yields of the reaction using the catalytic system $Pd(PPh_3)_4/AsPh_3$. Yields in parentheses are those from the reaction without $AsPh_3$.

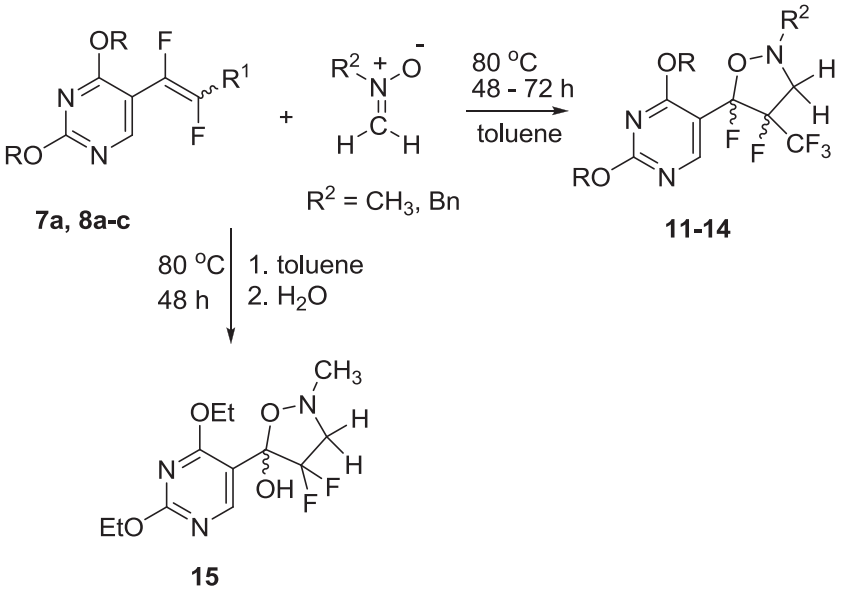
improved the yield of this reaction, so the catalytic system $Pd(PPh_3)_4/AsPh_3$ was assumed particularly beneficial and was used in transformations of this type (Table 1). The exceptions were compounds **7b**, **8b** and **9b** as under the reaction conditions the *t*-butoxy groups underwent hydrolysis reactions which significantly decreased the yields of these compounds (Scheme 1). The coupling reactions with 2-bromo-1,1,3,3,3-pentafluoropropene failed totally. Monitoring of the reactions by ^{1}F NMR did not allow the detection of the formation of any fluorinated product, and the only product was the corresponding homocoupled C-5–C-5′ bipyrimidinyl (entry 8).

The direct 1,3-dipolar cycloaddition of 5-fluorovinyl pyrimidines **8a–c** as dipolarophiles and *N*-methyl- and *N*-benzyl-methylenenitrones was performed according to Scheme 2, and the results are presented in Table 2. The reaction procedure is simple and straightforward. The nitrones were generated in situ by reaction of paraformaldehyde with the hydrochloride of the appropriate substituted hydroxylamine in the presence of triethylamine, or had been prepared earlier according to known procedures [12]. Cycloadditions of the nitrones were carried out in a glass pressure tube in toluene at 80 °C for 48–72 h.

Each time two diastereoisomers of the product were obtained with significant dominance of one of them. As followed by ^{19}F NMR spectroscopy, the ratio of the two diastereoisomers differs from 3.9:1 to 4.9:1. The cycloaddition reactions were completely regiospecific. Moreover, only the isomer *E* was actively involved in the 1,3-dipolar cycloaddition, while the *Z* isomer remained unchanged (or almost unchanged) in the reaction mixture. Also, in a simple model system, the reaction of perfluoroprop-1-enyl benzene (*E*/*Z* ratio = 4.8:1) with *N*-methyl-methylenenitrone results in 1,3-dipolar cycloaddition giving 4,5-difluoro-2-methyl-5-phenyl-4-(trifluoromethyl)isoxazolidine **18** with diastereoisomeric ratio



Scheme 1. Suzuki–Miyaura coupling reactions between fluoroalkenes and 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidines **4–6**.



Scheme 2. The synthesis of fluoroisoxazolidines **11–15**.

Table 2
Dipolar cycloadditions of nitrones to 5-fluorovinyl pyrimidine derivatives.

Entry	Starting material (*E*/*Z* ratio)	Product (ratio of diastereoisomers)	R	R^1	R^2	Yield (%)
1	**8a** (2.1: 1)	**11** (3.9:1)	C_2H_5	CF_3	CH_2Ph	45[a]
2	**8a** (2.1: 1)	**12** (4.1:1)	C_2H_5	CF_3	CH_3	58[a]
3	**8b** (2.3: 1)	**13** (4.7:1)	*t*-Bu	CF_3	CH_3	53[a]
4	**8c** (2.5: 1)	**14** (4.9:1)	CH_2Ph	CF_3	CH_3	55[a]
5	**7a**	**15**	C_2H_5	F	CH_3	38

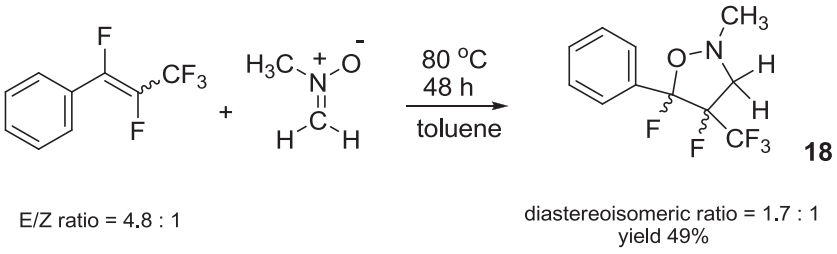
[a] Isolated yield based on the mixture of *E* and *Z* stereoisomers.

1.7:1 (Scheme 3). This observation can be seen when the dipolarophile configuration undergoes the partial inversion. To understand this phenomenon one can assume (i) kinetic control of the cycloaddition (*E* vs *Z* different reaction rate for reaction with nitrone) or (ii) possible not clear concerted reaction mechanism. In the case of electron-deficient dipolarophiles the two step pathway with a zwitterionic intermediate may compete with the concerted mechanism [13]. However, the isomerization can also occur through the displacement of fluoride anion at C-1′ under formation of a well stabilized oxocarbenium anion and then the re-addition of fluoride. The cycloaddition of **7a** and the formation of compound **15** follow the plausible mechanism of isomerization at the stage of products, with water as a nucleophile.

The structures of compounds **11–15** were determined on the basis of ^1H, ^{19}F and ^{13}C NMR spectra and MS spectrometry. Moreover, the structure of compound **13**, arised from stereoisomer *E* and displayed the *trans* configuration between two fluorine atoms, was confirmed from the single crystal X-ray data (Fig. 1) [14]. Unfortunately, detailed analysis of the ^{19}F and ^1H NMR spectra, using the *J* values was impossible because the signals were unusually broad and without detectable couplings between H, F and H, H atoms.

Standard attempts at removal of the protective ethyl and benzyl groups from pyrimidines **12** and **14** failed and did not produce the expected pseudouridine analogue. The use of trimethylchlorosilane in the presence of NaI as well as heating in acetic acid in the presence of NaI led to cleavage of the N–O bond of the isoxazolidine ring and gave compound **16** (multiplets assigned to the two clearly distinguishable protons of a CH_2 group in the ^1H NMR spectrum and a multiplet assigned to CF in the ^{19}F NMR spectrum). Attempts at removal of the benzyl groups by catalytic hydrogenolysis on palladium led also to reductive cleavage of the isoxazolidine ring. In all the above reactions, the highly electronegative F-1′ atom was abstracted from the C-1′ which is particularly susceptible to nucleophilic attack. The mechanism of the reaction of compound **15** in the CH_3COOH/NaI was different and the cleavage of the N–O bond led to a pyrimidine derivative with a linear substituent $C(O)CF_2CH_2NHCH_3$ at C-5 (a triplet assigned to a CH_2 group with equivalent protons in the ^1H NMR spectrum, J = 14 Hz and a triplet assigned to a CF_2 group in the ^{19}F NMR spectrum, J = 14 Hz).

The isoxazolidine analogue of pseudouridine **17** was obtained in a yield of 77% as a result of non-standard hydrolysis of compound **13** in anhydrous THF at room temperature using on almost equimolar amount of HCl (Scheme 4).



Scheme 3. The synthesis of 4,5-difluoro-2-methyl-5-phenyl-4-(trifluoromethyl)isoxazolidine.

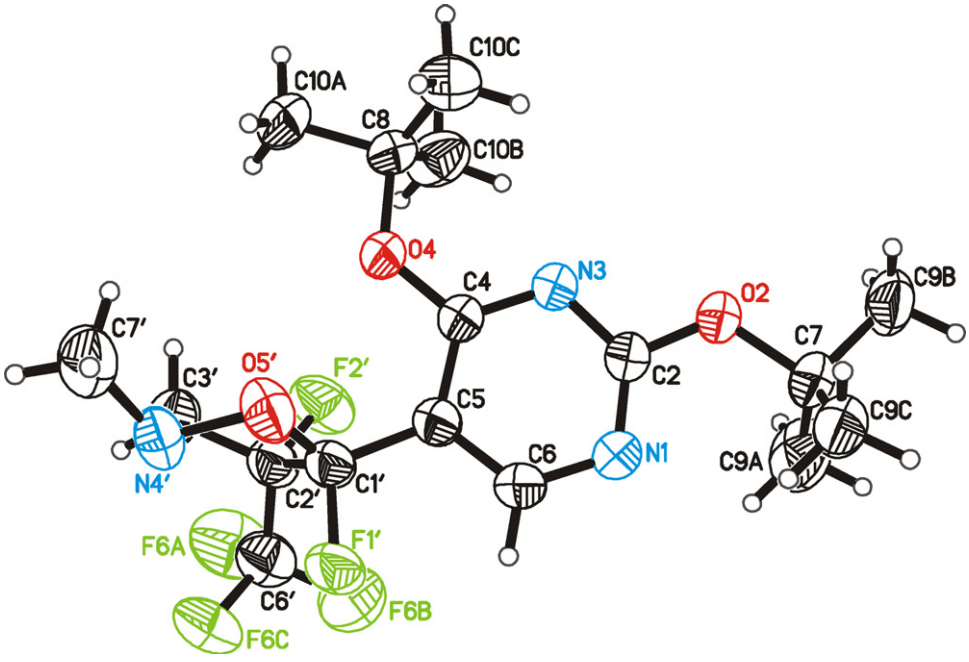
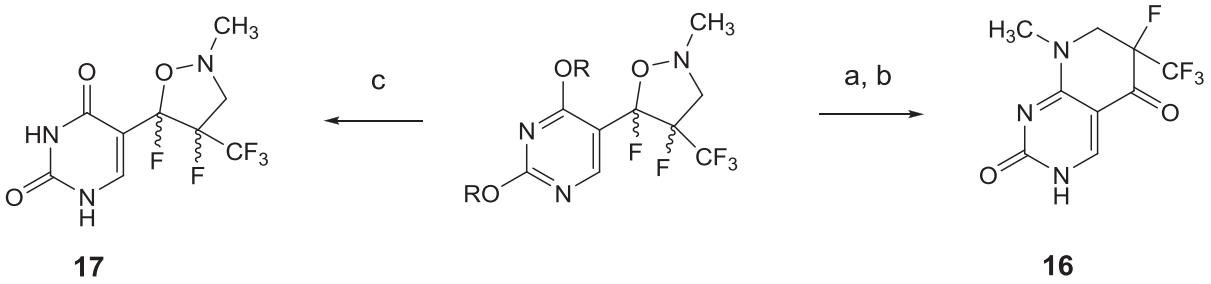


Fig. 1. ORTEP drawing of the X-ray crystallographic structure of compound **13** [15]. The thermal ellipsoids are drawn at the 50% probability level.



Scheme 4. Conditions: (a) Me_3SiCl, NaI, CH_3CN, RT, 24 h; (b) CH_3COOH, NaI, 90 °C, 1–2 h; (c) 2–3 eq. HCl, anhydrous THF, RT, 24 h.

3. Conclusion

In summary, a simple synthesis of a new class of isoxazolidine derivatives of pyrimidine based on the reaction of nitrones and 5-fluorovinyl pyrimidines obtained by Suzuki–Miyaura coupling is presented. The fluorinated isoxazolidines were obtained as two diastereoisomers with complete regioselectivity and with a good degree of diastereoselectivity. The mild hydrolysis conditions led to removal of the pyrimidine protecting groups without breaking the N–O bond of the isoxazolidine ring and hence to a fluorinated analogue of pseudouridine. Further investigation of this transformsations is ongoing and the results will be reported in due course.

4. Experimental

4.1. Synthesis

5-(Dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidines **4–6** were prepared according to Refs. [11]. All other starting materials and reagents were obtained from Fluka or Sigma–Aldrich. Iodotrifluoroethylene, 2-bromo-3,3,3-trifluoropropene, 1-bromo-1,2,3,3,3-pentafluoropropene and 2-bromo-1,1,3,3,3-pentafluoropropene were purchased from SynQuest Labs Inc. Toluene was distilled from NaH and was stored over molecular sieves (0.4 nm). All reactions were monitored by TLC or ^{19}F NMR. Thin layer chromatography was performed with 60 F_{254} TLC plates (Merck). Column chromatography was performed with silica gel (Merck, particle size 0.063–0.200 mm, 70–230 mesh). The coupling and cycloaddition reactions were carried out under an argon atmosphere.

^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Gemini 300 MHz spectrometer (300.069 MHz for ^1H, 101.25 MHz for ^{13}C and 282.318 MHz for ^{19}F) in CD_3OD, $CDCl_3$, TFA-d and DMSO-d_6 as solvents. TMS was the internal standard in ^1H NMR, $CFCl_3$ was used as a reference for ^{19}F NMR. Chemical shifts for ^1H NMR are reported in ppm downfield from TMS and for ^{19}F NMR upfield from $CFCl_3$. The mass spectra were recorded on a AMD 402 spectrometer, ionisation was achieved through electron impact (EI). The elemental analyses were made on PerkinElmer apparatus. Melting points were determined on a Boetius apparatus and are reported uncorrected.

4.2. General synthetic procedure and analytical data of compounds 7–9

In a glass pressure tube equipped with a magnetic stirrer, 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidine **4–6** (3 mmol) was dissolved in THF (20–30 mL). Then $Pd(PPh_3)_4$ (105 mg, 0.09 mmol), $AsPh_3$ (150 mg, 0.5 mmol) and 5 mL of 2 M KOH were added to the tube. The reactants were kept under argon or nitrogen atmosphere. The fluorovinyl halide, (1,1,2-trifluoro-2-iodoethene, 2-bromo-3,3,3-trifluoroprop-1-ene, 2-bromo-1,1,3,3,3-pentafluoroprop-1-ene or 1-bromo-1,2,3,3,3-pentafluoroprop-1-ene, 6 mmol, 2.0 M excess), as a solution in THF, was added to the reaction mixture using a syringe. The reaction mixture was then heated under stirring at 65–70 °C for 6–12 h. The progress of the reaction was monitored by TLC checking of the loss of starting 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidine. After cooling the organic layer was separated and the aqueous residue was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with water and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, hexane, a gradient of hexane/CH_2Cl_2 from 3:1 to 1:2, v/v and CH_2Cl_2) affording the corresponding compounds **7–9**.

4.2.1. 2,4-Diethoxy-5-(1,2,2-trifluorovinyl)pyrimidine (7a)

Colorless oil; yield 484 mg, 65%; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 and 1.37 (t, J = 7 Hz, 6H, CH_2–**CH_3**), 4.37 and 4.42 (q, J = 7 Hz, 4H, **CH_2**–CH_3), 8,17 (d, J = 2 Hz, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −100.16 (dd, J = 30 Hz and J = 70 Hz, 1F, CF=C**F**F), −116.6 (dd, J = 70 Hz and J = 117 Hz, 1F, CF=C**F**F), −167.68 (dd, J = 30 Hz and J = 117 Hz, 1F, C**F**=CF_2); MS (EI) 70 eV, m/z (rel. int): 248 $[M]^+$ (64), 192 (51), 121 (83), 59 (100); Anal. Calcd. for $C_{10}H_{11}N_2O_2F_3$: C, 48.39; H, 4.47; N, 11.28. Found: C, 48.01; H, 4.19; N, 11.02.

4.2.2. 2,4-Di-tert-butoxy-5-(1,2,2-trifluorovinyl)pyrimidine (7b)

Colorless oil; yield 410 mg, 45%; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.62 (m, 18H, *t*-Bu), 8.25 (d, J = 2 Hz, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −101.2 (dd, J = 30 Hz and J = 71 Hz, CF=C**F**F), −115.9 (dd, J = 71 Hz and J = 116 Hz, CF=C**F**F), −167.4 (dd, J = 30 Hz and J = 116 Hz, C**F**=CF_2); MS (EI) 70 eV, m/z (rel. int): 304 $[M]^+$ (3), 192 (71), 57 (100); Anal. Calcd. for $C_{14}H_{19}N_2O_2F_3$: C, 55.26; H, 6.29; N, 9.20. Found: C, 55.01; H, 6.37; N, 9.01.

4.2.3. 2,4-Diethoxy-5-(perfluoroprop-1-enyl)pyrimidine (8a)

Colorless oil; yield 608 mg, 68%; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37–1.50 (m, 6H, CH_2–**CH_3**), 4.40–4.55 (m, 4H, **CH_2**–CH_3), 8.17 (d, J = 2 Hz, 1H, *Z* isomer, H-6) and 8.27 (d, J = 1 Hz, 1H, *E* isomer, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ *E* isomer: −67.99 (dd, J = 11 Hz and J = 22 Hz, 3F, CF_3), −136.32 (dq, J = 141 Hz and J = 22 Hz, 1F, C**F**=CFCF_3), −165.87 (dq, J = 141 Hz and J = 11 Hz, 1F, CF=C**F**CF_3), *Z* isomer: −67.81 (dd, J = 8 Hz and J = 14 Hz, 3F, CF_3), −112.13 (m, 1F, C**F**=CFCF_3), −151.23 (m, 1F, CF=C**F**CF_3); MS (EI) 70 eV, m/z (rel. int): 298 $[M]^+$ (64), 254 (99), 226 (100); HRMS: calculated for $C_{11}H_{11}N_2O_2F_5$ 298.07403. Found 298.07508.

4.2.4. 2,4-Di-tert-butoxy-5-(perfluoroprop-1-enyl)pyrimidine (8b)

Colorless oil; yield 425 mg, 40%; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.65 (m, 18H, *t*-Bu), 8.18 (s, 1H, *Z* isomer, H-6) and 8.29 (s, 1H, *E* isomer, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ *E* isomer: −66.4 (dd, J = 12 Hz and J = 22 Hz, 3F, CF_3), −134.9 (dq, J = 140 Hz and J = 22 Hz, 1F, C**F**=CFCF_3), −164.1 (dq, J = 140 Hz and J = 12 Hz, 1F, CF=C**F**CF_3), *Z* isomer: −66.3 (dd, J = 8 Hz and J = 14 Hz, 3F, CF_3),

−109.7 (m, 1F, C**F**=CFCF$_3$), −151.2 (m, 1F, CF=C**F**CF$_3$); MS (EI) 70 eV, *m*/*z* (rel. int): 354 [M]$^+$ (1), 242 (39), 57 (100); HRMS: calculated for [M-(C_8H_{18} + H_2)]$^+$: $C_7H_3N_2O_2F_5$ 242.01147. Found 242.00928.

*4.2.5. 2,4-Bis(benzyloxy)-5-(perfluoroprop-1-enyl)pyrimidine (**8c**)*

Colorless solid; m.p. 46–51 °C; yield 899 mg, 71%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.46–5.52 (m, 4H, CH_2), 7.34–7.48 (m, 10H, Ph), 8.28 (s, 1H, *Z* isomer, H-6) and 8.40 (s, 1H, *E* isomer, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ *E* isomer: −66.6 (dd, *J* = 11 Hz and *J* = 22 Hz, 3F, CF_3), −135.1 (dq, *J* = 141 Hz and *J* = 22 Hz, 1F, C**F**=CFCF$_3$), −164.0 (dq, *J* = 141 Hz and *J* = 11 Hz, 1F, CF=C**F**CF$_3$), *Z* isomer: −66.1 (dd, *J* = 8 Hz and *J* = 14 Hz, 3F, CF_3), −110.6 (m, 1F, C**F**=CFCF$_3$), −148.9 (m, 1F, CF=C**F**CF$_3$); MS (EI) 70 eV, *m*/*z* (rel. int): 422 [M]$^+$ (6), 331 (12), 91 (100); HRMS: calculated for $C_{21}H_{15}N_2O_2F_5$ 422.10538. Found 422.10845.

*4.2.6. 2,4-Di-ethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrimidine (**9a**)*

Colorless oil; yield 480 mg, 61%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 and 1.36 (t, *J* = 7 Hz, 6H, CH_2–**CH_3**), 4.35 and 4.39 (q, *J* = 7 Hz, 4H, **CH_2**–CH_3), 5.71 (q, *J* = 1 Hz, 1H, CF_3C=C**H**H), 6.04 (q, *J* = 1 Hz, 1H, CF_3C=CH**H**), 8.08 (s, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −66.00 (s, 3F, CF_3); MS (EI) 70 eV, *m*/*z* (rel. int): 262 [M]$^+$ (69), 218 (100), 191 (86); Anal. Calcd. for $C_{11}H_{13}N_2O_2F_3$: C, 50.38; H, 5.00; N, 10.68. Found: C, 49.99; H, 4.79; N, 10.45.

*4.2.7. 2,4-Di-tert-butoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrimidine (**9b**)*

White crystal; m.p. 38–42 °C; Yield 382 mg, 40%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63 (s, 18H, *t*-Bu), 5.67 (q, *J* = 1 Hz, 1H, CF_3C=C**H**H), 6.01 (q, *J* = 1 Hz, 1H, CF_3C=CH**H**), 8.16 (s, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.18 (s, 3F, CF_3). MS (EI) 70 eV, *m*/*z* (rel. int): 318 [M]$^+$ (2), 206 (100), 57 (79); Anal. Calcd. for $C_{15}H_{21}N_2O_2F_3$: C, 56.60; H, 6.65; N, 8.80. Found: C, 56.31; H, 6.79; N, 8.57.

*4.3. General synthetic procrdure and analitical data of compounds **11–15** and **18***

A mixture of paraformaldehyde (36 mg, 1.2 mmol), triethylamine (152 mg, 1.5 mmol) and *N*-methylhydroxylamine hydrochloride or *N*-benzylhydroxylamine hydrochloride (1.2 mmol) in anhydrous toluene (10 mL) was placed in a glass pressure tube equipped with a magnetic stirrer and stirred at 70 °C for 1 h. The solution was cooled to room temperature, the corresponding 2,4-dialkoxypyrimidine **7a**, **8a–c** (1 mmol) was then added and the solution was heated at 80 °C for 48–72 h. The solvent was evaporated and the residue was washed a few times with $CHCl_3$. The organic layers were dried with Na_2SO_4 and evaporated under reduced pressure to afford a crude mixture which was purified by column chromatography (silica gel, hexane, a gradient of hexane/CH_2Cl_2 and a gradient of CH_2Cl_2/CH_3OH). The same procedure was applied for compound **18**.

*4.3.1. 2-Benzyl-5-(2,4-diethoxypyrimidin-5-yl)-4,5-difluoro-4-(trifluoromethyl)isoxazolidine (**11**)*

Solidified yellow oil; yield 195 mg, 45%; diastereoisomeric ratio 3.9:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (t, *J* = 7 Hz, 3H, CH_2–**CH_3**), 1.42 (t, *J* = 7 Hz, 3H, CH_2–**CH_3**), 3.41 (brs, 1H, H-3a′), 3.86 (brs, 1H, H-3b′), 4.15–4.52 (m, 6H, CH_2 and **CH_2**–CH_3), 7.26–7.42 (m, 5H, Ph), 8.41 (s, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.25 and −76.71 major (brs, 3F, CF_3), −100.13 and −112.19 major (brs, 1F, F-1′), −166.04 major and −167.74 (brs, 1F, F-2′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.0 (s, CH_2–**CH_3**), 14.3 (s, CH_2–**CH_3**), 56.6 (s, CH_2), 59.1 (brs, C-3′), 63.1 (s, **CH_2**–CH_3), 63.8 (s, **CH_2**–CH_3), 101.7 (dm, *J* = 203 Hz, C-2′), 104.6 (d, *J* = 28 Hz, C-5)), 114.4 (dd, *J* = 238 Hz and *J* = 30 Hz, C-1′), 121.2 (dq, *J* = 283 Hz and *J* = 32 Hz, CF_3)), 127.5, 128.1, 128.6 and 128.9 (s, Ph), 158.8 (brs, C-6), 166.0 (s, C-2), 168.2 (d, *J* = 2.8 Hz, C-4); MS (EI) 70 eV, *m*/*z* (rel. int): 433 [M]$^+$ (14), 91 (100); Anal. Calcd. for $C_{19}H_{20}N_3O_3F_5$: C, 52.66; H, 4.65; N, 9.70. Found: C, 52.47; H, 4.81; N, 9.49.

*4.3.2. 5-(2,4-Diethoxypyrimidin-5-yl)-4,5-difluoro-2-methyl-4-(trifluoromethyl)isoxazolidine (**12**)*

Solidified oil; yield 207 mg, 58%; diastereoisomeric ratio 4.1:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, *J* = 7 Hz, 3H, CH_2–**CH_3**), 1.43 (t, *J* = 7 Hz, 3H, CH_2–**CH_3**), 3.01(s, 3H, CH_3), 3.20 (brs, 1H, H-3a′), 4.03 (brs, 1H, H-3b′), 4.44 (q, *J* = 7 Hz, 2H, **CH_2**–CH_3), 4.48 (q, *J* = 7 Hz, 2H, **CH_2**–CH_3), 8.43 (s, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.98 and −77.06 major (brs, 3F, CF_3), −99.17 and −112.72 major (brs, 1F, F-1′), −165.82 major and −166.72 (brs, 1F, F-2′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.0 (s, CH_2–**CH_3**), 14.3 (s, CH_2–**CH_3**), 45.9 (brs, CH_3), 62.4 (brs, C-3′), 63.1 (s, **CH_2**–CH_3), 63.8 (s, **CH_2**–CH_3), 102.4 (dm, *J* = 202 Hz, C-2′), 104.9 (d, *J* = 29 Hz, C-5), 114.5 (dd, *J* = 240 Hz and *J* = 31 Hz, C-1′)), 121.3 (dq, *J* = 285 Hz and *J* = 31 Hz, CF_3)), 158.4 (brs, C-6,), 166.1 (s, C-2), 168.3 (d, *J* = 3.1 Hz, C-4)); MS (EI) 70 eV, *m*/*z* (rel. int): 357 [M]$^+$ (100), 298 (34), 254 (86); Anal. Calcd. for $C_{13}H_{16}N_3O_3F_5$: C, 43.70; H, 4.52; N, 11.76. Found: C, 43.59; H, 4.29; N, 11.49.

*4.3.3. 5-(2,4-Di-tert-butoxypyrimidin-5-yl)-4,5-difluoro-2-methyl-4-(trifluoromethyl) isoxazolidine (**13**)*

White crystal; m.p. = 111–113 °C; yield 219 mg, 53%; for X-ray analysis the compound was crystallized from hexane. Diastereoisomeric ratio 4.7:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 major and 1.66 (s, 9H, *t*-Bu), 1.64 major and 1.67 (s, 9H, *t*-Bu), 3.00 (brs, 3H, CH_3), 3.15 (brs, 1H, H-3a′), 4.01 (brs, 1H, H-3b′), 8.37 major and 8.44 (brs, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.06 and −77.26 major (brs, 3F, CF_3), −99.52 and −113.63 major (brs, 1F, F-1′), −165.15 major and −168.57 (brs, 1F, F-2′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.3 (s, C–**CH_3**), 28.4 (s, C–**CH_3**), 45.7 (s, CH_3), 63.4 (brs, C-3′), 81.1 (s, **C**–CH_3), 83.0 (s, **C**–CH_3), 102.5 (m, C-2′), 105.2 (d, *J* = 29 Hz, C-5), 114.6 (dd, *J* = 238 Hz and *J* = 30 Hz, C-1′), 121.0 (dq, *J* = 285 Hz and *J* = 31 Hz, CF_3), 158.4 (brs, C-6), 165.0 (s, C-2), 167.7 (d, *J* = 3 Hz, C-4); MS (EI) 70 eV, *m*/*z* (rel. int): 413 [M]$^+$ (13), 357 (20), 301 (55), 139 (100), 57 (56); Anal. Calcd. for $C_{17}H_{24}N_3O_3F_5$: C, 49.39; H, 5.85; N, 10.16. Found: C, 49.44; H, 6.34; N, 10.01.

*4.3.4. 5-(2,4-Di-benzyloxypyrimidin-5-yl)-4,5-difluoro-2-methyl-4-(trifluoromethyl) isoxazolidine (**14**)*

Solidified yellow oil; yield 265 mg, 55%; diastereoisomeric ratio 4.9:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.71 (brs, 3H, CH_3), 2.92 (brs, 1H, H-3a′), 3.85 (br s, 1H, H-3b′), 5.39 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 7.25–7.50 (m, 10H, Ph), 8.48 (s, 1H, H-6); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.90 and −77.27 major (brs, 3F, CF_3), −99.24 and −113.68 major (brs, 1F, F-1′), −165.75 major and −168.44 (br s, 1F, F-2′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 45.4 (s, CH_3), 62.3 (d, *J* = 18 Hz, C-3′), 69.3 (s, CH_2), 69.6 (s, CH_2), 102.6 (dm, *J* = 200 Hz, C-2′), 105.4 (d, *J* = 30 Hz, C-5), 114.5 (ddm, *J* = 238 Hz and *J* = 30 Hz, C-1′), 121.2 (dqm, *J* = 285 Hz and *J* = 33 Hz, CF_3), 128.0–135.9 (s, Ph), 158,2 (brs, C-6), 165.7 (s, C-2), 168.1 (d, *J* = 4 Hz, C-4); MS (EI) 70 eV, *m*/*z* (rel. int): 481 [M]$^+$ (14), 390 (3), 91 (100); Anal. Calcd. for $C_{23}H_{20}N_3O_3F_5$: C, 57.38; H, 4.19; N, 8.73. Found: C, 57.12; H, 4.40; N, 8.51.

*4.3.5. 5-(2,4-Diethoxypyrimidin-5-yl)-4,4-difluoro-2-methylisoxazolidin-5-ol (**15**)*

Solidified oil; yield 116 mg, 38%; ratio 3.5:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, *J* = 7 Hz, 6H, CH_2–**CH_3**), 2.84 (brs, 3H, CH_3), 2.95 (brs, 1H, H-3a′), 3.66 (brs, 1H, H-3b′), 4.33 (q, *J* = 7 Hz, 2H **CH_2**–CH_3), 4.44 (q, *J* = 7 Hz, 2H, **CH_2**–CH_3), 8.37 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −105.27 major (br d, *J* = 230 Hz, 1F, F-2a′), −107.18

major (br d, J = 230 Hz, 1F, F-2b′), −107.20 (br d, J = 226 Hz, 1F, F-2a′), −115.01 (br d, J = 226 Hz, 1F, F-2b′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.1 (s, CH_2–**CH_3**), 14.3 (s, CH_2–**CH_3**), 45.1 (s, CH_3), 63.1(s, **CH_2**–CH_3), 63.6 (s, **CH_2**–CH_3), 64.4 (t, J = 27 Hz, C-3′), 100.1 (dd, J = 30 Hz and J = 25 Hz, C-1′), 108.9 (s, C-5), 127.6 (t, J = 262 Hz, C-2′), 157.3 (s, C-6), 165.2 (s, C-2), 168.0 (s, C-4); MS (FAB): m/z = 306 $[M + 1]^+$; Anal. Calcd. for $C_{12}H_{17}N_3O_4F_2$: C, 47.21; H, 5.61; N, 13.76. Found: C, 46.91; H, 5.83; N, 13.50.

4.3.6. 4,5-Difluoro-2-methyl-5-phenyl-4-(trifluoromethyl)isoxazolidine (18)

Obtained from perfluoroprop-1-enyl benzene (208 mg, 1 mmol) under typical procedure; oil; yield 131 mg, 49%; diastereoisomeric ratio 1.7:1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.98 (s, 3H, CH_3), 3.07 (brs, 1H, H-3a′), 4.03 (brs, 1H, H-3b′), 7.32–7.51 (m, 5H, Ph); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.46 and −76.20 major (brs, 3F, CF_3), −101.32 and −111.75 major (brs, 1F, F-1′), −160.69 major and −169.03 (brs, 1F, F-2′); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 46.4 major and 49.5 (brs, CH_3), 59.6 and 61.8 major (brs, C-3′), 102.8 (m, C-1′), 115.5 (dm, J = 230 Hz, C-2′), 120.9 (qm, J = 283 Hz, CF_3), 127.3, 127.9, 128.1 and 130.5 (s, Ph); GC–MS, m/z: 267 $[M]^+$; Anal. Calcd. for $C_{11}H_{10}N_1O_1F_5$: C, 49.45; H, 3.77; N, 5.24. Found: C, 49.21; H, 3.92; N, 5.07.

4.4. Hydrolysis of protective groups and analytical data of compounds 16 and 17

4.4.1. 6-Fluoro-8-methyl-6-(trifluoromethyl)-7,8-dihydropyrido[2,3-d]pyrimidine-2,5(3H,6H)-dione (16)

Sodium iodide (168 mg, 1.12 mmol) was added to a solution of compound **12** (100 mg, 0.28 mmol) in glacial acetic acid (3 mL) and the mixture was heated at 90 °C for 3 h. The solvent was removed by evaporation under reduced pressure and water (4 mL) was added to the dark residue. The solution was partially decolorized by the addition of a small amount of $Na_2S_2O_3$ and then extracted with ethyl acetate (4 × 4 mL). The combined organic layers were washed with water and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, CH_2Cl_2, a gradient of CH_2Cl_2/CH_3OH from 50:1 to 10:1, v/v) affording the compound **16**.

White crystal; m.p. = 252–255 °C; yield 51 mg, 68%; ^{1}H NMR (CD_3OD, 300 MHz): δ 3.27 (s, 3H, CH_3), 4.09 (m, 1H, H-3a′), 4.14 (m, 1H, H-3b′), 8.43 (s, 1H, H-6), (DMSO-d_6, 300 MHz): δ 3.13 (s, 3H, CH_3), 4.02–4.20 (m. 2H, H-3a′ and H-3b′), 8.47 (s, 1H, H-6), 12.15 (bs, 1H, NH); ^{19}F NMR (DMSO-d_6, 282 MHz): δ −78.01 (d, J = 9 Hz, 3F, CF_3), −178.60 (m, 1F, F-2′); ^{13}C NMR (DMSO-d_6, 101 MHz): δ 35.3 (s, CH_3), 49.2 (d, J = 26 Hz, C-3′), 87.1 (dq, J = 195 Hz and J = 30 Hz, C-2′), 100.2 (s, C-5), 124.4 (dq, J = 286 Hz and J = 30 Hz, CF_3), 150.4, 153.9 and 161.4 (s, C-2, C-4 and C-6), 177.9 (d, J = 19 Hz, C-1′); MS (EI) 70 eV, m/z (rel. int): 265 $[M]^+$ (100), 196, (12), 123 (25); Anal. Calcd. for $C_9H_7N_3O_2F_4$: C, 40.77; H, 2.66; N, 15.85. Found: C, 41.09; H, 2.36; N, 15.71.

4.4.2. 5-(4,5-Difluoro-2-methyl-4-(trifluoromethyl)isoxazolidin-5-yl)pyrimidine-2,4(1H,3H)-dione (17)

To a stirred solution of acetyl chloride (57 mg, 0.72 mmol) and methanol (32 mg, 1 mmol) in anhydrous THF (1 mL) at 0 °C was added dropwise a solution of compound **13** (100 mg, 0.24 mmol) in anhydrous THF (1 mL) The reaction was kept at the above temperature for an additional 1 h and then was stirred overnight at room temperature. The solvents were removed by evaporation under reduced pressure and the white residue was washed with a mixture of hexane and CH_2Cl_2 1:1 (v/v). The remaining crude product was crystallized from a small amount of ethanol affording the compound **17**. Any attempts of purification or analyses of compound **17** on a silica gel lead to decomposition of it.

White crystal; m.p. = 195–198 °C; yield 55 mg, 77%; diastereoisomeric ratio after crystalisation 9.4:1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.87 (s, 3H, CH_3), 3.34 (brs, 1H, H-3a′), 4.14 (brs, 1H, H-3b′), 7.63 (brs, 1H, H-6), 11.37 (brs, 2H, NH), (TFA-d, 300 MHz): δ 3.75 (m, 3H, CH_3), 4.44 (m, 1H, H-3a′), 5.07 (m, 1H, H-3b′), 8.18 (m, 1H, H-6); ^{19}F NMR (DMSO-d_6, 282 MHz): δ −69.16 (brs, 3F, CF_3) and −71.40 major (m, 3F, CF_3), −94.75 (brs, 1F, F-1′) and −106.88 major (m, 1F, F-1′), −163.33 major (dqm, J = 16 Hz and J = 8 Hz, 1F, F-2′) and −163.34 (brs, 1F, F-2′); ^{13}C NMR (TFA-d, 101 MHz): δ 47.4 and 45.8 (s, CH_3), 60.9 and 61.4 (d, J = 25 Hz, C-3′), 99.1 (dm, J = 210 Hz, C-2′), 107.8 (d, J = 25 Hz, C-5), 114.0 (m, C-1′), 122.7 (dq, J = 280 Hz and J = 29 Hz, CF_3), 147.4 and 147.6 (s, C-2), 152.0 (s, C-6), 165.9 and 166.3 (s, C-4); MS (EI) 70 eV, m/z (rel. int): 302 $[M + 1]^+$ (2), 240 (43), 139 (100); Anal. Calcd. for $C_8H_8N_3O_3F_5$: C, 35.89; H, 2.68; N, 13.95. Found: C, 35.55; H, 2.93; N, 13.62.

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[14] Crystal data for **13**: $C_{17}H_{24}F_5N_3O_3$, colorless, formula weight 413.39, monoclinic, space group P21/n, unit cell dimensions: a = 12.7994(3) Å, b = 10.0435(2) Å, c = 16.0070(4) Å, β = 100.738(2)°, volume = 2021.69(8) Å^3, Z = 4, calculated density = 1.358 g/cm^3, T = 293(2) K, F(0 0 0) = 864, 8130 reflections collected, 3944 unique with R_{int} = 0.0113, final R_1 = 0.0484, wR_2 = 0.1347 ($I > 2.\sigma_I$).
[15] Crystallographic data for compound **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 821873, Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk.