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Graphical Abstract

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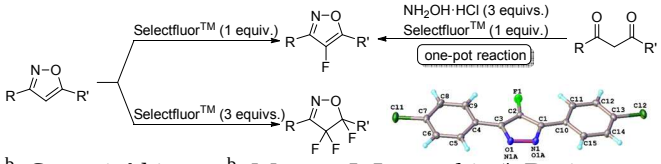

Kazuyuki Sato[a,b*], Graham Sandford[a*], Keiji Shimizu[b], Satomi Akiyama[b], Marcus J. Lancashire[a], Dmitry S.Yufit[a], Atsushi Tarui[b], Masaaki Omote[b], Itsumaro Kumadaki[b], Shinya Harusawa[c] and Akira Ando[b]

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Synthesis of fluorinated isoxazoles using Selectfluor™: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes

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Abstract: 3,5-Disubstituted 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline products were obtained from reaction of the corresponding isoxazoles with Selectfluor™ depending upon the reaction conditions. Although the fluorinations proceeded using conventional heating, microwave (μW) irradiation considerably shortened reaction times and enabled a high yielding one-pot cascade fluorination-cyclization from simple diketone substrates. In addition, a related 4-fluoroisoxazole-3-carboxyamide derivative was synthesized.

Keywords: fluoroheteroaromatic; selective fluorination; 4-fluoroisoxazole; 4,4,5-trifluoroisoxazoline TRPV1 antagonist.

1. Introduction

There is a continuing requirement for the development of efficient and environmentally benign routes for the synthesis of novel fluorinated aromatic and heterocyclic systems for incorporation into life science discovery programs, because many fluorinated pharmaceutical and agrochemical substances contain such structural units.[1] For the purpose of synthesizing fluorinated compounds, electrophilic fluorinating agents of the N-F class such as *N*-fluoropyridinium salts (F-Py-X),

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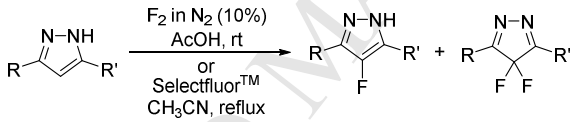
Selectfluor™ and NFSI are commonly used by medicinal chemists due to the relative ease of handling these shelf-stable, solid reagents and wide commercial availability. Many fluorinated 6-membered heteroaromatic derivatives find applications in a wide variety of drugs and plant protection systems and, consequently, there are many examples of the synthesis of fluorinated 6-membered heteroaromatic rings by selective fluorination strategies in the literature as typified by the preparation of a range of fluoro-pyridine and -pyrimidine systems.[2,3] On the other hand, selective fluorination of 5-membered heteroaromatic systems is rare and, in particular, there are only very few reports concerning the synthesis of fluorinated 5-membered heteroaromatic systems that have two ring heteroatoms, such as fluoro-pyrazoles, isoxazoles and thiazole derivatives.[4–6]

We recently reported selective fluorination of pyrazoles using fluorine gas or Selectfluor™ to give 4-fluoropyrazole or 4,4-difluoro-1*H*-pyrazole derivatives depending on the reaction conditions in moderate to good yields (Scheme 1).[7] As part of a wider research programme aimed at synthesizing fluorinated 5-membered heteroaromatic systems, in this paper, we report our studies concerning the fluorination of isoxazoles using Selectfluor™.



Scheme 1. Selective fluorination of pyrazoles.

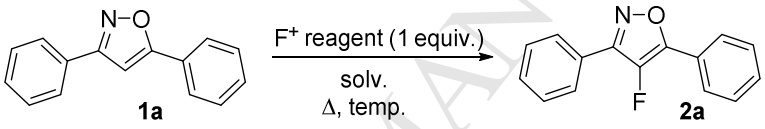
Studies concerning the synthesis of fluoroisoxazole derivatives are very rare, despite the potential utility of these systems in the life science industries. Reactions of fluorinated building blocks provide two methods for the synthesis of fluoroisoxazoles: condensation of 2-fluoro-1,3-dicarbonyl derivatives with hydroxylamine was reported by Bumgardner[5a] and, more recently, gold catalyzed fluorocyclization of 2-alkyne *O*-methyloximes gave rise to 4-fluoroisoxazole products[5b]. Only a very few examples of the most direct method for synthesizing fluoro-isoxazoles by electrophilic fluorination have been reported by Stephens.[5c] Low yields of fluoroisoxazoles were prepared using Selectfluor™ and a trifluorinated system was obtained as a minor by-product in one of their syntheses. In contrast, it was reported[5b] that attempted gold catalyzed electrophilic fluorination of 3,5-diphenylisoxazole gave no fluorinated product upon reaction with Selectfluor™ and reaction of related phenylisoxazoles with Selectfluor™ in acetonitrile were not successful, demonstrating the difficulty of carrying out such potentially simple transformations. Therefore, given conflicting

literature reports, we aimed to develop general, robust and accessible procedures for the synthesis of fluoro-isoxazoles by electrophilic fluorination reactions.

2. Results and Discussion

Following our results concerning the fluorination of pyrazoles[7], the corresponding 3,5-diphenylisoxazole (**1a**) was fluorinated in a similar manner by using Selectfluor™ assisted by microwave (μW) irradiation to give 3,5-diphenyl-4-fluoroisoxazole (**2a**) in moderate yield. Reaction conditions were optimized with respect to reaction time, solvent and reaction temperature as shown in Table 1.

Table 1. Fluorination of 3,5-diphenyl-4-fluoroisoxazole and reaction optimization.



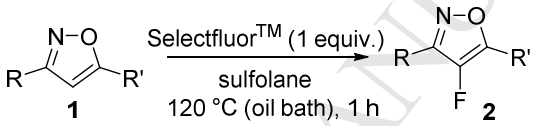
Entry	Solv.	F^+ reagent	Heated by	Temp. (°C)	Time (min)	Yield (%)[a]
1	CH_3CN	Selectfluor™	μW	90	15	21 (19)[b]
2	CH_3CN	Selectfluor™	μW	90	60	34
3	CH_3CN	Selectfluor™	μW	150	60	38
4	CH_3CN	Selectfluor™	μW	150	120	38
5	CH_3CN	Selectfluor™	μW	200	60	37
6	CH_3CN	F-Py-BF_4[c]	μW	150	60	nd
7	CH_3CN	NFSI	μW	150	60	trace
8	CH_3CN	F-2,6-diClPy-OTf[d]	μW	150	60	33
9	CH_3CN	F-2,6-diMePy-OTf[e]	μW	150	60	nd
10	EtOH	Selectfluor™	μW	150	60	5
11	THF	Selectfluor™	μW	150	60	nd
12	DMF	Selectfluor™	μW	150	60	9
13	NMP	Selectfluor™	μW	150	60	nd
14	sulfolane	Selectfluor™	μW	150	60	42 (38)[b]
15	sulfolane	Selectfluor™	μW	150	15	56 (44)[b]
16	sulfolane	Selectfluor™	oil bath	90	60	- (26)[b]
17	sulfolane	Selectfluor™	oil bath	120	60	- (44)[b]
18	sulfolane	Selectfluor™	oil bath	150	60	55 (42)[b]

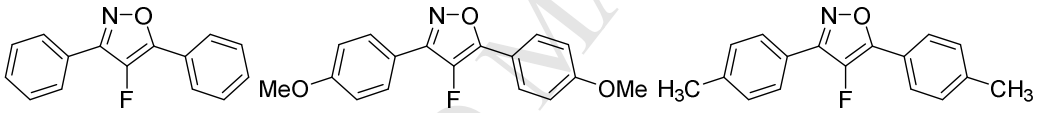
[a] ^{19}F NMR yield calculated from benzotrifluoride (BTF) as an internal standard.
[b] The numbers in parentheses show isolated yield.
[c] F-Py-BF_4 : *N*-fluoropyridinium tetrafluoroborate.
[d] F-2,6-diClPy-OTf : *N*-fluoro-2,6-dichloropyridinium triflate.
[e] F-2,6-diMePy-OTf : *N*-fluoro-2,6-dimethylpyridinium triflate.

Some *N*-fluoropyridinium salts (F-Py-X) and NFSI fluorinating agents were ineffective in bringing about fluorination, but the desired product (**2a**) was obtained in moderate yield by using Selectfluor™ (entries 1–9). Sulfolane was found to be the most effective solvent for this reaction (entries 10–14). In attempts to improve the yield various salts such as NaOTf, AgOTf, $Sc(OTf)_3$ and NaOEt were added to the reaction mixture, but these additives did not improve the yield of fluoroisoxazole product. Simple heating by conventional oil bath also gave the desired fluoroisoxazole product in similar yield as shown in entries 15–18. These results contrast with earlier reports[5b] regarding the fluorination of reaction of (**1a**) with Selectfluor™.

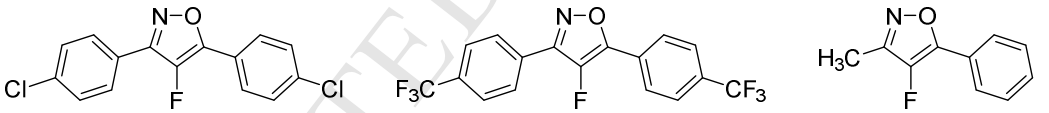
Using the optimized conditions (Table 1, entry 17 : sulfolane, 120 °C, 1 h), fluorination of several related isoxazoles were investigated and the results are summarized in Table 2.

Table 2. Selective fluorination of isoxazoles.





2a, 44%[a] **2b**, 32%[a] (41%)[a,b] **2c**, 44%[a]



2d, 35%[a] **2e**, 16%[a] **2f**, 41%[a]

[a] Isolated yield. [b] The reaction was carried out at 90 °C for 2 h.

3,5-Diarylisoxazoles that have electron donating group substituents gave the desired products in slightly higher yields in comparison to substrates bearing electron withdrawing groups, as would be expected for an electrophilic substitution process. A stronger donating group such as -OMe gave significant quantities of tar that decreased the yield of (**2b**), but milder reaction conditions (90 °C, 2 h) improved the yield.

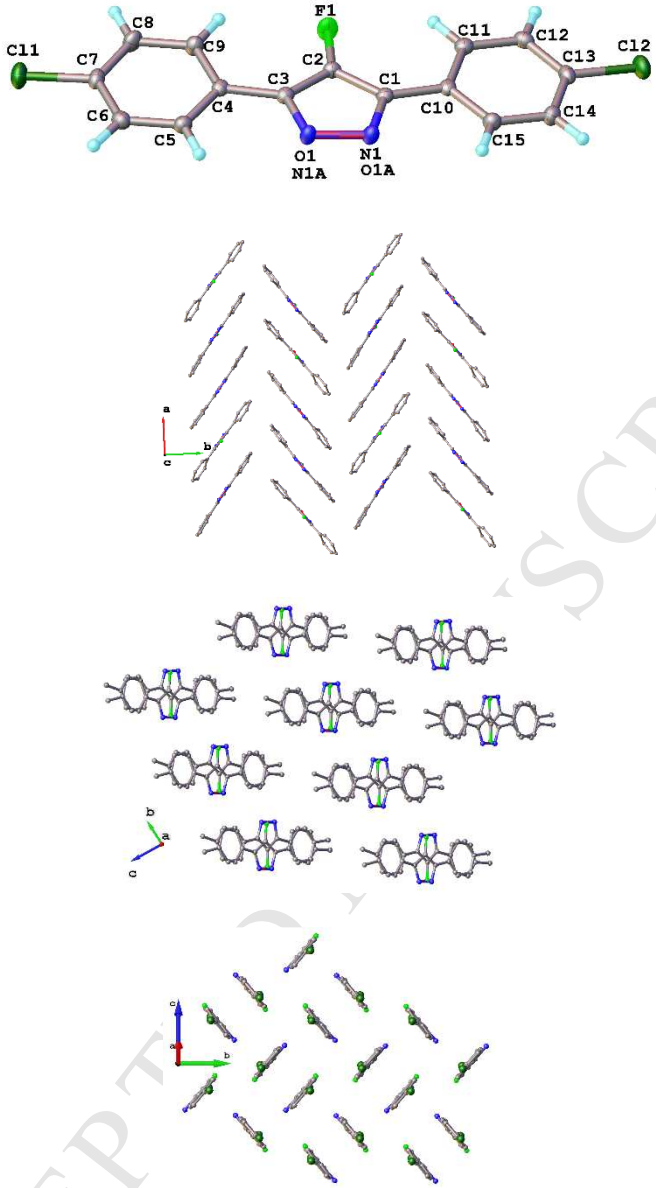


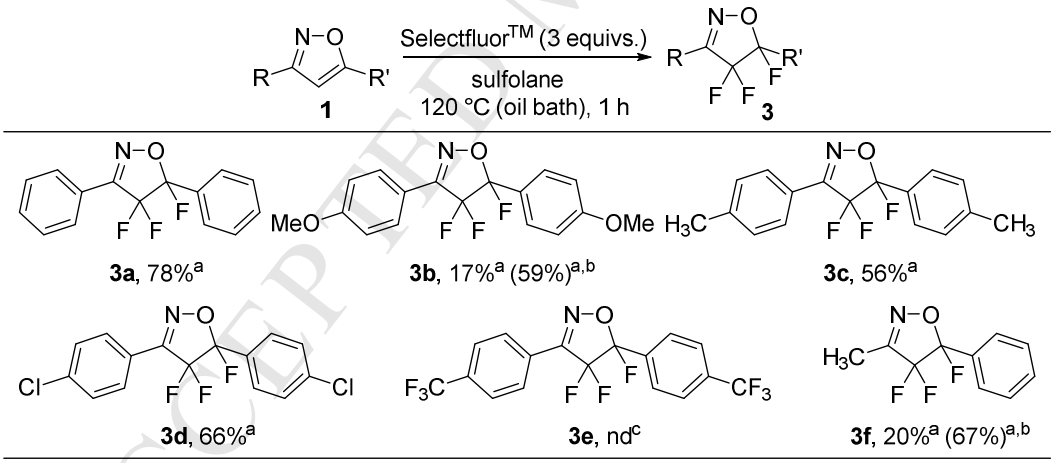
Figure 1. Molecular structure of 4-fluoro-3,5-di-(*p*-chlorphenyl)isoxazole (**2d**) and different packing motifs in crystal structures of (**2a**), (**2c**) and (**2d**).

For isoxazole substrates bearing other alkyl substituents, fluorination reactions gave the desired fluoroisoxazoles (**2c**–**f**) in moderate yields. All monofluorinated isoxazole products were isolated by column chromatography and characterized by NMR and mass spectrometry. In addition, the molecular structures of compounds (**2a**), (**2c**) and (**2d**) were confirmed by X-ray crystallography (Fig. 1). All these molecules are essentially planar, show similar N/O disorder in the heterocycle and π…π aromatic stacking interactions occur in the crystal. Nevertheless, the crystal packing in each system is quite different: molecules (**2a**) form layers of herring-bone packed molecules, in (**2c**)

disordered molecules are linked into aromatic stacks, while the layers in structure (**2d**) are constructed from herring-bone packed antiparallel dimers.

In attempts to increase the yield of the monofluorinated systems, we found that using an excess amount of Selectfluor™ gave another type of fluorinated system, 4,4,5-trifluoroisoxazolines (**3**), rather than increased amounts of 4-fluoroisoxazole products. Generation of a single 4,4,5-trifluoroisoxazoline derivative (**3**) was reported as a side product in a previous paper by Stephens and coworkers.[5c] In our case, products (**3**) were obtained in moderate to good yields using an excess amount of Selectfluor™ and the results are summarized in Table 3. 3,5-Di-*p*-methoxyphenylisoxazole and 3-methyl-5-phenylisoxazole (**1b** and **1f**) gave a complex mixture of products and, (**3b**) and (**3f**) were obtained in low yield, respectively. The use of milder conditions in acetonitrile (reflux, 90 °C) improved the yield of the trifluorinated systems considerably. However, *p*-trifluoromethyl substituents seriously decreased the reactivity of the isoxazole substrate and, consequently, the 4-fluoroisoxazole (**2e**) was isolated in low yield rather than the trifluoroisoxazoline (**3e**).

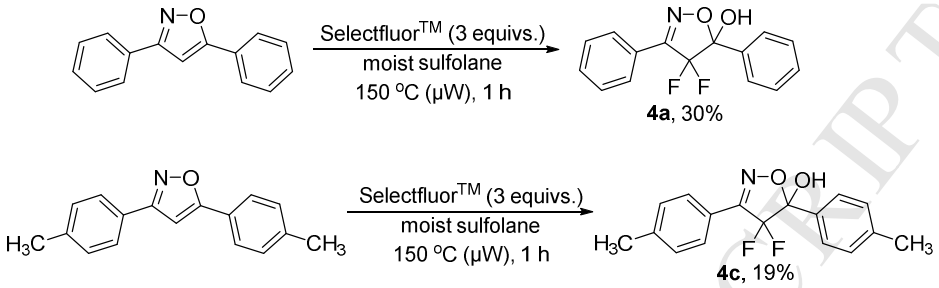
Table 3. Selective fluorination of various isoxazoles using excess amount of Selectfluor™.



[a] Isolated yield. [b] The reaction was carried out at 90 °C (reflux condition) in CH_3CN until full conversion of isoxazole. [c] The corresponding 4-fluoroisoxazole (**2e**) was isolated in 27%.

It was important to very rigorously dry the sulfolane solvent by vacuum distillation over sodium wire before attempting this trifluorination process because, when moist sulfolane was used (dry sulfolane from chemical suppliers used as received), a hydroxylated derivative was obtained after purification by column chromatography (Scheme 2).

Scheme 2. Synthesis of 4,4-difluoro-3,5-bis(phenyl)-isoxazol-5-ol derivatives (**4**).



The structures of **4a** and **4c** were confirmed by X-ray crystallography (Fig. 2). Both molecules adopt almost identical conformations in their crystals and are linked by O-H…N hydrogen bonds into infinitive chains.

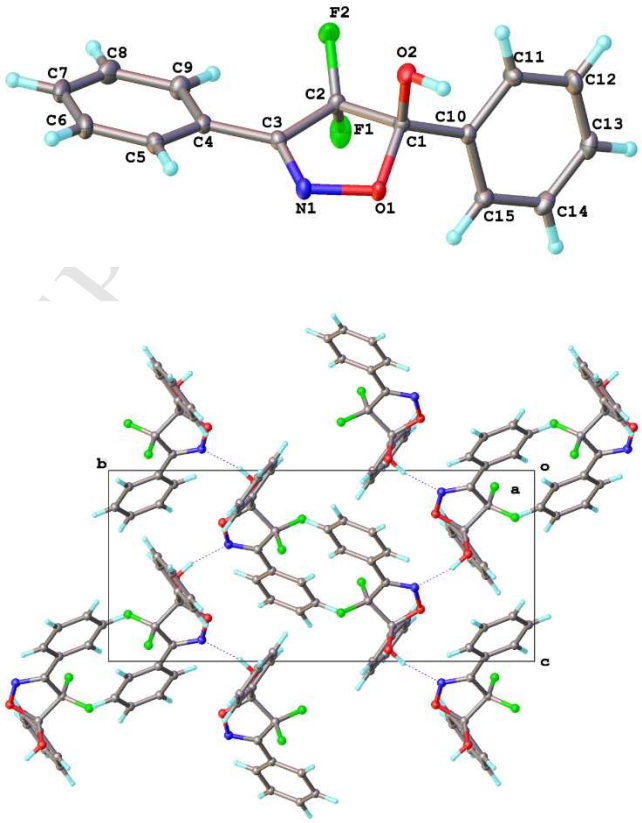
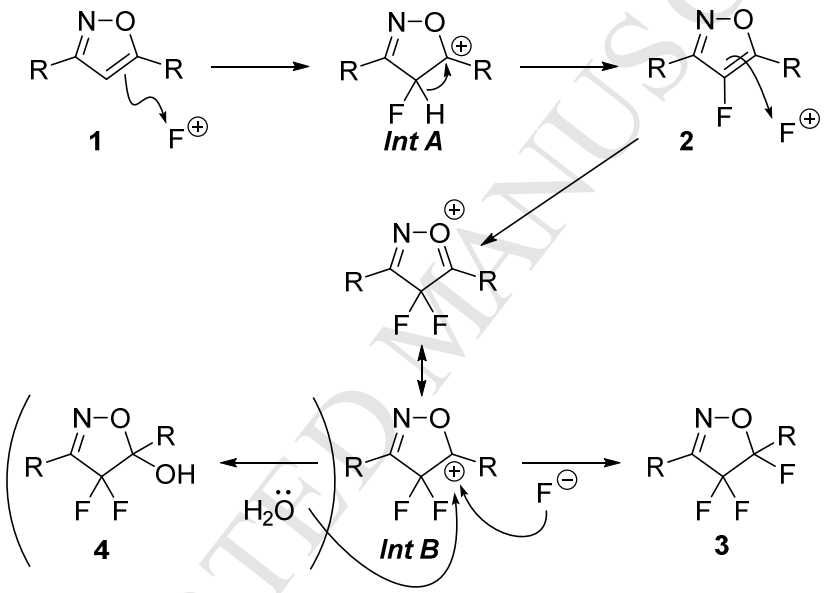


Figure 2. Molecular structure of 4,4-difluoro-3,5-diphenyl-isoxazol-5-ol (**4a**) and packing of the molecules in the crystal (hydrogen bonds are shown in dotted lines).

A mechanism for the formation of the monofluoro-, trifluoro and difluoro-hydroxyl systems is given in Scheme 2. Initial fluorination of the isoxazoles (**1**) gives the monofluorinated product (**2**) by a typical electrophilic aromatic substitution process. Since 4-fluoroisoxazoles are still significantly reactive towards electrophiles, reaction with a second equivalent of electrophilic fluorinating reagent Selectfluor^{TM} gives difluorinated intermediates which are immediately trapped by fluoride ion to give 4,4,5-trifluoroisoxazolines (**3**) (Scheme 3). The source of fluoride ion in these reactions is most probably derived from the BF_4^- counterion of Selectfluor^{TM}. The presence of any water in the sulfolane reaction medium gives rise to the hydroxyl group in (**4**).



Scheme 3. Proposed mechanism for selective fluorination of isoxazoles.

To provide a more consistent and readily operated synthesis of 4-fluoroisoxazole derivatives, we assessed a one-pot synthesis of 4-fluoroisoxazole **2** from the corresponding diketone **5** which in case of (**5c**), R=R'=*p*-Tol exists in the disordered enol form in the crystal (Fig. 3).

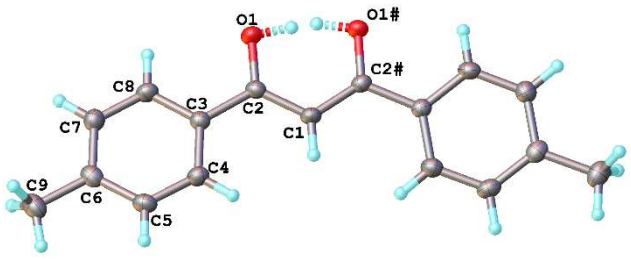
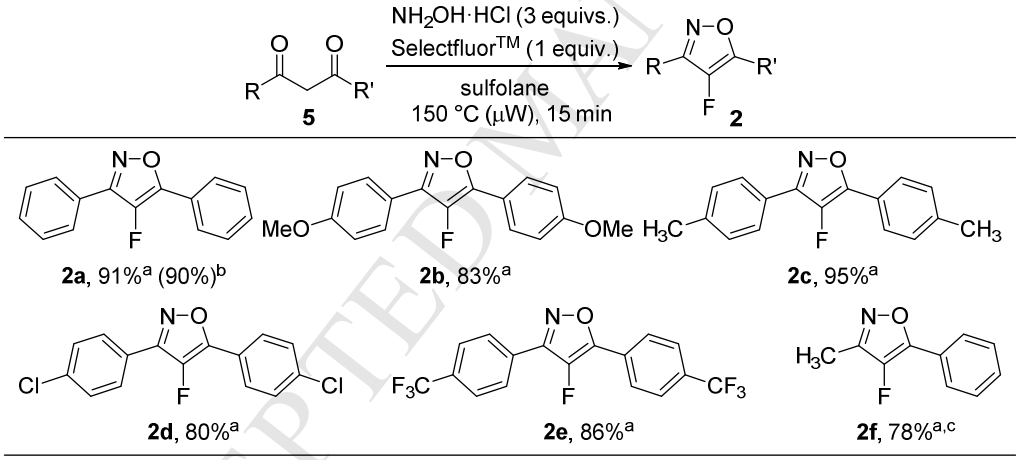


Figure 3. Molecular structure of diketone **5c** (R=R'=*p*-Tol, both components of disordered hydrogen atoms are shown).

Fortunately, reaction of diketone (**5**), hydroxylamine and Selectfluor™ in a single-pot, μW assisted process provided a great improvement in the yield of fluoroisoxazole as shown in Table 4. By this one-pot process, 4-fluorinated isoxazoles were obtained together with a small amount of monofluorodiketone derivative in most cases but, even when 3 equivs. of Selectfluor™ was used, the corresponding 4,4,5-trifluoroisoxazolines (**3**) were not obtained. The presence of monofluorinated diketones in the reaction mixtures, as observed by ^{19}F NMR spectroscopy, indicates that fluorination of the diketone substrates occurs before cyclisation leading to higher yields of the desired fluoroisoxazole products.

Table 4. One-pot synthesis of 4-fluoroisoxazole derivatives (**2**).

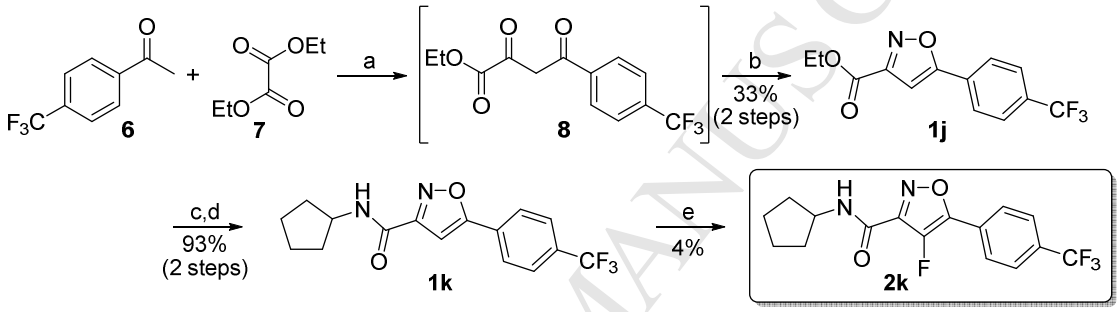


[a] Isolated yield. [b] Isolated yield by using conventional heating (oil bath) at 150 °C for 1 h.
[c] Regioisomeric mixtures (these isomers were calculated by ^{1}H NMR and its ratio was **2f** : its regioisomer = 86:14).

Based on the successful fluorination of isoxazoles, we used our methodology for the synthesis of a biologically active fluoroisoxazole system. Transient receptor potential vanilloid 1 (TRPV1) is a Ca^{2+} permeant non-selective cation channel expressed in a subpopulation of primary afferent neurons and led to the cloning of the first vanilloid (capsaicin) receptor by Julius and colleagues in 1997.[8] Recently a new series of TRPV1 antagonists that are expected to aid in management of acute and chronic pain was reported and, 4-fluoroisoxazole-3-carboxyamides showed moderate potency in a TRPV1 assay.[9] Using the synthetic methodology described above, we targeted the synthesis of 4-fluoroisoxazole-3-carboxyamide (**2j**) following the strategy shown in Scheme 4

because this system has been reported to be a potent TRPV1 antagonist.[9b] Reaction of diethyl oxalate and *p*-trifluoromethylacetophenone to form the corresponding diketoester (**8**) was followed by condensation with hydroxylamine hydrochloride to give the isoxazole (**1j**). Hydrolysis and amidation of **1j** gave the corresponding isoxazole-3-carboxyamide (**1k**). The fluorination of **1k** as the final stage gave a desired TRPV1 antagonist (**2k**), although its yield was very low. To improve the yield, **1j** or related 3-hydroxymethyl-isoxazole (**1l**), were used as the substrates but no fluoroisoxazole products were obtained. Unfortunately, our one-pot strategy also failed to give higher yields of (**2k**) from (**8**) despite many attempts using a range of reaction conditions.

Scheme 4. Synthesis of 4-fluoroisoxazole-3-carboxyamide as a TRPV1 antagonist.



[a]LiHMDS, THF, -78 °C to rt, 1 h. [b]$NH_2OH.HCl$ (2 equivs.), EtOH, reflux, 16 h. [c]LiOH, THF/H_2O, r.t., 1 h.
[d]oxalyl chloride, DMF, Et_3N, cyclopentylamine, CH_2Cl_2, 16 h,. [e]Selectfluor™ (2 equivs.), sulfolane, 120 °C, 5 h.

3. Conclusions

In conclusion, we demonstrated that the C-4 fluorination of 3,5-disubstituted isoxazoles is possible when Selectfluor™ is used as the fluorinating agent using both conventional oil bath heating and μW irradiation. We also showed that using an excess amount of Selectfluor™ gave the corresponding 4,4,5-trifluoroisoxazolines in moderate to good yields if thoroughly dry sulfolane is used as the reaction medium. The synthesis of 4-fluoroisoxazole derivatives can best be achieved in high yields by a one-pot process involving heating the 1,3-diketone substrate, Selectfluor™ and hydroxylamine in sulfolane using microwave heating.

4. Experimental

4.1 General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on JNM-GX400 spectrometers. ^{19}F NMR spectra were recorded on Hitachi FT-NMR R-90H and Bruker 400 Ultrashield spectrometers. Chemical

shifts of ^{1}H NMR and ^{13}C NMR are reported in ppm from tetramethylsilane (TMS: 0 ppm) as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from benzotrifluoride (BTF: 0 ppm) as an internal standard unless otherwise noted. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometers and a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode. Accurate mass analysis was performed on a Xevo QtoF mass spectrometer (Waters Ltd, UK) with an accurate solids analysis probe (ASAP). Melting points were measured on Yanagimoto micro melting point apparatus MP-S3. IR spectra were recorded on JASCO FT/IR-410 spectrophotometer. Analytical gas-liquid chromatography (GLC) was carried out on Hitachi G-3500 gas chromatograph (column; TO-5 0.25 mm x 15 m, carrier; He at 2.2 ml/min). Peak areas were calculated on Hitachi D-2500 Chromato-integrator. Microwave reactions were performed in microwave tubes with clip lids using Biotage Initiator microwave reactor. All commercially available reagents were used without further purification. All experiments were carried out under argon atmosphere unless otherwise noted.

4.2 General procedure for selective fluorination of isoxazoles to synthesise **2** *assisted by μW irradiation.*

Isoxazole (**1**; 1 mmol) and Selectfluor™ (1 mmol) were added to a microwave vial and suspended in sulfolane (4 mL). The vial was sealed and heated by microwave irradiation for 15 minutes at 150 °C. The resulting mixture was quenched with $NaHCO_3$ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.3 General procedure for selective fluorination of isoxazoles to synthesise **2** *heated by oil bath.*

Under an Ar atomosphere, isoxazole (**1**; 1 mmol) and Selectfluor™ (1 mmol) were suspended in sulfolane (4 mL) and stirred for 1 h at 120 °C. The resulting mixture was quenched with $NaHCO_3$ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.4 General procedure for the synthesis of 4,4,5-trifluoroisoxazolines **3**.

Under an Ar atomosphere, isoxazole (**1**; 1 mmol) and Selectfluor™ (3 mmol) were suspended in sulfolane (4 mL) and stirred for 1 h at 120 °C. The resulting mixture was quenched with $NaHCO_3$ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**3**).

4.5 General procedure for the synthesis of 4,4-difluoroisoxazol-5-ols **4***.*

A mixture comprising of isoxazole (**1**, 1 mmol) and Selectfluor™ (3 mmol) in moist sulfolane (4 mL) was irradiated by microwave heating at 150 °C for 1 h. The product was extracted into chloroform, washed sequentially with sat. $NaHCO_3$ and brine, then dried ($MgSO_4$) and the solvent was removed *in vacuo*. Column chromatography on silica gel using hexane:ether:triethylamine (70:10:1) as eluent gave the 5-hydroxyl product (**4**).

4.6 General procedure for the one-pot synthesis of 4-fluorinated isoxazoles **2** *assisted by μW irradiation.*

Diketone (**5**; 1 mmol), hydroxylamine hydrochloride (3 mmol) and Selectfluor™ (1 mmol) were added to a microwave vial and suspended in sulfolane (4 mL). The vial was sealed and heated by microwave irradiation for 15 minutes at 150 °C. The resulting mixture was quenched with $NaHCO_3$ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.7 Synthesis of ethyl 5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**1j**).

Under an Ar atomosphere, to a solution of *p*-trifluoromethylacetophenone (**6**; 2 mmol) and diethyl oxalate (**7**; 4 mmol) in THF (10 mL) was added 1.3 M of LiHMDS in THF (1.69 mL, 2.2 mmol) at -78 °C. The resulting mixture was gradually warmed to rt and stirred for 16 h. The mixture was quenched with 10% HCl and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and, then the reaction residue was dissolved in EtOH (2 mL) and H_2O (3 mL). $NH_2OH{\cdot}HCl$ (278 mg, 4 mmol) was added and the resulting solution was heated at reflux for 16 h. The resulting mixture was quenched with brine and extracted with AcOEt, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2) to give the product (**1j**) (190 mg, 33 %).

4.8 Synthesis of N-cyclopentyl-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (**1k**).

To a solution of **1j** (285 mg, 1 mmol) in THF (5 mL) was added a solution of LiOH (71 mg, 1.7 mmol) in H_2O (5 mL) at rt and, the mixture was stirred for 1 h. The resulting mixture was quenched with 10% HCl, and extracted with AcOEt. The AcOEt layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and, then the reaction residue was dissolved in CH_2Cl_2 (8 mL). A solution of oxalyl chloride (0.25 mL, 3 mmol) in CH_2Cl_2 (1.5 mL) was added to the residue solution and stirred for 20 min. A few drops of DMF were added and the mixture was stirred for 2 h at rt. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (8 mL). Et_3N (0.5 mL) and cyclopentylamine (5 mL) were added and the solution was stirred for 16 h at rt. The resulting mixture was quenched with 10% HCl and extracted with AcOEt, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2) to give the product (**1k**) (300 mg, 93 %).

5. Spectroscopic Data

*5.1 Ethyl 5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**1j**).* (0.09 g, 33%); colorless solid; M.p. 133.0–134.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, *J* = 7.1 Hz), 4.50 (2H, q, *J* = 7.1 Hz), 7.04 (1H, s), 7.76–7.78 (2H, m), 7.93–7.96 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.46, 62.67, 101.6, 123.7 (q, *J* = 271.7 Hz), 126.4 (q, *J* = 3.8 Hz), 126.4, 129.8 (q, *J* = 1.3 Hz), 132.6 (q, *J* = 32.9 Hz), 157.3, 159.8, 170.1; ^{19}F NMR (90 MHz, $CDCl_3$) δ: -0.31 (3F, s); MS *m/z*: 285 (M^+); HRMS Calcd for $C_{13}H_{10}F_3NO_3$: 285.0613 (M^+), Found: 285.0613; IR (KBr) cm^{-1}: 3134, 2990, 1725.

*5,2 N-Cyclopentyl-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (**1k**).* (0.30 g, 93%); colorless solid; M.p. 204.5–205.5 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.51–1.81 (6H, m), 2.04–2.15 (2H, m), 4.41 (1H, m), 6.78 (1H, br d, *J* = 6.7 Hz), 7.07 (1H, s), 7.75–7.77 (2H, m), 7.91–7.93 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.74, 33.01, 51.33, 100.5, 123.5 (q, *J* = 271.7 Hz), 126.0 (q, J = 3.8 Hz), 126.1, 129.7 (q, *J* = 1.3 Hz), 132.2 (q, *J* = 32.9 Hz), 157.8, 159.3, 169.6; ^{19}F NMR (90 MHz, $CDCl_3$) δ: -0.30 (3F, s); MS *m/z*: 324 (M^+); HRMS Calcd for $C_{16}H_{15}F_3N_2O_2$: 324.1086 (M^+), Found: 324.1084.

*5.3 4-Fluoro-3,5-diphenylisoxazole (**2a**).* (0.10 g, 44%); colorless solid; M.p. 102.0–103.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 7.45–7.55 (6H, m), 7.88–7.90 (2H, m), 7.94–7.97 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 125.4 (d, *J* = 4.9 Hz), 126.1 (d, *J* = 5.1 Hz), 127.0 (d, *J* = 3.9 Hz), 127.2 (d, *J* = 3.5 Hz), 129.1 129.2, 130.3 (d, *J* = 1.1 Hz), 130.6, 141.7 (d, *J* = 258.7 Hz), 153.3 (d, *J* = 10.6 Hz), 153.7 (d, *J* = 19.3 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -115.4 (1F, s); MS *m/z*: 239 (M^+); HRMS Calcd for $C_{15}H_{10}NOF$: 239.0746 (M^+), Found: 239.0755; IR (KBr) cm^{-1}: 3067, 1466, 1215.

*5.4 4-Fluoro-3,5-bis(4-methoxyphenyl)isoxazole (**2b**).* (0.12 g, 41%); colorless solid; M.p. 137.0–138.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 3.88 (3H, s), 3.88 (3H, s), 7.02–7.05 (4H, m), 7.80–7.90 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 55.7, 114.6, 114.7, 119.1 (d, *J* = 5.1 Hz), 119.7 (d, *J* = 3.9 Hz), 127.1 (d, *J* = 4.8 Hz), 128.7 (d, *J* = 3.7 Hz), 140.7 (d, *J* = 255.4 Hz), 152.9 (d, *J* = 10.5 Hz), 153.5 (d, *J* = 19.7 Hz), 161.0 (d, *J* = 1.5 Hz), 161.4; ^{19}F NMR (90 MHz, $CDCl_3$) δ: -117.5 (1F, s); MS *m/z*: 299 (M^+); HRMS Calcd for $C_{17}H_{14}NO_3F$: 299.0958 (M^+), Found: 299.0959; IR (KBr) cm^{-1}: 2973, 2944, 1648, 1609, 1516, 1467, 1252.

*5.5 4-Fluoro-3,5-di-p-tolylisoxazole (**2c**).* (0.11 g, 44%); colorless solid; M.p. 152.5–153.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 2.43 (6H, s), 7.31–7.34 (4H, m), 7.76–7.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.50, 21.54, 123.1 (d, *J* = 5.0 Hz), 123.9 (d, *J* = 3.9 Hz), 125.0 (d, *J* = 4.9 Hz), 126.7 126.8, 129.5 (d, *J* = 5.3 Hz), 140.2 (d, *J* = 1.3 Hz), 140.5, 141.0 (d, *J* = 256.8 Hz), 152.9 (d, *J* = 10.5 Hz), 153.4 (d, *J* = 19.4 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -116.1 (1F, s); MS *m/z*: 267 (M^+); HRMS Calcd for $C_{17}H_{14}NOF$: 267.1059 (M^+), Found: 267.1068; IR (KBr) cm^{-1}: 1647, 1614, 1514, 1470.

*5.6 3,5-Bis(4-chlorophenyl)-4-fluoroisoxazole (**2d**).* (0.11 g, 35%); colorless solid; M.p. 170.0–172.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 7.48–7.53 (4H, m), 7.80–7.83 (2H, m), 7.87–7.89 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 124.3 (d, *J* = 5.1 Hz), 125.2 (d, *J* = 4.0 Hz), 126.7 (d, *J* = 5.0 Hz), 128.5 (d, *J* = 3.7 Hz), 129.6, 129.7, 136.6 (d, *J* = 1.9 Hz), 137.0 (d, *J* = 0.7 Hz), 141.6 (d, *J* = 258.7 Hz), 152.5 (d, *J* = 10.5 Hz), 153.0 (d, *J* = 19.4 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -114.6 (1F, s); MS *m/z*: 307 (M^+); HRMS Calcd for $C_{15}H_8NOCl_2F$: 306.9967 (M^+), Found: 306.9969; IR (KBr) cm^{-1}: 1651, 1599, 1496, 1457, 1092.

*5.7 4-Fluoro-3,5-bis(4-(trifluoromethyl)phenyl)isoxazole (**2e**).* (0.06 g, 16%); colorless solid; M.p. 156.0–157.0 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ: 7.79–7.82 (4H, m), 8.00–8.09 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 123.5 (q, *J* = 271.7 Hz), 123.5 (q, *J* = 271.6 Hz), 125.4 (d, *J* = 5.2 Hz), 125.9 (q, *J* = 3.8 Hz), 126.1 (q, *J* = 3.8 Hz), 127.3 (d, *J* = 3.7 Hz), 128.5 (m), 129.6 (m), 131.9 (qd, *J* = 32.8, 1.5 Hz), 132.4 (q, *J* = 32.8 Hz), 142.1 (d, *J* = 261.1 Hz), 152.1 (d, *J* = 10.4 Hz), 152.5 (d, *J* = 19.5 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -0.29 (6F, s), -113.1 (1F, s); MS *m/z*: 375 (M^+); HRMS Calcd for $C_{17}H_8NOF_7$: 375.0494 (M^+), Found: 375.0498; IR (KBr) cm^{-1}: 1650, 1619, 1538, 1321, 1175, 1136.

*5.8 4-Fluoro-3-methyl-5-phenylisoxazole (**2f**).* (0.07 g, 71%); colorless oil; ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, d, *J* = 0.5 Hz), 7.40–7.51 (3H, m), 7.79–7.82 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.70 (d, *J* = 5.8 Hz), 125.0 (d, *J* = 4.8 Hz), 125.8 (d, *J* = 5.0 Hz), 128.8, 129.7 (d, *J* = 1.3 Hz), 142.1 (d, *J* = 254.9 Hz), 151.7 (d, *J* = 15.9 Hz), 151.8 (d, *J* = 18.2 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -118.3 (1F, s); MS *m/z*: 177 (M^+); HRMS Calcd for $C_{10}H_8FNO$: 177.0590 (M^+), Found: 177.0586.

*5.9 N-Cyclopentyl-4-fluoro-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (**2k**).* (0.01 g, 4%); colorless solid; M.p. 188.5–189.0 °C (recrystallized from MeOH); ^{1}H NMR ($CDCl_3$) δ: 1.52–1.78 (6H, m), 2.07–2.15 (2H, m), 4.42 (1H, m), 6.62 (1H, br d, *J* = 6.1 Hz), 7.78–7.80 (2H, m), 7.96–7.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 33.0, 51.3, 123.4 (q, *J* = 271.8 Hz), 125.4 (d, *J* = 4.8 Hz), 126.1 (q, *J* = 3.8 Hz), 128.1 (m), 132.1 (m), 142.1 (d, *J* = 266.6 Hz), 148.7 (d, *J* = 8.5 Hz), 153.5 (d, *J* = 17.9 Hz), 156.2 (d, *J* = 3.7 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -0.37 (3F, s), -111.0 (1F, s); MS *m/z*: 342 (M^+); HRMS Calcd for $C_{16}H_{14}F_4N_2O_2$: 342.0991 (M^+), Found: 342.0995.

*5.10 4,4,5-Trifluoro-3,5-diphenyl-4,5-dihydroisoxazole (**3a**).* (0.22 g, 78%); colorless oil; ^{1}H NMR ($CDCl_3$) δ: 7.48–7.58 (6H, m), 7.66–7.68 (2H, m), 7.88–7.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.3 (ddd, *J* = 241.5, 36.5, 21.1 Hz), 124.1 (m), 124.8 (ddd, *J* = 290.5, 256.1, 34.4 Hz), 127.3 (m), 127.4 (d, *J* = 1.7 Hz), 128.3 (m), 128.9, 129.5, 131.4 (d, *J* = 1.7 Hz), 132.5, 154.8 (dd, *J* = 25.6, 23.7 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -38.4 (1F, dd, *J* = 273, 8 Hz), -52.9 (1F, dd, *J* = 8, 3 Hz), -61.0 (1F, dd, *J* = 273, 3 Hz); MS *m/z*: 277 (M^+); HRMS Calcd for $C_{15}H_{10}NOF_3$: 277.0714 (M^+), Found: 277.0716; IR (neat) cm^{-1}: 3067, 1140, 1057, 1039.

*5.11 4,4,5-Trifluoro-3,5-bis(4-methoxyphenyl)-4,5-dihydroisoxazole (**3b**).* (0.20 g, 59%); colorless solid; M.p. 59.5–61.5 °C (recrystallized from hexane); ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H), 3.87 (s, 3H), 6.99–7.02 (4H, m), 7.56–7.59 (2H, m), 7.82–7.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.31, 55.39, 111.0 (ddd, *J* = 239.7, 36.1, 21.2 Hz), 113.9, 114.6, 116.1 (dd, *J* = 3.0, 1.4 Hz), 119.9 (dd, *J* = 27.9, 0.9 Hz), 124.4 (ddd, *J* = 271.9, 254.6, 35.4 Hz), 128.4 (dd, *J* = 5.2, 1.4 Hz), 128.7 (d, *J* = 1.9 Hz), 154.0 (dd, *J* = 25.3, 23.7 Hz), 161.5 (d, *J* = 1.8 Hz), 162.5; ^{19}F NMR (90 MHz, $CDCl_3$) δ: -38.3 (1F, dd, *J* = 273, 8 Hz), -51.6 (1F, dd, *J* = 8, 4 Hz), -61.0 (1F, dd, *J* = 273, 4 Hz); MS *m/z*: 337 (M^+); HRMS Calcd for $C_{17}H_{14}F_3NO_3$: 337.0926 (M^+), Found: 337.0923; IR (KBr) cm^{-1}: 2967, 2936, 1613, 1518, 1265.

*5.12 4,4,5-Trifluoro-3,5-di-p-tolyl-4,5-dihydroisoxazole (**3c**).* (0.17 g, 56%); colorless solid; M.p. 73.0–74.0 °C (recrystallized from MeOH); ^{1}H NMR ($CDCl_3$) δ: 2.42 (m, 6H), 7.29–7.31 (4H, m), 7.53–7.55 (2H, m), 7.76–7.78 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.39, 21.65, 110.6 (ddd, *J* = 240.2, 36.2, 21.1 Hz), 120.9 (m), 124.5 (ddd, *J* = 272.1, 255.0, 34.7 Hz), 125.0 (m), 126.8 (m), 126.9 (d, *J* = 1.8 Hz), 129.1, 129.8, 141.2 (d, *J* = 1.8 Hz), 142.7, 154.4 (dd, *J* = 25.5, 23.6 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -38.4 (1F, dd, *J* = 273, 8 Hz), -52.4 (1F, dd, *J* = 8, 4 Hz), -61.1 (1F, dd, *J* = 273, 4 Hz); MS *m/z*: 305 (M^+); HRMS Calcd for $C_{17}H_{14}F_3NO$: 305.1027 (M^+), Found: 305.1035; IR (KBr) cm^{-1}: 2969, 1136, 1042.

*5.13 3,5-Bis(4-chlorophenyl)-4,4,5-trifluoro-4,5-dihydroisoxazole (**3d**).* (0.23 g, 66%); colorless solid; M.p. 111.0–111.5 °C (recrystallized from hexane); ^{1}H NMR ($CDCl_3$) δ: 7.48–7.51 (4H, m), 7.57–7.59 (2H, m), 7.80–7.82 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.6 (ddd, *J* = 241.9, 36.2, 21.2 Hz), 121.9 (m), 124.2 (ddd, *J* = 272.6, 255.6, 34.1 Hz), 126.2 (m), 128.2 (d, *J* = 1.8 Hz), 128.3 (m), 128.9, 129.6, 137.6 (d, *J* = 2.2 Hz), 138.7, 153.7 (dd, *J* = 25.6, 23.8 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -38.5 (1F, dd, *J* = 274, 8 Hz), -53.0 (1F, dd, *J* = 8, 4 Hz), -60.9 (1F, dd, *J* = 274, 4 Hz); MS *m/z*: 345 (M^+); HRMS Calcd for $C_{15}H_8C_{l2}F_3NO$: 344.9935 (M^+), Found: 344.9928; IR (KBr) cm^{-1}: 3097, 1094, 1046.

*5.14 4,4,5-Trifluoro-3-methyl-5-phenyl-4,5-dihydroisoxazole (**3f**).* (0.14 g, 67%); colorless oil; ^{1}H NMR ($CDCl_3$) δ: 2.23 (3H, d, *J* = 2.3 Hz), 7.45–7.55 (3H, m), 7.58–7.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.59 (m), 109.9 (ddd, *J* = 239.4, 36.3, 20.4 Hz), 123.9 (ddd, *J* = 270.2, 254.1, 34.6 Hz), 126.8 (dd, *J* = 5.2, 1.6 Hz), 128.1 (dd, *J* = 27.0, 1.1 Hz), 128.4, 130.9 (d, *J* = 1.9 Hz) 154.4 (dd, *J* = 28.5, 24.6 Hz); ^{19}F NMR (90 MHz, $CDCl_3$) δ: -43.9 (1F, m), -53.8 (1F, m), -66.3 (1F, m); MS

m/z: 215 (M^+); HRMS Calcd for $C_{10}H_8F_3NO$: 215.0558 (M^+), Found: 215.0559; IR (KBr) cm^{-1}: 3069, 1147, 1114, 1043.

*5.15 4,4-Difluoro-3,5-diphenyl-isoxazol-5-ol (**4a**).* (0.08 g, 30%); orange powder; M.p. 103–106 °C; ^1H NMR ($CDCl_3$) δ: 3.73 (1H, s), 7.58–7.46 (6H, m), 7.71–7.67 (2H, m), 7.89 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 126.83 (d, *J* = 1.4 Hz), 127.04 (d, *J* = 1.5 Hz), 128.59, 129.08, 130.36, 131.60; ^{19}F (376 MHz, internal standard: $CFCl_3$ as 0 ppm, $CDCl_3$) δ: -100.39 (d, *J* = 266.3 Hz), -120.09 (d, *J* = 266.3 Hz); HRMS Calcd for $C_{15}H_{12}F_2NO$: 276.0841 ($[MH]^+$), Found: 276.0842; IR (neat) cm^{-1}: 2982, 1450, 1365, 1242, 1127, 1098.

*5.16 4,4-Difluoro-3,5-bis(4'-methylphenyl)-isoxazol-5-ol (**4c**).* (0.06 g, 19%); orange powder; M.p. 119–122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.40 (3H, s), 2.41 (3H, s), 3.92 (1H, s), 7.30–7.24 (4H, m), 7.54 (2H, d, *J* = 8.2 Hz), 7.75 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.33, 21.62, 126.75 (d, *J* = 1.4 Hz), 126.95 (d, *J* = 1.3 Hz), 128.27, 129.79, 140.42, 142.10; ^{19}F (376 MHz, internal standard: $CFCl_3$ as 0 ppm, $CDCl_3$) δ: -100.26 (d, *J* = 265.6 Hz), -120.53 (d, *J* = 265.8 Hz); HRMS Calcd for $C_{17}H_{16}NF_2O$: 304.1140 ($[MH]^+$), Found: 304.1137; IR (neat) cm^{-1}: 1362, 1243, 1128, 1091, 1027.

6. X-Ray crystallography

The single crystal X-ray diffraction data for the compound **5** have been collected on an Agilent XCalibur diffractometer (Saphire-3 CCD detector, graphite monochromator,) and for all other compounds on a Bruker D8 Venture (Photon 100 CMOS detector, Iμ S microsource, focusing mirrors) diffractometer using λMoKα radiation, λ =0.71073Å. All data were collected at the temperature 120.0(2)K maintained by Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats. The structures was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL[10] and Olex2[11] software. All non-disordered non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined in riding mode. The disordered atoms were refined with fixed SOF=0.5 in isotropic approximation. The structure **2c** shows the whole molecule disorder and was refined isotropically with a number of geometry constrains. The crystallographic data and refinement paramaters are shown in Table 5,

crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1440941-1440946.

Table 5. Crystal data and structure refinement

Compound	**2a**	**2c**	**2d**	**4a**	**4c**	**5c**
Empirical formula	$C_{15}H_{10}FNO$	$C_{17}H_{14}FNO$	$C_{15}H_8Cl_2FNO$	$C_{15}H_{11}F_2NO_2$	$C_{17}H_{15}F_2NO_2$	$C_{17}H_{16}O_2$
Formula weight	239.24	267.29	308.12	275.25	303.30	252.30
Crystal system	tetragonal	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P4_1$	P1	$P2_1/c$	$P2_1/c$	$P2_1/n$	C2/c
a/Å	17.2287(16)	4.9701(8)	14.3733(2)	8.37740(10)	12.7558(3)	11.2849(8)
b/Å	17.2287(16)	6.9708(10)	7.58840(10)	18.4265(3)	8.4290(2)	11.8771(5)
c/Å	23.098(2)	9.8488(13)	12.2635(3)	8.60770(10)	14.8259(4)	10.6797(7)
α/°	90.00	86.142(11)	90.00	90.00	90.00	90.00
β/°	90.00	85.356(12)	105.1303(13)	106.7387(15)	106.521(2)	114.044(8)
γ/°	90.00	81.025(12)	90.00	90.00	90.00	90.00
Volume/$Å^3$	6856.0(11)	335.42(8)	1291.22(4)	1272.44(3)	1528.25(7)	1307.23(14)
Z	24	1	4	4	4	4
$\rho_{calc}g/cm^3$	1.391	1.323	1.585	1.437	1.318	1.282
μ/mm^{-1}	0.099	0.092	0.507	0.115	0.103	0.083
Reflections collected	86503	6768	27038	19475	19890	7898
Independent refl., Rint	7647, 0.1995	1787, 0.0729	3765, 0.0481,	3387, 0.0372	3330,0.0585,	1745,0.0507,
Data/restraints/parameters	7647/1/974	1787/3/117	3765/0/213	3387/0/185	3330/0/205	1745/1/94
Goodness-of-fit on F^2	1.013	1.415	1.051	1.008	1.033	1.025
Final R_1 [I≥2σ (I)]	0.0686	0.1247	0.0340	0.0422	0.0708	0.0603
Final wR_2 [all data]	0.1816	0.4073	0.0926	0.1136	0.2084	0.1784

7. Acknowledgments

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8. References and notes

1. (a) Fluorine-Containing Synthons; Soloshonok, V. A. Ed.; ACS Publications Division and Oxford University Press: Washington, D.C., 2005. (b) Uneyama, K. Organofluorine Chemistry; Blackwell Publishing: Oxford, 2006. (c) Bégué, J.-P., Bonnet-Delpon, D.; Bioorganic and Medicinal Chemistry of Fluorine; John Wiley & Sons Ltd.: New Jersey, 2008. (d) Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009.

2. For the synthesis of fluorinated pyridine: (a) Umemoto, T.; Tomizawa, G. J. Org. Chem. 1989, 54, 1726–1731. (b) Stavber, S.; Zupan, M. Tetrahedron Lett. 1990, 31, 775–776. (c) Gakh, A. A.; Tuinman, A. A.; Adcock, J. L.; Compton, R. N. Tetrahedron Lett. 1993, 34, 7167–7170. (d) O'Neill, P. M.; Storr, R. C.; Kevin Park, B. Tetrahedron 1998, 54, 4615–4622. (e) Fang, B.; Tao, H.; Kan, X.; Shang, Y. Heterocyclic Commun. 2004, 10, 305–306.

3. For the synthesis of fluorinated pyrimidine: (a) Robins, M. J.; Naik, S. R. J. Chem. Soc., Chem. Commun., 1972, 18–19. (b) Yemul, S. S.; Kagan, H. B. Tetrahedron Lett. 1980, 21, 277–280. (c) Boudakian, M. M.; Hyde, G. A. J. Fluorine Chem. 1984, 25, 435–446. (d) Cabaj, J. E.; Wuts, P. G. M.; Henegar, K. E. J. Org. Chem. 1994, 59, 5090–5092. (e) Rangwala, H. S.; Giraldes, J. W.; Gurvich, V. J., J. Labelled Compd. Radiopharm. 2011, 54, 340–343.

4. For the synthesis of fluorinated pyrazole: (a) Sloop, J. C.; Jackson, J. L.; Schmidt, R. D. Heteroat. Chem. 2009, 20, 341–345. (b) Qian, J.; Liu, Y.; Zhu, J. Jiang, B.; Xu, Z. Org. Lett. 2011, 13, 4220–4223.

5. For the synthesis of fluorinated isoxazole: (a) Bumgardner, C.L.; Sloop, J.C. J. Fluorine Chem. 1992, 56, 141-146. (b) Jeong, Y.; Kim, B.-I.; Lee, J. K.; Ryu, J.-S. J. Org. Chem. 2014, 79, 6444–6455. (c) Stephens, C. E.; Blake, J. A. J. Fluorine Chem. 2004, 125, 1939–1945.

6. For the synthesis of fluorinated thiazole: (a) Campbell, T. F.; Stephens, C. E. J. Fluorine Chem. 2006, 127, 1591–1594. (b) Hatfield, J. M.; Eidell, C. K.; Stephens, C. E. Tetrahedron Lett. 2013, 54, 1025–1028.

7. (a) Breen, J. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Fray, J.; Patel, B. Beilstein J. Org. Chem. 2011, 7, 1048–1054. (b) Breen, J. R.; Sandford, G.; Patel, B.; Fray, J. Synlett 2015, 26, 51–54.

8. (a) Caterina, M. J.; Schumacher, M. A.; Tominaga, M.; Rosen, T. A.; Levine, J. D.; Julius, D. Nature 1997, 389, 816–824. (b) Szallasi, A.; Cortright, D. N.; Blum, C. A.; Eid, S. R. Nat. Rev. Drug Discovery 2007, 6, 357-372.

9. (a) Palin, R.; Abernethy, L.; Ansari, N.; Cameron, K.; Clarkson, T.; Dempster, M.; Dunn, D.; Easson, A.-M.; Edwards, D.; Maclean, J.; Everett, K.; Feilden, H.; Ho, K.-K.; Kultgen, S.; Littlewood, P.; McArthur, D.; McGregor, D.; McLuskey, H.; Neagu, I.; Neale, S.; Nisbet, L.-A.; Ohlmeyer, M.; Pham, Q.; Ratcliffe, P.; Rong, Y.; Roughton, A.; Sammons, M.; Swanson, R.; Tracey, H.; Walker, G. Bioorg. Med. Chem. Lett. 2011, 21, 892-898. (b) Roughton, A. L.; Ho, K.-K.; Ohlmeyer, M.; Neagu, I.; Kultgen, S. G.; Ansari, N.; Rong, Y.; Ratcliffe, P. D.; Palin, R. PCT Int. Appl. WO2009016241 A1, 2009.

10. Sheldrick, G. M., Acta Cryst., Sect. A: 2008, 64, 112-122.

11. Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K., Puschmann H., J.Appl.Cryst., 2009, 42, 339-341.