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Access to 5-Fluoroisoxazoles via the Nitrosation of Geminal Bromo-Fluoro Arylcyclopropanes

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ABSTRACT

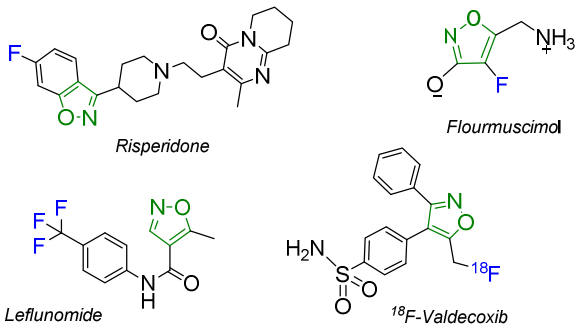
A new method for the synthesis of 3-aryl-5-fluoroisoxazoles via the reaction of nitrosonium chlorosulfate with 2-aryl-1-bromo-1-fluorocyclopropanes containing acceptor substituents in the aromatic ring has been developed. The reaction proceeds highly regioselectively thus providing 3-aryl-5-fluoroisoxazoles in good yields. The structure of isoxazoles was corroborated by the *DU8+* hybrid DFT/parametric computational approach.

1.Introduction

5-Haloisoxazoles are a valuable class of compounds. Chloro- and bromoisoxazoles have been shown to possess herbicidal[1] and anthelminthic[2] activities. 5-Bromo- and iodoisoxazoles are versatile precursors in metal-catalyzed cross-coupling reactions,[3] the reaction of 5-chloroisoxazoles with sodium or tetrabutylammonium borohydride affords unambiguously 5-unsubstituted isoxazoles[4] valuable intermediates in synthetic organic chemistry.

The most commonly used methods to prepare 5-haloisoxazoles involve the reaction of phosphorus oxyhalide ($POCl_3$, $POBr_3$) with 3-arylisoxazolones[1,2,5,6] and the [3+2]-cycloaddition of an *in situ* generated nitrile oxide to a halogenated or metallated triple bond.[7-9] Both methods have limitations on the halogen incorporated into the molecule. The first one gives access to 5-chloro- and bromoisoxazoles. The second is suitable mainly for production of 5-bromo- and iodoisoxazoles. 5-Haloisoxazoles, including fluorinated heterocycles, were also obtained via diazotization of 5-aminoisoxazoles in large excess of HHal but the yields of the target products were less no more than 40%.[10] At last, 5-chloro/bromoisoxazoles can be synthesized via nitrosation of the corresponding *gem*-dihalocyclopropanes.[11,12] It is relatively new but a convenient route for producing 5-chloro- and 5-bromoisoxazoles. We have recently shown that this reaction has a broad scope and can be used for the synthesis of both arylated and alkylated 5-haloisoxazoles including polycyclic ones.[13] This approach is also appealing due to availability and structural variety of the initial *gem*-dihalocyclopropanes by the Doering reaction under phase-transfer catalysis conditions. From this point of view fluorinated cyclopropanes are of special interest: we expected that nitrosation of such compounds will give rise to little known 5-fluoroisoxazoles.

A number of fluorine-containing (het)arenes are privileged scaffolds exhibiting broad biological activity[14,15] and among them compounds containing isoxazole fragment, for example, *Risperidone* (antipsychoticmedication), *Flourmuscimol* (psychoactive substance), *Leflunomide* (antirheumatic, immunomodulating drug). Fluoroaryl and fluoroalkyl analogues of *Valdecoxib* were found to possess potent inhibitory activities against cyclooxygenase-2 comparable to that of the parent *Valdecoxib*.[16,17] Fluoroalkyl and fluoroaryl radiolabeled (^{18}F) analogues of *Valdecoxib* were recently reported as potential radiotracers for imaging COX-2 drugs with positron emission tomography (PET) and as EGFR bioprobes.[18] Thus evolution of



novel methods for incorporating fluorine into organic molecules will no doubt continue to increase the abundance of this element in new efficient drugs.

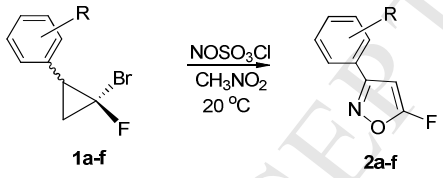
Recently we have found that nitrosation of alkylated mixed *gem*-bromofluorocyclopropanes with SO_3-activated nitrosyl chloride afforded 5-fluoroisoxazoles.[19] Given that the use of other nitrosating reagents, namely nitrosonium tetrafluoroborate, in reaction with such mixed *gem*-bromofluorocyclopropanes resulted in the formation of fluorinated pyrimidins[20] and isoxazolines,[21] rather than isoxazoles, our preliminary results encouraged us to continue this work in order to establish the generality of the reaction.

Here we report a procedure for the synthesis of 3-aryl-5-fluoroisoxazoles via nitrosation of arylated *gem*-bromofluoroocyclopropanes under the action of nitrosonium chlorosulfate.[22]

2. Result and discussion

As follows from the previous investigations, *gem*-dihaloarylcyclopropanes with deactivated aromatic rings react smoothly with nitrosating agents and afford good yields of 5-haloisoxazoles.[23] For this reason a series of 2-aryl-1-bromo-1-fluorocyclopropanes **1a-f** was chosen to be studied in this work. We have found that the reaction between cyclopropanes **1a-f** (used as a 1:1 mixture of *E/Z*-isomers) and nitrosonium chlorosulfate carried out in nitromethane at room temperature gave the desired fluoroisoxazoles **2a-f** in good yields (~60-79%). In contrast to *alkylated* 1-bromo-1-fluorocyclopropanes, which under similar conditions gave a mixture of regioisomeric 3- and 4-alkyl-5-fluoroisoxazoles,[19] the only regioisomer was formed in the case of arylated cyclopropanes **1a-f**. The observed high regioselectivity of nitrosation is in agreement with that of the previously studied arylated *gem*-dichloro/bromocyclopropanes.[11,12]

Table 1. Access to 3-aryl-5-fluoroisoxazoles **2a-f** via nitrosation of gem-bromofluoroarylcyclopropanes in nitromethane.



	R	**1a-f** : [NO^+] ratio	Product	Yield, %
1a	3-Br	1: 1.6	**2a**	64
1b	3-Cl	1: 1.5	**2b**	77
1c	3-NO_2	1: 2.0	**2c**	75
1d	4-NO_2	1: 2.0	**2d**	79
1e	2-NO_2	1: 2.0	**2e**	63
1f	2-Cl	1: 2.0	**2f**	60

Only traces – less than 5% – of 3-aryl-5-bromoisoxazoles were detected in the ^{1}H NMR spectra of the reaction mixtures in the case of cyclopropanes **1a,c** (see Table, Supp. Mater.) thus attesting to the high selectivity of nitrosonium chlorosulfate for fluoroisoxazoles. All compounds were isolated by column chromatography and characterized by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass-spectrometry and elemental analysis.

The ^{1}H NMR spectra of **2a-f** exhibit the absorption of the isoxazole ring proton at ~5.8-6.0 ppm (doublet, $^3J_{HF}$ = 7.5 Hz). The value of chemical shift unambiguously indicates that the isoxazole ring proton is attached at the C(4) carbon atom. Similarly, in the ^{13}C NMR spectra, the upfield signal appeared as a doublet at ~78.0 ppm with a two-bond coupling ($^2J_{CF}$ = 16.8 Hz) was uniquely assigned to the HC(4) isoxazole carbon atom. Two remaining quaternary carbon atoms of the isoxazole ring appear as doublets with a three-bond ($^3J_{CF}$ = 5.9 Hz) and one-bond couplings ($^1J_{CF}$ = 296.5 Hz) at ~163.0 and ~170.0 ppm, respectively. Because of their similar chemical shifts and dissymmetry in the isoxazole ring nucleus caused by the presence of two vicinal heteroatoms strongly affecting the chemical shifts of both proton and carbon nuclei in the ring, the signals cannot be unambiguously assigned to either C(3) or C(5) carbon atoms. Insufficient information in the literature on fluorinated isoxazoles (NMR data for very few 5-fluoroisoxazoles is found in the literature)[10,24] offer little help in solving this problem. Moreover, recent report on the synthesis of 5-fluoro-4-methyl-3-phenylisoxazole seems to be doubtful.[25] The spectral data given for this compound are in disagreement with proposed structure and with our results. Thus, the observed doublet of the CH_3 group protons in the ^{1}H NMR spectrum is obviously due to the presence of fluorine atom, however, the value of the coupling constant (20 Hz) is too large for ^{4}J especially for the case when coupling atoms are mediated via a double bond. Next, according to the authors, the chemical shift of the C-F carbon atom in the ^{13}C NMR spectrum appears at 89.5 ppm, that is in disagreement with characteristic region for C(5) carbon of the isoxazole ring. So, the task at hand was to unambiguously confirm the structure of the isoxazoles **2a-f**.

First, as an alternative approach to differentiating between the initially postulated 3-aryl-5-fluoro- and all other potential candidate structures, we turned to ^{13}C NMR and compared the experimental data with the values computed with recently developed *DU8+* hybrid DFT/parametric approach.[26] This fast and accurate method was instrumental in many revisions of misassigned organic structures, especially that of natural products.[27] As follows from Figs.1 and 2, *DU8+* provides strong and convincing evidence that the major products of these reactions are 3-aryl-5-fluoroisoxazoles. Fig. 1 compares the calculated ^{13}C NMR chemical shifts for all six possible positional isomers of *m*-chlorophenyl-fluoro-isoxazoles. The 3-(*m*-chlorophenyl)-5-fluoroisoxazole emerged as a clear winner by a large margin (rmsd over all 9 carbons is 1.0 ppm). Fig. 2 shows similar excellent matches between the computed and experimental ^{13}C chemical shifts for 5-fluoroisoxazole products **2a-d,f**, 0.95<rmsd<1.12 ppm.

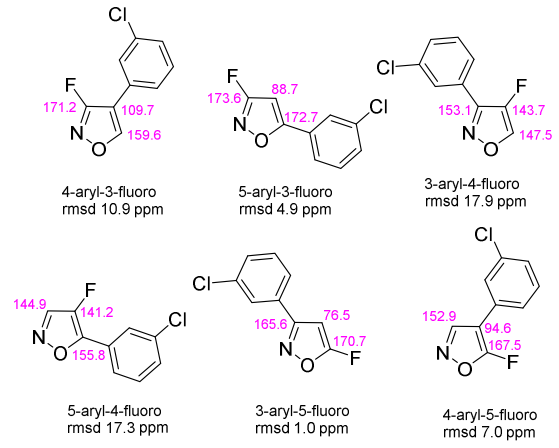


Figure 1. Comparison of calculated ^{13}C NMR chemical shifts for the isoxazole core in all six positional isomers of *m*-chlorophenyl-fluoro-isoxazole.

The only outlier was the *o*-nitro product **2e**, which gave a higher rmsd of 2.23 ppm, primarily due to deviations for the two quaternary carbons connecting the two rings. Without these two, the match over the remaining 7 carbons improves to 1.22 ppm.[28]

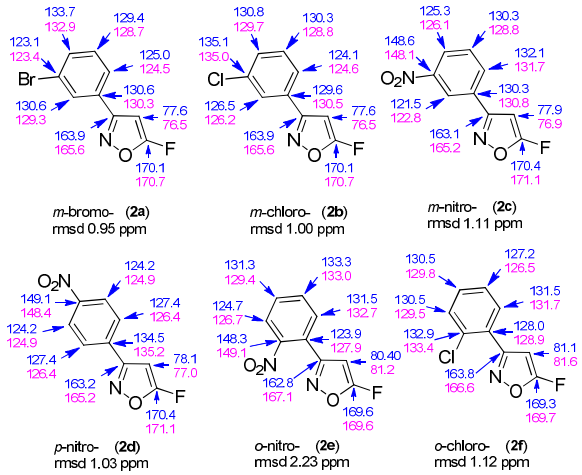


Figure 2. Comparison of calculated and experimental ^{13}C NMR chemical shifts for 3-aryl-5-fluoroisoxazoles **2a-f** (blue – experimental values, magenta – calculated with *DU8+*; rmsd values are for all 9 carbons).

Halogenated arylpropanes **3** were also isolated as minor products in some cases (see Table, Supp. Mater.). Although the yield of the open-chain byproduct never exceeded 20%, for completeness we have isolated it from the reaction of cyclopropane **1a** and fully characterized it. Based on ^{1}H, ^{13}C and ^{19}F NMR data and mass-spectrometry analysis the isolated compound was identified as 2-bromo-1-(3-bromophenyl)-1,3-dichloro-2-fluoropropane **3a**. The ^{1}H NMR spectrum of **3a** exhibits the signals of three aliphatic protons at 3.94, 4.35 and 5.40 ppm, with their multiplicity and ^{1}H-^{19}F coupling being in agreement with the structure of propane **3a**. The ^{13}C NMR also showed the anticipated ^{13}C-^{19}F coupling, with C-2 of the propane fragment appearing as a doublet at 108.0 ppm with a large one-bond coupling constant ($^{1}J_{CF}$ = 264.2 Hz), while C-1 and C-3 both appeared as doublets with smaller two-bond couplings ($^{2}J_{CF}$ = 20.5 and 30.0 Hz). The shape of the cluster of peaks for the molecular ion in mass spectrum revealed that compound **3a** contains two chlorine and two bromine atoms. Ion with mass of 203 pointed to benzylic location of one of the chlorine atoms.

DU8+ calculations of ^{13}C chemical shifts for both diastereomers, *rel-(1R,2R)*-**3a** and *rel-(1R,2S)*-**3a**, revealed excellent matches for all carbon atoms. However calculated rmsd make it possible to confidently differentiate between diastereomers (Figure 3) and indicate that **3a** is likely *rel-(1R,2S)*-**3a** diastereomer.

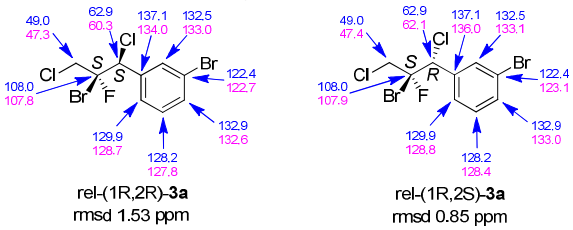


Figure 3. Comparison of experimental and computed ^{13}C chemical shifts for two diastereomers of **3a**.

In addition, the stereoselective formation of *rel-(1R,2S)*-**3a** diastereomer is favorable mechanistically as in the major conformer of the benzylic **Radical Z** (intermediate shown in Figure 4), the approach indicated by the red arrow is blocked by the bromine atom (van der Waals surfaces are shown in projections from the side and from the top).

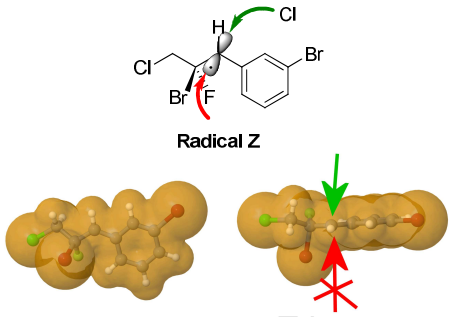
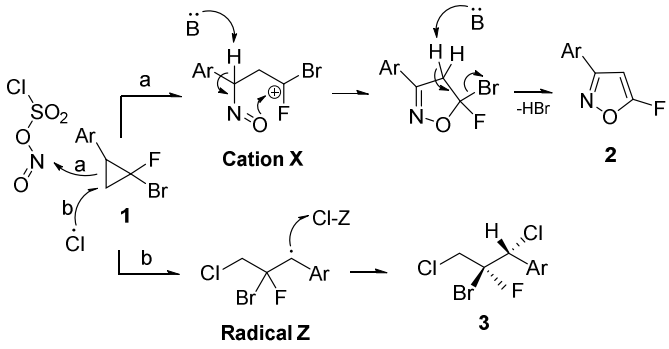


Figure 4. Approach to benzylic radical from the front face in the shown major conformer is obstructed by protruding bromine atom; van der Waals surface is shown.

Scheme shows combined mechanistic rationale for the formation of the major products, isoxazoles (path *a*), and the minor open-chain dichloride byproduct (path *b*). In path *a*, electrophilic attack of nitrosonium cation could be expected to produce either aryl- or bromo-fluoro-stabilized initial carbocation **Cation X**. Clearly, the stabilization of the cation by halogens prevails; also NO^{+} localizes to the benzylic carbon, see path *a*. In subsequent steps, resembling nitroso-oxime tautomeric equilibrium, the initial cation is intramolecularly captured by the oxygen end of the nitroso group, yielding isoxazoline, which in turn undergoes dehydrobromination to furnish the major product, isoxazole **2**.



Scheme. Mechanistic rationale for the formation of major products, isoxazoles **2**, and open-chain byproduct **3**.

We are also assuming that the adduct of nitrosyl chloride and SO_3 exists in equilibrium with free NOCl, which is known to partially decompose via homolytic dissociation.[29] This supports a hypothesis that the minor product of 1,3-addition, dichloride **3**, is a product of a radical ring-opening of cyclopropane with chlorine atom (path *b*) forming a bond with unsubstituted methylene and generating the benzylic **Radical Z**. Radical path *b* is therefore different from path *a* in both, the locus of the initial attack and the kind of bond that gets cleaved.[30] We managed to diminish nearly twice the amount of halogenated arylpropanes **3** by changing the order of reagents mixing (see Table, Supp. Mater.).[19]

3. Conclusion

We have developed a straightforward and efficient protocol for the synthesis of 3-aryl-5-fluoroisoxazoles starting from readily accessible fluorine-containing dihalocyclopropanes and nitrosonium chlorosulfate. The structure of isoxazoles was corroborated by the DU8+ hybrid DFT/parametric computational approach. The reaction shows excellent regioselectivity and scalability to gram scale. This process is in fact the first general method for the synthesis of 5-fluoroisoxazoles.

4. Experimental section

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer (400.1, 100.6, and 376.3 MHz for ^{1}H, ^{13}C, and ^{19}F, respectively) at room temperature; chemical shifts were measured with reference to the solvent for ^{1}H ($CDCl_3$, δ = 7.24 ppm) and ^{13}C ($CDCl_3$, δ = 77.13 ppm) and to $CFCl_3$ ($CFCl_3$, δ = 0.00 ppm) as an external standard for ^{19}F. Mass spectra were obtained with a GC-MS instrument using electron-impact ionization (EI, 70eV). HRMS measurements were performed with an electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Analytical thin-layer chromatography was carried out with silica gel plates (supported on aluminum). IR spectra were recorded with Nicolet IR200 (Thermo Scientific) FT-IR spectrometer with ZnSe ATR (45° incident angle), resolution 4 wavenumbers, 20 scans per experiment.

*Nitrosation of bromofluorocyclopropane **1a** with nitrosonium chlorosulfate* (*General procedure*). A 50 ml round bottom flask was charged with 2g (6.8 mmol) of 1-bromo-2-(3-bromophenyl)-1-fluorocyclopropane **1a** in 2.3 mL of nitromethane. Over 10-20 min a freshly prepared suspension of 1.55 g (10.7mmol) of nitrosonium chlorosulfate in 20.7 mL of dry nitromethane was added to this solution at 20°C under stirring.[31] Reaction progress was monitored by TLC. After completion of the reaction (~1-2 h) reaction mixture was gel-filtrated through a layer of silica gel. The pad of silica gel was washed with dichloromethane (3 x 10 mL). The solvent from combined organic solutions was removed under reduced pressure and the residue was subjected to separation on a slurry-packed silica gel column, ethyl acetate – petroleum ether, 1 : 20, to yield:

2-bromo-1-(3-bromophenyl)-1,3-dichloro-2-fluoropropane *rel-(1R,2S)*-**3a**[32] (0.07 g, 7%) as colorless oil; [Found: C, 29.30; H, 2.40. $C_9H_7Br_2Cl_2F$ requires C, 29.63; H, 1.93%]; R_f 0.86; d_H (400 MHz $CDCl_3$) 7.77 (1H, s, CH_{Ar}), 7.57 (1H, d, ^{3}J 8.0 Hz, CH_{Ar}), 7.54 (1H, d, ^{3}J 8.0 Hz, CH_{Ar}), 7.30 (1H, t, ^{3}J 8.0 Hz, CH_{Ar}), 5.40 (1H, d, $^{3}J_{HF}$ 17.0 Hz, CH), 4.35 (1H, dd, $^{2}J_{HH}$ 12.4 Hz, $^{3}J_{HF}$ 8.2 Hz, CH_2Cl), 3.94 (1H, t, $^{2}J_{HH}$=$^{3}J_{HF}$ 12.4 Hz, CH_2Cl); d_C (100.6 MHz, $CDCl_3$) 137.1 ($C(1)_{Ar}$), 132.9 (CH_{Ar}), 132.5 (CH_{Ar}), 129.9 (CH_{Ar}), 128.2 (CH_{Ar}), 122.4 (CBr), 108.0 (d, $^{1}J_{CF}$ 264.2 Hz, CBrF), 62.9 (d, $^{2}J_{CF}$ 20.5 Hz, CHCl), 49.0 (d, $^{2}J_{CF}$ 30.0 Hz, CH_2Cl); d_F (376 MHz, $CDCl_3$) -116.2 (1F, m, Br-C-F); m/z (EI): cluster 362 (4.6), 364 (13), 366 (12), 368 (4), 370 (0.5) M^+, cluster 327 (0.4), 329 (1), 331 (0.6), 333 (0.1) [M^+ - Cl], cluster 283 (2.2), 285 (3.4), 287 (1.5), 289 (0.2) [M^+- Br], cluster 248 (2.8), 250 (3.7), 252 (1) [M^+- Br - Cl], cluster 247 (2.8), 249 (4.2), 251 (1.5) [M^+- Br - Cl - H], cluster 203 (60), 205 (100), 207 (30) [BrC_6H_4-$CHCl^+$], cluster 169 (5), 171 (2) [M^+- 2Br - Cl], cluster 168 (5.4), 170 (2) [M^+- 2Br - Cl - H], 134 (43) [M^+- 2Br - 2Cl], 133 (50) [M^+- 2Br - 2Cl - H], 89 (17), 63 (20%).

3-(3-bromophenyl)-5-fluoro-1,2-oxazole 2a (1.05 g, 64%) as colorless cryst.; m. p. 42°C; [Found: C, 44.47; H, 2.19; N, 5.65. C_9H_5BrFNO requires C, 44.66; H, 2.08; N, 5.79]; R_f 0.53; d_H (400 MHz, $CDCl_3$) 7.88 (1H, s, CH_{Ar}), 7.66 (1H, d, ^{3}J 7.8 Hz, CH_{Ar}), 7.59 (1H, d, ^{3}J 7.8 Hz, CH_{Ar}), 7.33 (1H, t, ^{3}J 7.8 Hz, CH_{Ar}), 5.85 (1H, d, $^{3}J_{HF}$ 7.5 Hz, $C(4)H_{is}$); d_C (100.6 MHz, $CDCl_3$) 170.1 (d, $^{1}J_{CF}$ 295.5 Hz, F-C-O), 163.8 (d, $^{3}J_{CF}$ 5.6 Hz, C=N), 133.7 (CH_{Ar}), 130.6 (CH_{Ar} + $C(1)_{Ar}$), 129.4 (CH_{Ar}), 125.0 (CH_{Ar}), 123.1 (CBr), 77.6 (d, $^{2}J_{CF}$ 16.9 Hz, $C(4)_{is}$); d_F (376 MHz, $CDCl_3$) -102.9 (1F, d, $^{3}J_{HF}$ 7.5 Hz, O-C-F); m/z (EI): cluster 241 (1.8), 243 (1.7) M^+, cluster 213 (13), 215 (13) [M^+- CO], cluster 186 (12), 188 (11.5) [M - CO - HCN = $BrC_6H_4CF]^+$, 134 (100) [M - CO - Br]$^+$, 107 (95) $[C_6H_4CF]^+$, 102 (12) $[C_6H_4CN]^+$, 88 (9), 75 (15) $[C_6H_3]^+$, 50 (10%).

Isoxazoles 2b-2f:

3-(3-chlorophenyl)-5-fluoro-1,2-oxazole 2b (1.52 g, 77%) obtained from 2.50 g of 1-bromo-2-(3-chlorophenyl)-1-fluorocyclopropane **1b** as colorless cryst.; m.p. 31°C; R_f 0.53 (EtOAc : petroleum ether = 1 : 20); d_H (400 MHz, $CDCl_3$) 7.72 (1H, s, CH_{Ar}), 7.61 (1H, d, ^{3}J 7.7 Hz, CH_{Ar}), 7.43 (1H, d, ^{3}J 7.7 Hz, CH_{Ar}), 7.38 (1H, t, ^{3}J 7.7 Hz, CH_{Ar}), 5.85 (1H, d, $^{3}J_{HF}$ 7.5 Hz, $C(4)H_{is}$); d_C (101 MHz, $CDCl_3$) 170.1 (d, $^{1}J_{CF}$ 295.6 Hz, F-C-O), 163.9 (d, $^{3}J_{CF}$ 5.6 Hz, C=N), 135.1 (C-Cl), 130.7 (CH_{Ar}), 130.3 (CH_{Ar} + $C(1)_{Ar}$), 126.5 (CH_{Ar}), 124.5 (CH_{Ar}), 77.6 (d, $^{2}J_{CF}$ 16.9 Hz, $C(4)_{is}$); d_F (376 MHz, $CDCl_3$) -103.0 (1F, d, $^{3}J_{HF}$ 7.5 Hz, O-C-F); m/z (EI): cluster 197 (5), 199 (1.5) M^+, cluster 169 (35), 171 (16) [M^+- CO], cluster 142 (53), 144 (21) [M - CO - HCN = $ClC_6H_4CF]^+$,134 (17) [M- CO - Cl]$^+$, cluster 111 (12), 113 (3.5) $[C_6H_4Cl]^+$, 107 (100) $[C_6H_4CF]^+$, 102 (5) $[C_6H_4CN]^+$, 75 (52) $[C_6H_3]^+$, 50 (38%); HRMS: MH^+, found 198.0110, 200.0078. $C_9H_6ClFNO^+$ requires 198.0116, 200.0087.

5-fluoro-3-(3-nitrophenyl)-1,2-oxazole 2c (0.47 g, 75%) obtained from 0.78 g (3.0 mmol) of 1-bromo-2-(3-nitrophenyl)-1-fluorocyclopropane **1c** as a yellow oil; [Found: C, 52.03; H, 2.63, N 13.21. $C_9H_5FN_2O_3$ requires C, 51.93; H, 2.42; N, 13.46%]; d_H (400 MHz, $CDCl_3$) 8.58 (1H, s, CH_{Ar}), 8.34 (1H, d, ^{3}J 8.0 Hz, CH_{Ar}), 8.14 (1H, d, ^{3}J 8.0 Hz, CH_{Ar}), 7.70 (1H, t, ^{3}J 8.0 Hz, CH_{Ar}), 6.03 (1H, d, $^{3}J_{HF}$ 7.6 Hz, $C(4)H_{is}$); d_C (101 MHz, $CDCl_3$) 170.4 (d, $^{1}J_{CF}$ 296.4 Hz, F-C-O), 163.1 (d, $^{3}J_{CF}$ 5.9 Hz, C=N), 148.6 (C-NO_2), 132.1 (CH_{Ar}), 130.32 ($C(1)_{Ar}$), 130.25 (CH_{Ar}), 125.3 (CH_{Ar}), 121.5 (CH_{Ar}), 77.9 (d, $^{2}J_{CF}$ 16.8 Hz, $C(4)_{is}$); d_F (376 MHz, $CDCl_3$) -101.9 (1F, d, $^{3}J_{HF}$ 7.6 Hz, F-C-O); IR spectrum, cm^{-1}: 1640 (C=N), 1540, 1380 (NO_2); m/z (EI): 208 (89) M^+, 189 (15) [M^+- F], 180 (4) [M^+ - CO], 153 (10) [M^+- CO - HCN = $NO_2C_6H_4CF^+$], 150 (30) [M^+ – NO – CO = $C_8H_5FNO^+$], 134 (100) [M - CO - NO_2]$^+$, 122 (10) $[C_6H_4NO_2]^+$, 114 (25) $[C_6H_4C_2N]^+$, 107 (72) $[C_6H_4CF]^+$, 102 (10) $[C_6H_4CN]^+$,76 (60) $[C_6H_4]^+$, 63 (18) $[C_5H_3]^+$, 50 (49), 43 (29%).

5-fluoro-3-(4-nitrophenyl)-1,2-oxazole 2d (0.35 g, 79%) obtained from 0.55 g (2.00 mmol) of 1-bromo-1-fluoro-2-(4-nitrophenyl)cyclopropane **1d** as yellow cryst.; m.p. = 108-110 °C; [Found: C, 51.65; H, 2.55; N, 13.12. $C_9H_5FN_2O_3$ requires C, 51.93; H, 2.42; N, 13.46%]; R_f 0.65 (EtOAc : petroleum ether = 1 : 5); d_H (400 MHz, $CDCl_3$) 8.32 (2H, d, ^{3}J 8.8 Hz, $2CH_{Ar}$), 7.95 (2H, d, ^{3}J 8.8 Hz, $2CH_{Ar}$), 6.02 (1H, d, $^{3}J_{HF}$ 7.4 Hz, $C(4)H_{is}$); d_C (101 MHz, $CDCl_3$) 170.4 (d, $^{1}J_{CF}$ 297.1 Hz, F-C-O), 163.2 (d, $^{3}J_{CF}$ 5.9 Hz, C=N), 149.1 (C-NO_2), 134.5 ($C(1)_{Ar}$), 127.4 ($2CH_{Ar}$), 124.2 ($2CH_{Ar}$), 78.1 (d, $^{2}J_{CF}$ 16.8 Hz, $C(4)_{is}$); d_F (376 MHz, $CDCl_3$) -101.9 (1F, d, $^{3}J_{HF}$ 7.4 Hz, F-C-O); m/z (EI): 208 (1) M^+, 180 (22) [M^+ - CO], 163 (21) [M^+ – CO – OH], 153 (40) [M^+ – CO – HCN = $NO_2C_6H_4CF^+$], 150 (8) [M^+ – NO – CO = $C_8H_5FNO^+$], 134 (70) [M^+ – CO – NO_2], 122 (11) $[C_6H_4NO_2]^+$, 114 (4) $[C_6H_4C_2N]^+$, 107 (100) $[C_6H_4CF]^+$, 102 (15) $[C_6H_4CN]^+$, 76 (13) $[C_6H_4]^+$, 50 (15%).

5-fluoro-3-(2-nitrophenyl)-1,2-oxazole 2e (0.18 g, 63%) obtained from 0.40 g (1.30 mmol) of 1-bromo-1-fluoro-2-(2-nitrophenyl)cyclopropane **1e** as yellow cryst.; m.p. = 114-116°C; [Found: C, 51.90; H, 2.65; N, 13.26. $C_9H_5FN_2O_3$ requires C, 51.93; H, 2.42; N, 13.46%]; R_f 0.70 (EtOAc : petroleum ether = 1 : 5); d_H (400 MHz, $CDCl_3$) 8.06 (1H, d, ^3J 7.8 Hz, CH_{Ar}), 7.78-7.72 (1H, m, CH_{Ar}), 7.72-7.66 (2H, m, CH_{Ar}), 5.74 (1H, d, $^3J_{HF}$ 7.4 Hz, C(4)H_{is}); d_C (101 MHz, $CDCl_3$) 169.6 (d, $^1J_{CF}$ 296.4 Hz, F-C-O), 162.8 (d, $^3J_{CF}$ 5.9 Hz, C=N), 148.3 (C-NO_2), 133.3 (CH_{Ar}), 131.5 (CH_{Ar}), 131.3 (CH_{Ar}), 124.7 (CH_{Ar}), 123.9 (C(1)$_{Ar}$), 80.4 (d, $^2J_{CF}$ 16.8 Hz, C(4)$_{is}$); d_F (376 MHz, $CDCl_3$) -103.5 (1F, d, $^3J_{HF}$ 7.4 Hz, F-C-O).

3-(2-chlorophenyl)-5-fluoro-1,2-oxazole 2f (0.47 g, 60%) obtained from 1.00 g (4.0 mmol) of 1-bromo-2-(2-chlorophenyl)-1-fluorocyclopropane **1f** as a colorless oil; R_f 0.46 (EtOAc : petroleum ether = 1 : 20); d_H (400 MHz, $CDCl_3$) 7.72 (1H, dd, ^4J 1.7 Hz, ^3J 7.6 Hz, CH_{Ar}), 7.49 (1H, dd, ^4J 1.2 Hz, ^3J 7.6 Hz, CH_{Ar}), 7.42 (1H, dt, ^4J 1.7 Hz, ^3J 7.6 Hz, CH_{Ar}), 7.37 (1H, dt, ^4J 1.2 Hz, ^3J 7.6 Hz, CH_{Ar}), 6.06 (1H, d, $^3J_{HF}$ 7.6 Hz, C(4)H_{is}); d_C (101 MHz, $CDCl_3$) 169.3 (d, $^1J_{CF}$ 294.8 Hz, F-C-O), 163.8 (d, $^3J_{CF}$ 6.4 Hz, C=N), 132.9 (C-Cl), 131.5 (CH_{Ar}), 130.5 (2CH_{Ar}), 128.0 (C(1)$_{Ar}$), 127.2 (CH_{Ar}), 81.1 (d, $^2J_{CF}$ 16.9, C(4)$_{is}$); d_F (376 MHz, $CDCl_3$) -104.0 (1F, d, $^3J_{HF}$ 7.6 Hz, F-C-O); m/z (EI) cluster 197 (5), 199 (2) M^+, cluster 169 (48), 171 (16) [M^+- CO], cluster 142 (80), 144 (26) [M- CO – HCN = $ClC_6H_4CF]^+$, 134 (35) [M-CO – Cl]$^+$, 107 (100) $[C_6H_4CF]^+$, 102 (12) $[C_6H_4CN]^+$, 75 (18) $[C_6H_3]^+$, 50 (7%); HRMS: MH^+, found 198.0116, 200.0085. C_9H_6ClFNO requires 198.0116, 200.0087.

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32. may contain traces of *rel-(1R,2S)*-**1,2-dibromo-1-(3-bromophenyl)-3-chloro-2-fluoropropane** d_H (400 MHz, $CDCl_3$) 5.47 (1H, d, $^3J_{HF}$ 20.2 Hz, CH), 4.39 (1H, dd, $^2J_{HH}$ 12.3 Hz, $^3J_{HF}$ 7.8 Hz, CH_2Cl), 4.03 (1H, dd, $^2J_{HH}$ 12.3 Hz, $^3J_{HF}$ 11.0 Hz, CH_2Cl), the aromatic protons overlap with that of *rel-(1R,2S)*-**3a**; m/z (EI): cluster 406 (0.8), 408 (2.6), 410 (3.1), 412 (1.5), 414 (0.2) M^+, cluster 327 (15), 329 (33), 331 (23), 333 (5) [M^+- Br], cluster 291 (1), 293 (2), 295 (1) [M^+- Br - Cl - H], cluster 248 (15), 250 (20), 252 (5) [M^+- 2Br], cluster 247 (10), 249 (20), 251 (10) [BrC_6H_4-$CHBr^+$], 134 (100) [M^+-3Br –Cl], 133 (80) [M^+- 3Br - Cl - H], 107 (18), 63 (30), 50 (25%).

- access to 5-fluoroisoxazoles from geminal bromofluoroarylcyclopropanes
- high regioselectivity ensures good yields of 5-fluoroisoxazoles