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# Nuclear fluorination of 3,5-diarylisoxazoles with Selectfluor®

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**Abstract**

C-4 Fluorination of a series of 3,5-diarylisoxazoles has been accomplished using the N-F reagent Selectfluor®. With substrates containing neutral or activating substituents on the 5-phenyl ring, acetonitrile at room temperature or at reflux could be used as solvent. However, when deactivating substituents were present, a higher reaction temperature was required for which sulfolane was found to be a good solvent. At this higher temperature, a unique trifluorination of the isoxazole nucleus by an addition mechanism occurred as a side reaction.


*Keywords:* Heterocycle; Isoxazole; Fluorination; Selectfluor®; Sulfolane; Substituent effects

## 1. Introduction

3,5-Diarylisoxazoles have been studied recently as potential anti-cancer [1] and anti-microbial agents [2], as potential estrogen receptor modulators [3], as liquid crystals [4], and as linear dyes with application to light-harvesting systems [5]. Previously, we have described the convenient C-4 halogenation (Cl, Br, or I) of a series of these compounds, using *N*-halosuccinimides [6]. In that study, the effect of the substituent on the 5-phenyl ring was found to exert a profound influence on the reactivity of the isoxazole.

As fluorinated compounds often possess unique biological [7] and physiochemical [8] properties compared to the parent systems, we have become interested in the fluorination of these and other heterocycles. Our literature search revealed that while the synthesis of 4-fluoro-3,5-diphenylisoxazole via a ring-closure process has been described [9], there has been no report of the direct C-4 fluorination of 3,5-diarylisoxazoles. In fact, there appears to have been no report of the direct fluorination of any isoxazole at any ring position. As a number of easily handled N-F fluorinating reagents are now readily available [10], we decided to explore their use for the fluorination of our isoxazole system. Herein, we describe our work in this area leading to convenient procedures for the selective C-4 fluorination of 3,5-diarylisoxazoles. In addition, we also describe the isolation of a trifluorinated by-product from some of our higher-temperature reactions, which was formed by an addition reaction to the isoxazole nucleus following the initial substitution.

## 2. Results and discussion

The N-F fluorinating reagents used in this study are shown in Fig. 1. Initial experiments were carried out with the parent isoxazole **4a** and Selectfluor® (**1**) (1.1 eq.) (Scheme 1). Although no reaction occurred in acetonitrile at room temperature after several hours, a reaction did occur at reflux. However, although the desired 4-fluoroisoxazole was formed quite selectively, consumption of the starting material was always incomplete (~30–50% conversion by TLC analysis) even upon extended reaction times (>24 h). A similar outcome was observed when nitromethane was used as solvent, while no fluorination occurred when acetic acid or methanol was used. Attempts to drive the reaction that occurred in acetonitrile by including additives such as

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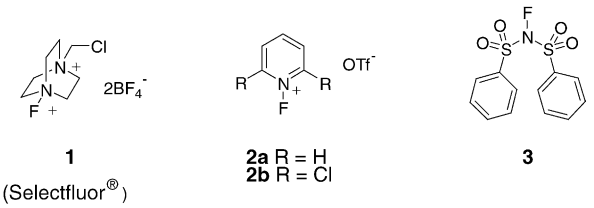



Fig. 1. Structures of N-F reagents tested.

trifluoroacetic acid [11], nitrobenzene [12], $KHCO_3$, or NaOTf [10e] were unsuccessful. The use of excess fluorinating reagent (2 eq.) also afforded no apparent increase in conversion. We thus, speculate that a competitive *N*-fluorination of the isoxazole nitrogen may be the reason for the incomplete reaction, a possibility that has been put forth by other authors [13] with regard to the fluorination of nitrogen heterocycles. Indeed, a trace amount of a polar product that may have been the N-F isoxazole was often observed by TLC, however attempts to isolate this compound were unsuccessful. Hydrolysis of the N-F adduct on TLC or upon work-up would regenerate the starting isoxazole.

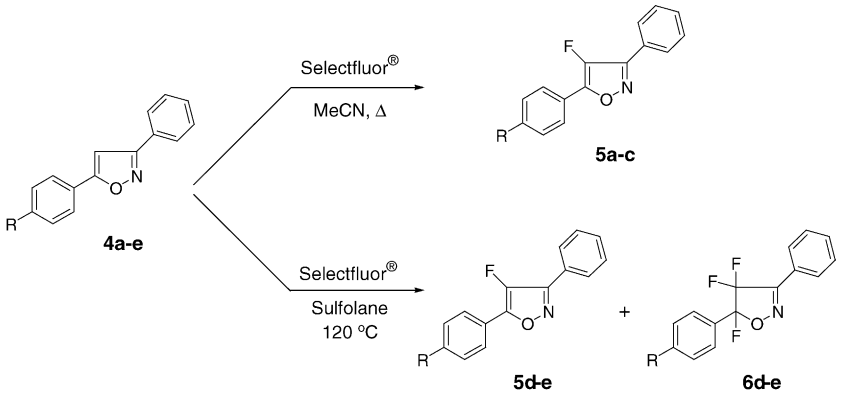
In a continued effort to improve the reaction, other N-F fluorinating reagents were explored. No reaction occurred when parent isoxazole **4a** was treated with *N*-fluoropyridinium triflate (**2a**) or with N-fluorobenzenesulfonimide (**3**) (1.1 eq., refluxing acetonitrile). However, fluorination did take place when the more reactive *N*-fluoro-2,6-dichloropyridinium triflate (**2b**) was used, although an incomplete conversion was again observed which offered no apparent improvement compared to the less expensive Selectfluor®.

In the end, the use of Selectfluor® in refluxing acetonitrile without any additive was judged to be the best of the conditions explored for fluorinating isoxazole **4a**. Despite the incomplete conversion, we were still pleased to obtain 4-fluoroisoxazole **5a** in 32% yield, using these conditions following silica gel chromatography, to remove residual starting material. The compound was fully characterized by $^1H$, $^{13}C$, and $^{19}F$ NMR, as well as by IR, MS and combustion analysis (Tables 1 and 2).

The $^{19}F$ NMR spectrum of **5a** revealed one up-field singlet (−177.9 ppm), which is consistent with that previously reported [9], while the $^1H$ NMR lacked the characteristic singlet for the C-4 proton of the starting isoxazole. In the $^{13}C$ NMR, a significant downfield shift was observed for C-4 of the fluorinated isoxazole (140.9 ppm) compared to that of the parent isoxazole (98.6 ppm). The $^{13}C$ NMR also showed the expected $^{13}C$-$^{19}F$ coupling, with C-4 appearing as a doublet with a large one-bond coupling ($^1JC$-F = 256 Hz), and C-3 and C-5 appearing both as doublets with smaller two-bond couplings ($^2JC$-F = 10.9 and 18.9 Hz). Three- and four-bond $^{13}C$-$^{19}F$ couplings to each of the phenyl rings were also observed. Finally, the mass spectrum was noticeably similar to that of the parent isoxazole (**4a**) [14] in that the most intense signals were those corresponding to the 5-$PhCO^+$ ($M^+ - 134$) and 5-$Ph^+$ ($M^+ - 162$) ions. Fragments resulting from loss of HF, CO, and the FCCO radical were also observed.

With the parent 4-fluoroisoxazole in hand, we next turned to the fluorination of the substituted isoxazoles **4b-e**. Reaction of the methyl-substituted isoxazole **4b** with Selectfluor® proceeded as did the parent, giving **5b** in 34% yield. Fluorination of the activated methoxy substituted analogue **4c**, in contrast, led to a complex mixture (TLC analysis) consisting of the 4-fluoroisoxazole **5c**, starting material, and several other unidentified products possibly arising from non-selective phenyl fluorination and/or demethylation [15]. The reaction was much more selective at room temperature, however, yielding only the 4-fluoroisoxazole as a new product. Separation from remaining starting material gave the desired product **5c** in 28% yield. As the parent isoxazole did not react with Selectfluor® at room temperature, the methoxy-substituted analogue is clearly activated.

Fluorination of the deactivated bromo- and trifluoromethyl-substituted isoxazoles **4d** and **4e** was also explored.




Scheme 1.

Table 1
Yield, mp, combustion analysis and mass spectral data for compounds **5a–e** and **6d–e**

| Product | Yield[a] (%) | Mp (°C), (recryst. solvent) | Formula (MW) | Combustion analysis | | m/z (Irel, %) |
|---|---|---|---|---|---|---|
| | | | | Calculated | Found | |
| **5a** | 32 | 101–102.5[b] (EtOH) | C15H10FNO (239.24) | C, 75.30; H, 4.21; N, 5.85 | C, 74.56; H, 4.21; N, 5.67 | 239 (68), 219 (9), 211 (36), 180 (13), 105 (100), 77 (83) |
| **5b** | 34 | 96–97 (EtOH) | C16H12FNO (253.27) | C, 75.88; H, 4.78; N, 5.53 | C, 75.67; H, 4.65; N, 5.25 | 253 (100), 233 (8), 225 (36), 194 (19), 119 (84), 91 (58), 77 (25), 65 (36) |
| **5c** | 28 | 103–104 (MeOH) | C16H12FNO2 (269.27) | C, 71.37; H, 4.49; N, 5.20 | C, 70.98; H, 4.22; N, 5.32 | 269 (73), 254 (22), 241 (5), 226 (35), 135 (100), 107 (22), 92 (34), 77 (64) |
| **5d** | 39 | 136–136.5 (MeOH) | C15H9BrFNO (318.14) | C, 56.63; H, 2.85; N, 4.40 | C, 56.35; H, 2.72; N, 4.27 | 319 (71), 317 (75), 291 (18), 289 (22), 260 (8), 258 (9), 185 (95), 183 (100), 157 (65), 155 (67), 107 (20), 77 (44) |
| **5e** | 30 | 127.5–128 (MeOH) | C16H9F4NO (307.24) | C, 62.55; H, 2.95; N, 4.56 | C, 62.41; H, 2.90; N, 4.48 | 307 (53), 287 (6), 279 (20), 248 (9), 173 (71), 145 (100), 77 (44) |
| **6d** | 10[c] | 77–78 | C15H9BrF3NO (356.14) | C, 50.59; H, 2.55; N, 3.93 | C, 50.77; H, 2.53; N, 3.83 | 357 (18), 355 (18), 238 (15), 236 (17), 153 (69), 103 (100), 77 (49) |
| **6e** | 10[c] | 88.5–89.5 | C16H9F6NO (345.24) | C, 55.66; H, 2.63; N, 4.06 | C, 55.85; H, 2.53; N, 3.93 | 345 (44), 226 (11), 153 (29), 103, (100), 77 (64) |

[a] Pure compound after chromatography.
[b] White solid; Lit Mp: 67–69 °C (brown solid) [9].
[c] Based on starting isoxazole.

Consistent with our previous work with this series of isoxazoles [6], the reaction of either these compounds with Selectfluor® in refluxing acetonitrile was quite sluggish, giving only traces of the desired 4-fluoroisoxazoles. As a much higher reaction temperature appeared needed, we decided to explore the use of higher boiling solvents. A scan of the literature revealed that the use of higher reaction temperatures for fluorination of aromatics with N-F reagents has been quite limited. We were most encouraged by a report of the fluorination of a nitro-substituted quinoline with NFSI (**3**) at 130 °C, although this reaction was performed without solvent [16]. The only examples that we found related to higher boiling solvents involve the use of the relatively non-polar 1,1,2-trichloroethane at reflux (bp 110–115), which has led to varied results [10c,16]. As we felt the polar Selectfluor® would perform best in solution, we opted to explore a few of the common polar aprotic solvents [dimethylformamide (DMF), dimethylsulfoxide (DMSO), sulfolane, dimethylsulfone] for our fluorination.

To our satisfaction, a significant amount of fluorination took place when isoxazole **4d** was reacted with Selectfluor® at 120 °C for 3–4 h in three-fourth of these solvents, with the notable exception being DMSO. As no new product was formed when DMSO was used, it appears that Selectfluor® may react with this solvent (no report of the reaction of non-deprotonated sulfoxides with Selectfluor® could be found. However, a reaction with sulfides is known to occur [10f]. The reaction with sulfimides is also known [17]). Of the other three solvents, sulfolane emerged as our solvent of choice, as the use of dimethylsulfone was complicated by sublimation and reactions in DMF became much darker in color. While sulfolane has been much utilized for fluorination via halex substitution reactions [18], we could not find any report of it being used previously with N-F reagents.

Utilizing the higher reaction temperature, 4-fluoroisoxazoles **5d** and **5e** were obtained in 39% and 30% yield, respectively. Again, conversion was incomplete and a significant amount of starting material remained unchanged in each case. Interestingly, a small amount (10%) of a more lipophilic by-product was also isolated from these high-temperature reactions which was determined to be the 4,4,5-trifluoroisoxazoline **6** (Scheme 1) based largely on the multiplicity observed in the $^{19}F$ and $^{13}C$ NMR (Table 2), as well as the mass spectrum (Table 1). For example, the $^{19}F$ NMR spectrum of **6d** showed three double doublets (dd), two with both a large geminal coupling ($^{2}J$F-F = 273 Hz) and a smaller vicinal coupling ($^{3}J$F-F = 3.7 or 8.6 Hz), and one with only two vicinal couplings ($^{3}J$F-F = 3.7 and 8.6 Hz). The key signal in the $^{13}C$ NMR, among others, is the triple doublet (ddd) observed for C-4 of the isoxazoline with $^{1}J$C-F = 274 Hz, $^{1}J$C-F′ = 256 Hz, and $^{2}J$C-F = 34.3 Hz. Finally, proposed structures for the two most prevalent ions observed in the mass spectrum of **6d** are shown in Fig. 2. The formation of azirines (as shown in path b) in the mass spectrum of isoxazoles is well established [14].

Table 2
IR, $^{1}H$, $^{13}C$, and $^{19}F$ NMR data for compounds 5**a–e** and 6**d–e**

| Product | IR (KBr), $cm^{-1}$ | $^{1}H$ NMR[a], δ, J (Hz) | $^{13}C$ NMR (DMSO-d6) δ, J (Hz) | $^{19}F$ NMR[a], δ, *J* (Hz) |
|---|---|---|---|---|
| **5a** | 3067, 1650, 1467, 1448, 1422, 1215, 931, 774, 693, 480 | 7.54–7.65 (m, 6H), 7.83–7.89 (m, 4H) | 124.9 (d, *J* = 4.6), 125.0 (d, *J* = 4.6), 125.8 (d, *J* = 3.5), 126.8 (d, *J* = 2.9), 129.4, 129.6, 130.8, 131.0, 140.9 (d, *J* = 256), 152.8 (d, *J* = 10.9), 153.1 (d, *J* = 18.9) | −177.9 (s) |
| **5b** | 3073, 3039, 2916, 1649, 1469, 1421, 1215, 931, 818, 691, 491 | 2.37 (s, 3H), 7.40 (d, *J* = 7.8, 2H), 7.58 (m, 3H), 7.71 (d, *J* = 8.1, 2H), 7.84 (m, 2H) | 21.0, 122.1 (d, *J* = 5.2), 124.9 (d, *J* = 4.6), 125.9 (d, *J* = 4.0), 126.8 (d, *J* = 3.5), 129.3, 130.0, 130.8, 140.4 (d, *J* = 256), 140.7, 152.6 (d, *J* = 10.9), 153.3 (d, *J* = 19.6) | −178.6 (s) |
| **5c** | 3060, 3006, 2940, 2843, 1647, 1463, 1421, 1254, 1176, 1033, 829, 689 | 3.83 (s, 3H), 7.16 (d, *J* = 9.0, 2H), 7.58 (m, 3H), 7.78 (d, *J* = 9.0, 2H), 7.85 (m, 2H) | 55.4, 115.0, 117.5 (d, *J* = 5.2), 126.0 (d, *J* = 4.0), 126.8 (m, 2C), 129.4, 130.9, 139.8 (d, *J* = 255), 152.6 (d, *J* = 10.3), 153.3 (d, *J* = 19.4), 160.9 | −180.0 (s) |
| **5d** | 3100, 3066, 3034, 1647, 1468, 1399, 1215, 931, 829, 818, 687, 488 | 7.59 (m, 3H), 7.75 (d, *J* = 8.4, 2H), 7.82 (d, *J* = 8.7, 2H), 7.83–7.87 (m, 2H) | 124.0 (m, 2C), 125.7, 126.8 (d, *J* = 3.0), 126.9 (d, *J* = 5.2), 129.3, 131.0, 132.6, 141.0 (d, *J* = 258), 152.2 (d, *J* = 18.8), 152.9 (d, *J* = 11.3) | −176.7 (s) |
| **5e** | 3108, 3065, 1652, 1617, 1471, 1461, 1325, 1162, 1112, 1070, 845, 697, 498 | 7.60 (m, 3H), 7.86 (m, 2H), 7.97 (d, *J* = 8.7, 2H), 8.03 (d, *J* = 8.4, 2H) | 123.6 (q, *J* = 273), 125.4 (d, *J* = 3.5), 125.7 (d, *J* = 5.1), 126.2 (q, *J* = 3.5), 126.7 (d, *J* = 3.5), 128.3 (unresolved m), 129.2, 130.2 (q, *J* = 31.5), 130.9, 141.7 (d, *J* = 259), 151.6 (d, *J* = 19.4), 153.0 (d, *J* = 10.9) | −175.2 (s), −61.8 (s) |
| **6d** | 3091, 3068, 1593, 1295, 1252, 1133, 1047, 887, 827, 683, 649 | 7.49–7.58 (m, 5H), 7.66 (d, *J* = 9.0, 2H), 7.87 (d, *J* = 7.2, 2H) | 110.8 (ddd, *J* = 242, 36.3, 21.1), 123.6 (d, *J* = 1.9), 124.6 (ddd, *J* = 274, 256, 34.3), 126.0 (d, *J* = 2.2), 127.1 (d, *J* = 1.7), 127.1 (d, *J* = 27.9), 128.7 (dd, *J* = 5.1, 1.4), 129.3, 132.0, 132.4, 154.6 (dd, *J* = 25.5, 23.5) | −124.4 (dd, *J* = 273, 4.3), −117.0 (dd, *J* = 8.0, 4.3), −102.3 (dd, *J* = 273, 8.0) |
| **6e** | 3116, 3064, 1622, 1450, 1414, 1328, 1265, 1140, 1068, 887, 837, 651 | 7.50–7.62 (m, 3H), 7.79 (s, 4H), 7.89 (d, J = 7.5, 2H) | 111.5 (ddd, *J* = 242, 33.3, 18.0), 123.5 (d, *J* = 1.8), 123.6 (q, *J* = 273), 124.8 (ddd, *J* = 269, 257, 33.9) 125.7 (q, *J* = 3.4), 127.2 (d, *J* = 1.5), 127.7 (dd, *J* = 4.7, 2.0), 129.3, 131.9 (d, *J* = 28.1), 132.5, 133.3 (q, *J* = 31.5), 154.5 (dd, *J* = 25.3, 23.6) | −123.8 (dd, *J* = 273, 3.7), −117.3 (dd, *J* = 8.6, 3.7), −102.4 (dd, *J* = 273, 8.6), −64.2 (s) |

[a] DMSO-$d_6$ used as solvent for **5a–e**; $CDCl_3$ used as solvent for **6d–e**.

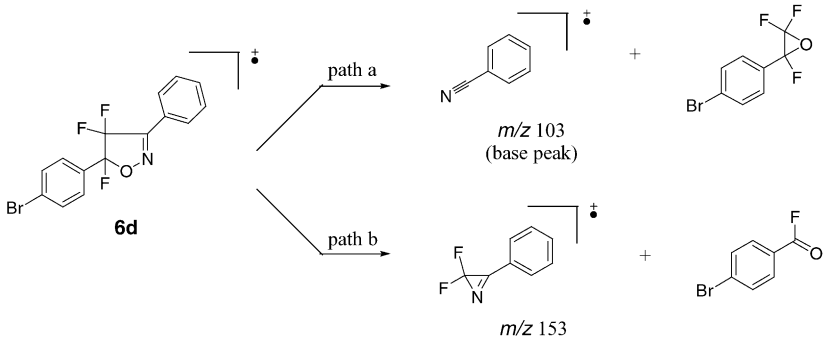
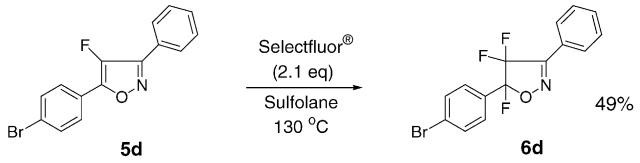



Fig. 2. Proposed structures for most prevalent ions in mass spectrum of **6d**.

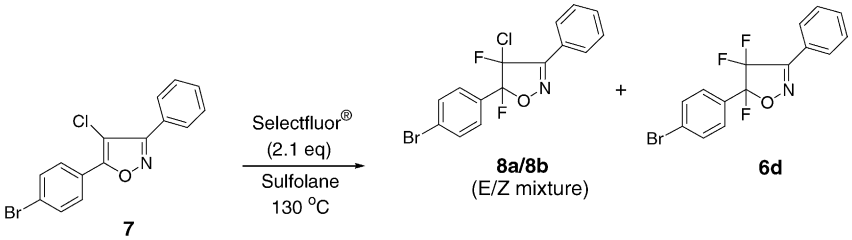



Scheme 2.

The unique trifluoroisoxazoline **6** was apparently formed by a formal addition of fluorine to the 4-fluoroisoxazole subsequent to its formation. This is supported by the fact that the trifluoro product **6d** was also obtained (49% yield) when 4-fluoroisoxazole **5d** was reacted similarly with Selectfluor® (2.1 molar eq. in this case) (Scheme 2).

To the best of our knowledge, such an addition to an aromatic ring upon reaction with an N-F reagent has not previously been described, although a similar addition has been reported to occur as a side reaction upon treating some glycols with Selectfluor® and a nucleophile [19]. Some of those authors [19b] suggest that fluoride anion released from the tetrafluoroborate counteranion serves as an opportunistic nucleophile, adding to the substrate following the electrophilic addition of fluorine. While such a mechanism would appear plausible in our case, the fact that we also observed a trace of the trifluorinated product by GC–MS when the triflate-containing reagent **2b** was used indicates that the fluorine can also come from the N-F cation of Selectfluor® or, more likely, from the HF that is present as a decomposition product (the MSDS for Selectfluor® indicates that HF is a decomposition product. We thank the reviewer for bringing this to our attention). Finally, we should note that a similar addition reaction has been observed upon chlorination of such isoxazoles with HCl(aq)/$H_2O_2$ [20]. In that case, a 4,4-dichloro-5-hydroxyisoxazoline was obtained, with $H_2O$ apparently serving as the nucleophile.

To further explore this interesting reaction, 4-chloroisoxazole **7** [6] was also reacted with Selectfluor® (2.1 molar eq.) at high temperature (Scheme 3). As determined by GC–MS and/or $^{19}F$ NMR, the main products from this reaction, in addition to starting material, were the two 4-chloro-4,5-difluoroisoxazoline diastereomers (**8a/8b**) and, unexpectedly, the 4,4,5-trifluoro derivative **6d**. This latter compound was apparently formed following an initial ipso substitution of the chlorine by fluorine to give 4-fluoroisoxazole **5d**. Indeed, a trace amount of **5d** was confirmed to be present in the crude reaction mixture, along with several other unidentified trace products. Upon purification by column chromatography, a mixture of **8a/8b** and **6d** was obtained which could not be further separated. The mixture was characterized by $^{19}F$ NMR (Section 4).




Scheme 3.

## 3. Conclusion

In conclusion, we have described the synthesis and characterization of a series of 3,5-diaryl-4-fluoroisoxazoles via electrophilic fluorination with Selectfluor®. A unique 4,4,5-trifluoroisoxazoline was also isolated as a side-product from some of our reactions. Sulfolane was found to be a good solvent for conducting electrophilic fluorinations with N-F reagents at higher than normal temperatures. Finally, this appears to be the first reported example of the direct fluorination of an isoxazole.

## 4. Experimental

Starting isoxazoles were prepared from the appropriate chalcone derivative via standard chemistry [21] and characterized by $^{13}C$ NMR as outlined in the literature [22]. Selectfluor® was either purchased from Aldrich or was obtained as a gift from Air Products and Chemicals Inc. Acetonitrile was distilled from calcium hydride. Sulfolane was dried by standing over activated molecular sieves (4A). Selecto silica gel (230–400 mesh) was used for column chromatography. With the exception of the $^{13}C$ NMR of **6d**, which was obtained on a Bruker 600 MHz instrument, all NMR spectra were recorded on a Varian Unity+300 instrument at ambient temperature. Chemical shifts for $^{19}F$ NMR were measured from hexafluorobenzene as internal standard and converted to the δ-scale with $CFCl_3$ as reference by the conversion relation $\delta(CFCl_3) = \delta(C_6F_6) - 162.9$ ppm [23]; spectra exhibiting $^{19}F$-$^{19}F$ coupling were run with acquisition time = 1.0 s to improve resolution. GC–MS data were obtained on a Shimadzu GC-17A/QP-5000 instrument operating in EI mode (70 eV). Other details are as previously described [6].

### 4.1. General procedure for synthesis of 4-fluoro-3,5-diarylisoxazoles 5a–c

A mixture of the isoxazole **4** (1.0 mmol) and Selectfluor® (1.05 mmol) in dry acetonitrile (5 ml) was heated at gentle reflux overnight under nitrogen. Excess water was then added to give a white precipitate, which was filtered, washed with water and air dried. Compounds **5a** and **5b** were purified by preparative plate chromatography ($SiO_2$, 0.5 mm thickness) eluting with hexanes:ethyl acetate (5:1), while compound **5c** was purified by column chromatography eluting with 2% ether in pentane. Each compound was then recrystallized. Compound data given in Tables 1 and 2.

### 4.2. General procedure for synthesis of 4-fluoro-3,5-diarylisoxazoles 5d–e and 4,4,5-trifluoro-3,5-diarylisoxazolines 6d–e

A mixture of the isoxazole **4** (3.0 mmol), Selectfluor® (3.15 mmol) and sulfolane (7.0 g) was heated under nitrogen in an oil bath set at 120 °C for 3 h (for **4d**) or 4 h (for **4e**). The pale yellow solution was then diluted with excess water to give a white solid, which was collected and rinsed with water. Column chromatography eluting with pentane gave pure compound **6**. Further elution with 2% ether in pentane gave pure compound **5**. Compounds **5d** and **5e** were then recrystallized. A similar reaction of **5d** (0.89 mmol) with Selectfluor® (1.86 mmol) (130 °C, 4 h) gave **6d** in 49% isolated yield. Compound data given in Tables 1 and 2.

### 4.3. Fluorination of 4-chloro-3,5-diarylisoxazole 7

A mixture of compound **7** (0.335 g, 1.0 mmol), Selectfluor® (0.74 g, 2.1 mmol) and sulfolane (2.0 g) was heated under nitrogen at 130 °C for 3 h. Dilution with excess water gave a yellow oil that was separated by decanting. The oil was dissolved in ether, washed with brine, and dried ($Na_2SO_4$). GC–MS of the extract showed that compounds **8a**, **8b**, **6d**, and **7** were major components (not quantified). A number of trace products were also present, of which only **5d** could be identified. Column chromatography eluting with pentane gave an inseparable mixture of **8a**, **8b**, and **6d** as a colorless oil (0.09 g), which solidified after standing several weeks. $^{19}F$ NMR ($CDCl_3$): **8a** or **8b**: −137.72 (d, $J$ = 4.8), −110.63 (d, $J$ = 4.8); **8a** or **8b**: −107.94 (d, $J$ = 2.1), −101.30 (d, $J$ = 2.7); signals for **6d** were also present. GC–MS data further supported the structure assignments.

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