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Title: Use of 1-pentafluorosulfanyl-phenylacetylenes for the preparation of SF<sub>5</sub>-substituted five-membered ring heterocycles through 1,3-dipolar cycloadditions. Isoxazoles and isoxazolines



Author: Simon E. Lopez Akira Mitani Priscila Pena Ion Ghiviriga William R. Dolbier Jr.

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1,3-Dipolar cycloadditions of nitrile oxides and nitrones with  $\mathsf{SF}_5\text{-substituted}$  alkynes

### Highlights for Review

- 1. 1,3-dipolar cycloadditions of nitrile oxides and nitrones are reported.
- 2.  $SF_5$ -substituted alkynes are used in 1,3-dipolar cycloaddition reactions.
- 3. Preparations of  $SF_5$ -substituted isoxazoles and isoxazolines are reported.

Page 3 of 18

### Use of 1-pentafluorosulfanyl-phenylacetylenes for the preparation of SF<sub>5</sub>-substituted five-membered

### ring heterocycles through 1,3-dipolar cycloadditions. Isoxazoles and isoxazolines

Simon E. Lopez,<sup>¥£</sup> Akira Mitani,<sup>¥</sup> Priscila Pena,<sup>¥</sup> Ion Ghiviriga,<sup>¥</sup> William R. Dolbier Jr.\*<sup>¥</sup>

<sup>¥</sup>Department of Chemistry, University of Florida, Gainesville, FL 32 611-72000, United States

<sup>£</sup>Departamento de Quimica, Universidad SimonBolivar, Valle de Sartenejas, Baruta, Caracas 1080A, Venezuela

\*Corresponding author email: wrd@chem.ufl.edu

#### Abstract

A synthetic methodology utilizing 1,3-dipolar cycloadditions was developed for the preparation of pentafluorosulfanyl-substituted heterocycles using SF<sub>5</sub>-substituted arylacetylenes as key building block dipolarophiles. A group of 4-SF<sub>5</sub>-isoxazoles were prepared in moderate yields using *in situ* generated nitrile oxides, and 4-SF<sub>5</sub>-substituted isoxazolines were obtained when nitrones were used as the 1,3-dipole.

Keywords: 1,3-dipolar cycloaddition, pentafluorosulfanyl, aryl SF5-acetylenes, isoxazole, isoxazoline

#### 1. Introduction

Fluorine substitution can have a high impact on the physicochemical properties of organic molecules, due to the high electronegativity, low polarizability, and small size of the fluorine atom [1]. Fluorinated substituents are often found to be advantageous in biological active compounds, such as pharmaceuticals [2] and agrochemicals [3]. Among such fluorine-containing substituents, the pentafluorosulfanyl group (SF<sub>5</sub>) has emerged as a possible alternative to the trifluoromethyl group (CF<sub>3</sub>) [4-11], a very commonly encountered substituent in biological active compounds, because the two groups share many typical characteristics, such as high electronegativity, steric size, chemical stability, and lipophilicity [12,13]. The SF<sub>5</sub> group has often been referred to as a "supertrifluoromethyl group" [1g]. The synthesis and utilization of pentafluorosulfanyl-containing compounds has been recently reviewed [14].

Isoxazoles and isoxazolines are important classes of five membered ring, nitrogen-containing heterocycles that are present in many biologically active compounds and natural products (Figure 1) [15]. The incorporation of the pentafluorosulfanyl group into such heterocycles through 1,3-dipolar cycloadditions is a subject that should be of interest to both academic and industrial research communities because of the potential applications of such compounds.

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### Figure 1. Examples of isoxazoles and isoxazolines with biological activity [16]

#### 2. Results and discussion

A variety of synthetic methodologies have been developed for the preparation of isoxazoles and isoxazolines, but 1,3-dipolar cycloadditions of nitrile oxides and nitrones to alkynes are among the most convenient routes [17]. The utility of  $SF_5$ -alkynes as building blocks has been clearly demonstrated in recent studies of preparations of pentafluorosulfanyl-substituted pyrroles, thiophenes, pyrazoles and triazoles (Scheme 1) [18]. The employment of  $SF_5$ -alkynes as dipolarophile building blocks for the

Scheme 1. Use of 1,3-dipolar cycloadditions to prepare SF<sub>5</sub>-substituted heterocyclics



preparation of pentafluorosulfanyl substituted isoxazoles and isoxazolines was therefore deemed to be a likely effective route to such compounds.

Thus, arylacetylenes **1a-c** were allowed to react with  $SF_5Cl$  at -40 °C, employing triethylborane as low temperature radical initiator to give the corresponding alkenyl chlorides **2a-c** in acceptable yields (Scheme 2) [19]. This reaction appears to be dependent upon the electronic character of the substituent that is on the aryl ring, with better yields observed for electron-donating groups (**2b** and **2c**). The obtained alkenyl chlorides were then dehydrohalogenated by treatment with lithium hydroxide in dimethylsulfoxide to form the required  $SF_5$ -substituted alkynes **3a-c** in good yields.

Phenylnitrile oxide **5a**, was generated *in situ* from benzohydroxyiminoyl chloride **4a** (Scheme 3), and it underwent 1,3-dipolar cycloaddition with phenyl-SF<sub>5</sub>-acetylene **3a** to obtain the SF<sub>5</sub>-substituted isoxazole, **6a**. Because of the known competitive dimerization of the *in situ* generated nitrile oxide intermediate [20], the number of equivalents of benzohydroxyiminoyl chloride and triethylamine was



Scheme 2. Preparation of SF<sub>5</sub>-arylacetylenes

increased in order to maximize the yield of the desired  $SF_5$ -isoxazole. Initial attempts that employed only one or two equivalents of triethylamine and benzohydroxyiminoyl chloride produced low yields of the desired isoxazole along with considerable amounts of the dimerization product (Table 1, entries 1-2), as was revealed by examination of proton NMR spectra of the crude product mixtures [21]. Since the rate of nitrile oxide dimerization appeared to be greater than that of the desired 1,3-dipolar cycloaddition, it was necessary to use a larger excess of both triethylamine and benzohydroxyiminoyl chloride, as well as to extend the reaction time. The best yields were obtained by using 5.5 equivalents of nitrile oxide precursor, which was added in portions over a period of 36 hours (Table 1, entry 5).



Scheme 3. 1,3-Dipolar cycloaddition reaction of SF<sub>5</sub>-phenylacetylene 3a with an *in situ*-generated nitrile oxide intermediate 5a.

Table 1. Opti	mization conditi	ons for the	e synthesis	of SF <sub>5</sub> -isoxazo	ole 6a
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	-SF <sub>5</sub> +	$\frac{N}{CI} = \frac{Et_3N}{4a}$	THF, rt	O <sup>N</sup> SF <sub>5</sub> 6a
Entry	4a (equiv.)	Et <sub>3</sub> N (equiv.)	Time (h)	Yield (%)
1	1.0	1.0	16	5
2	2.0	2.0	16	14
3	3.0	3.0	24	24
4	3.0	3.0	36	35
5	5.5	5.5	36	50
G				

By varying the *p*-substituents of both the aryl  $SF_5$ -acetylenes and the nitrile oxides, these optimized conditions were employed to prepare seven aryl  $SF_5$ -isoxazoles in moderate yields (Table 2).

Table 2. Preparation of aryl SF5-isoxazoles 6a-g via 1,3-dipolar cycloaddition reactions

RSF <sub>5</sub> + 3a (R=H) 3b (R=Me) 3c (R=OMe)	$\begin{array}{c} & & & \\ & & \\ R_1 & (5.5 \text{ equiv}) \\ & &$	Et <sub>3</sub> N (5.5 equi THF, rt 36 h	$V)$ $O^{N}$ $F_{5}$ R $6a-g$	<b>₹</b> 1
Compd. No	). R	$\mathbf{R}_1$	Yield (%)	
ба	Н	Н	50	
6b	Н	OMe	53	
бс	Me	Н	55	
6d	Me	F	59	
6e	Me	Me	50	
6f	OMe	OMe	58	
<u> </u>	OMe	F	-51	

It was also possible to prepare  $SF_5$ -isoxazolines **7a-c**, via the 1,3-dipolar cycloaddition reactions of nitrones with aryl  $SF_5$ -acetylenes (Scheme 4). Thus, moderate to good yields were obtained from the reaction of nitrones **6a-c** with alkynes **3a** or **b** in THF at room temperature for 20 hours.



Scheme 4. Preparation of aryl SF5-isoxazolines 8a-c via 1,3-dipolar cycloadditions

The structures of all products were fully characterized by proton, fluorine and carbon NMR spectroscopy and either HRMS or elemental analysis. Only one regioisomeric product was obtained for each of the reactions, and the regiochemistry exhibited by the products was assigned on the basis of a detailed NMR spectroscopic examination of oxazole **6f** and oxazoline **8c**.

Cross-peaks in the gHMBC spectrum of **6f** allow for the assignment of the <sup>1</sup>H and <sup>13</sup>chemical shifts in the *p*-methoxyphenyl moieties and of the oxazole carbons to which they are attached, at 169.4 and

160.0 ppm. The chemical shifts of these carbons were used to assign the methoxyphenyl substituents as *alpha* to O and N, and they also clearly demonstrate that the structure of the product is **6f** and not its



Figure 2. <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR assignments for products 6f and 8c

alternative regioisomer, in which one of these two chemical shifts would be expected to be much smaller, ca. 110 ppm. Cross-peaks in the HOESY spectrum of **6f**, between the equatorial fluorines in the SF<sub>5</sub> group at 77.5 ppm and both of the protons *ortho* to the oxazole substituent, at 7.64 and 7.45 ppm, agree with structure **6f** and not with the structure of its alternative regioisomer. Similar chemical shifts and nOes demonstrate that the structure of **8c** is as drawn, rather than its alternative regioisomer. The assigned proton, carbon and fluorine chemical shifts derived from these analyses are provided in Figure 1.

#### 3. Conclusions

A 1,3-dipolar cycloaddition based methodology was utilized for the synthesis of a series of pentafluorosulfanyl-substituted isoxazoles and isoxazolines using aryl SF<sub>5</sub>-acetylenes as key building blocks. Aryl SF<sub>5</sub>-isoxazoles were obtained in moderate yields from reactions of *in situ*-generated nitrile oxides with aryl SF<sub>5</sub>-acetylenes, and good yields of isoxazolines were obtained from the cycloadditions of these alkynes with nitrones.

### 4. Experimental

#### 4.1. General information

NMR spectra were obtained in CDCl<sub>3</sub> using TMS as the internal standard for <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR (75 MHz) and CFCl<sub>3</sub> for <sup>19</sup>F NMR (282 MHz), unless otherwise noted. All reagents were purchased at commercial quality and were used without further purification. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. High resolution mass spectrometric measurements were performed by the University of Florida Department of Chemistry Mass Spectrometry Services, using either an Agilent 6220 ESI-TOF instrument or a Thermo Scientific Trace DSQ GC-MS. Elemental analyses (% C,H,N) of compound **8a** was performed using a EA1108 CHNS-O instrument (Fisons Instruments). Starting materials (*E*)-1-chloro-2-pentafluorosulfanyl-1-phenylethene (**2a**) and 1-pentafluorosulfanyl-2-phenylacetylene (**3a**) were prepared according to our previous reported procedures [17]. Benzohydroxyiminoyl chlorides (**4a-d**) [22] and *N*-benzylideneaniline *N*-oxides (**7a-c**) [23] were prepared according to the literature.

#### *4.2. Preparation of 1-chloro-2-pentafluorosulfanyl-1-arylethenes (2b-c)*

Into a three-necked flask equipped with a dry-ice reflux condenser and a nitrogen inlet were added at -40  $^{\circ}$ C 15 mL of anhydrous hexane, arylacetylene (3 mmol), and SF<sub>5</sub>Cl (1.2 equiv). The solution was stirred at this temperature for 5 min, and then Et<sub>3</sub>B (0.1 equiv, 1 M in hexane) was added slowly using a syringe. The solution was vigorously stirred for 1 h at -30  $^{\circ}$ C, and then the mixture was allowed to warm to room temperature. The mixture was hydrolyzed with aqueous NaHCO<sub>3</sub> (10%), and the organic layer was dried over anhydrous MgSO<sub>4</sub>. The solvent was removed, and the crude product was passed through a column of silica gel, eluting with hexanes. Removal of solvent provided the products as colorless oils.

#### 4.2.1. (E)-1-Chloro-2-pentafluorosulfanyl-1-(4-methylphenyl)ethane (2b)

0.42 g (50%); <sup>1</sup>H NMR,  $\delta$  7.25 (d, J = 6.0 Hz, 2H), 7.23 (d, J = 6.0 Hz, 2H), 6.92 (m, 1H); <sup>19</sup>F NMR,  $\delta$  81.1 (p, <sup>2</sup> $J_{FF} = 152$  Hz, 1F), 68.9 (d, <sup>2</sup> $J_{FF} = 152$  Hz, 4F); <sup>13</sup>C NMR,  $\delta$  143.2, 140.2, 137.6 (p), 132.7, 128.9, 127.5, 21.4; HRMS (GC-CI): m/z Calcd.for C<sub>9</sub>H<sub>8</sub>ClF<sub>5</sub>S: 277.9955. Found: 277.9956.

#### *4.2.2.* (*E*)-1-Chloro-2-pentafluorosulfanyl-1-(4-methoxyphenyl)ethene (2*c*)

0.60 g (68%); <sup>1</sup>H NMR,  $\delta$  7.33 (d, J = 9.0 Hz, 2H), 6.91 (m, 3H), 3.84 (s, 3H); <sup>19</sup>F NMR,  $\delta$  81.4 (p, <sup>2</sup> $J_{FF}$  = 150 Hz, 1F), 68.9 (d, <sup>2</sup> $J_{FF}$  = 150 Hz, 4F); <sup>13</sup>C NMR,  $\delta$  160.8, 131.5 (m), 129.3, 127.5, 113.7, 55.3; HRMS (+ESI-DART): m/z Calcd. for [C<sub>9</sub>H<sub>9</sub>ClF<sub>5</sub>OS]<sup>+</sup>: 294.9983. Found: 294.9978.

### 4.3. Preparation of 1-pentafluorosulfanyl-2-(substitutedphenyl)acetylenes (3b-c)

To a solution of the corresponding alkene **2b-c** (5.67 mmol) in DMSO (5 mL) was added LiOH x H<sub>2</sub>O (1.2 g, 28.6 mmol, 5 equiv) at room temperature. The mixture was stirred for 2 hours at room temperature. The resultant mixture was poured into ice-water, neutralized with 2 M HCl, and extracted twice with diethyl ether (2 x 25 mL). The organic layers were combined, washed with brine, and then dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (elution with hexanes), to obtain the products as colorless oils.

### 4.3.1. 1-Pentafluorosulfanyl-2-(4-methylphenyl)acetylene (3b)

1.21 g (88%); <sup>1</sup>H NMR,  $\delta$  7.46 (d, J = 6 Hz, 2H), 7.21 (d, J = 6 Hz, 2H,), 2.40 (s, 3H, Me); <sup>13</sup>C NMR,  $\delta$  141.6, 132.5, 129.4, 114.2, 21.6 (C=C carbons not seen); <sup>19</sup>F NMR,  $\delta$  77.6 (p, 1F, <sup>2</sup> $J_{FF} = 168$  Hz), 83.8 (d, 4F, <sup>2</sup> $J_{FF} = 168$  Hz); HRMS (+ESI-DART): m/z Calcd. for [C<sub>9</sub>H<sub>7</sub>F<sub>5</sub>S]<sup>+</sup>: 242.0189. Found: 242.0198.

#### 4.3.2. 1-Pentafluorosulfanyl-2-(4-methoxyphenyl)acetylene (3c)

1.24 g (85%); <sup>1</sup>H NMR,  $\delta$  7.54 (d, J = 6 Hz, 2H), 6.94 (d, 2H, J = 6 Hz), 3.88 (s, 3H, OMe); <sup>13</sup>C NMR,  $\delta$  161.8, 134.4, 114.4, 109.0, 55.4 (C=C carbons not seen); <sup>19</sup>F NMR,  $\delta$  77.4 (p, 1F, <sup>2</sup> $J_{FF} = 170$  Hz), 83.3 (d, 4F, <sup>2</sup> $J_{FF} = 170$  Hz);HRMS (+ESI-DART): m/z Calcd for [C<sub>9</sub>H<sub>8</sub>F<sub>5</sub>OS + NH<sub>4</sub>]<sup>+</sup>: 276.0476. Found: 276.0480.

4.4. General procedure for the preparation of 3,5-diarylsubstituted-4-pentafluorosulfanylisoxazoles (**6a-g**) To a solution of the SF<sub>5</sub>-alkyne (1.1 mmol) in THF (3 mL) was added the benzohydroxyiminoyl chloride (2.2 mmol, 2 equiv). A solution of triethylamine (0.22 g, 2.2 mmol, 2 equiv) in 3 mL of THF was added dropwise to the mixture at room temperature over 30 minutes. After stirring for 16 hours at room temperature, a second portion of the SF<sub>5</sub>-alkyne (3.85 mmol, 3.5 equiv) in THF (9 mL) and triethylamine (0.78 g, 7.7 mmol) were added dropwise. The reaction mixture was stirred for 20 hours at room temperature. The resultant mixture was poured into water and extracted twice with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine, and then dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure. The crude products were purified by silica gel column chromatography (elution with hexanes-CHCl<sub>3</sub>; 65:35), to obtain the corresponding SF<sub>5</sub>-isoxazoles **6** as white solids.

### 4.4.1. 3,5-diphenyl-4-(pentafluorosulfanyl)isoxazole (6a) [24]

0.19 g (50%); mp = 149-150 °C; <sup>1</sup>H NMR,  $\delta$  7.66-7.69 (m, 2H), 7.49-7.68 (m, 8H); <sup>19</sup>F NMR,  $\delta$  81.9 (p, <sup>2</sup>*J*<sub>FF</sub> = 162 Hz, 1F), 77.2 (d, <sup>2</sup>*J*<sub>FF</sub> = 162 Hz, 4F); HRMS (+ESI-DART): m/z Calcd. for [C<sub>15</sub>H<sub>11</sub>F<sub>5</sub>NOS]<sup>+</sup>: 348.0476. Found: 348.0465.

#### 4.4.2. 3-(4-methoxyphenyl)-5-phenyl-4-(pentafluorosulfanyl)isoxazole (6b)

0.22 g (53%); mp = 116-118 °C; <sup>1</sup>H NMR,  $\delta$  7.66 (d, J = 9.0 Hz, 2H), 7.52 (m, 5H), 7.01 (d, J = 9.0 Hz), 3.87 (s, 3H, OCH<sub>3</sub>); <sup>19</sup>F NMR,  $\delta$  82.2 (p, <sup>2</sup> $J_{FF}$  = 144 Hz, 1F), 77.16 (d, <sup>2</sup> $J_{FF}$  = 144 Hz, 4F); <sup>13</sup>C NMR,  $\delta$ 158.4, 157.5, 157.4, 128.8, 128.3, 126.5, 126.0, 124.3, 117.7, 111.3, 52.8 (SF<sub>5</sub>-C not observed); HRMS (+ESI-DART): m/z Calcd. for [C<sub>16</sub>H<sub>13</sub>F<sub>5</sub>NO<sub>2</sub>S]<sup>+</sup>: 378.0582. Found: 378.0592.

### 4.4.3. 3-phenyl-5-(4-methylphenyl)-4-(pentafluorosulfanyl)isoxazole (6c)

0.22 g (55%); mp = 157-159 °C; <sup>1</sup>H NMR,  $\delta$  7.70 (m, 2H), 7.62 (m, 1H), 7.57 (m, 2H), 7.46 (d, J = 6 Hz, 2H), 7.33 (d, J = 6 Hz, 2H), 2.47 (s, 3H, CH<sub>3</sub>); <sup>19</sup>F NMR,  $\delta$  82.6 (p, <sup>2</sup> $J_{FF} = 144$  Hz, 1F), 77.7 (d, <sup>2</sup> $J_{FF} = 144$ 

Hz, 4F); <sup>13</sup>C NMR, δ 169.5, 160.2, 140.0, 131.3, 129.3, 129.2, 128.9, 128.5, 126.9, 125.3, 21.4 (SF<sub>5</sub>-C not observed); HRMS (+ESI-DART): m/z Calcd. for [C<sub>16</sub>H<sub>13</sub>F<sub>5</sub>NOS]<sup>+</sup>: 362.0633. Found: 362.0639.

#### 4.4.4. 3-(4-fluorophenyl)-5-(4-methylphenyl)-4-(pentafluorosulfanyl)isoxazole (6d)

0.25 g (59%); mp = 108-109 °C; <sup>1</sup>H NMR,  $\delta$  7.60 (d, J = 9.0 Hz, 2H), 7.55 (m, 2H), 7.38 (d, J = 9 Hz, 2H), 7.21 (t, J = 6 Hz, 2H), 2.49 (s, 3H, CH<sub>3</sub>); <sup>19</sup>F NMR,  $\delta$  82.6 (p, <sup>2</sup> $J_{FF}$  = 163 Hz, 1F), 77.6 (d, <sup>2</sup> $J_{FF}$  = 163 Hz, 4F); <sup>13</sup>C NMR,  $\delta$  169.9, 163.8 (d,  $J_{FC}$  = 155 Hz), 159.3, 142.0, 131.5, 129.3, 129.0, 124.4, 123.7, 115.4, 21.6 (SF<sub>5</sub>-C not observed); HRMS (+ESI-DART): m/z Calcd. for [C<sub>16</sub>H<sub>12</sub>F<sub>6</sub>NOS]<sup>+</sup>: 380.0538. Found: 380.0535.

### 4.4.5. 3-(4-methylphenyl)-5-(4-methylphenyl)-4-(pentafluorosulfanyl)isoxazole (6e)

0.21 g (50%); mp = 134-136 °C; <sup>1</sup>H NMR,  $\delta$  7.57 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 2.45 (s, 3H, CH<sub>3</sub>), 2.43 (s, 3H); <sup>13</sup>C NMR,  $\delta$  141.8, 140.0, 129.3, 129.2, 129.0, 128.9, 21.5, 21.4 (quaternary aromatic carbons and C-SF<sub>5</sub><sup>-</sup> not seen); <sup>19</sup>F NMR,  $\delta$  82.3 (p, <sup>2</sup>*J*<sub>FF</sub> = 160 Hz, 1F), 77.2 (d, <sup>2</sup>*J*<sub>FF</sub> = 160 Hz, 4F); HRMS (+ESI-DART): m/z Calcd. for [C<sub>17</sub>H<sub>15</sub>F<sub>5</sub>NOS]<sup>+</sup>: 376.0789. Found: 376.0803.

4.4.6. 3-(4-methoxyphenyl)-5-(4-methoxyphenyl)-4-(pentafluorosulfanyl)isoxazole (**6**f)

0.26 g (58%); mp = 124-126 °C; <sup>1</sup>H NMR (500 MHz),  $\delta$  7.64 (d, J = 6.0 Hz, 2H), 7.45 (d, J = 6 Hz, 2H), 7.03 (d, J = 6 Hz, 2H), 7.00 (d, J = 6 Hz, 2H), 3.89 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>); <sup>19</sup>F NMR (470 MHz),  $\delta$  83.2 (p, <sup>2</sup> $J_{FF}$  = 160 Hz, 1F), 77.5 (d, <sup>2</sup> $J_{FF}$  = 160 Hz, 4F); <sup>13</sup>C NMR (125.8 MHz),  $\delta$  169.4, 161.4, 160.8, 160.0 130.8, 130.7 120.5, 118.9, 114.0, 113.7, 55.4, 55.3 (SF<sub>5</sub>-C not seen); HRMS (+ESI-DART): m/z Calcd. for [C<sub>15</sub>H<sub>15</sub>F<sub>5</sub>NO<sub>3</sub>S]<sup>+</sup>: 408.0687. Found: 408.0696.

#### 4.4.7. 3-(4-fluorophenyl)-5-(4-methoxyphenyl)-4-(pentafluorosulfanyl)isoxazole (6g)

0.22 g (51%); mp = 112-114 °C; <sup>1</sup>H NMR,  $\delta$  7.85 (d, *J* = 9.0 Hz, 2H), 7.50 (m, 2H), 7.15 (m, 2H), 7.03 (d, *J*= 9.0 Hz, 2H), 3.90 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR,  $\delta$  169.9, 164.9, 161.0 (d, *J*<sub>FC</sub> = 202 Hz), 131.8, 131.1,

124.7, 118.9, 115.8 (d,  ${}^{2}J_{FC} = 14$  Hz), 114.4, 114.3, 55.8 (C-SF<sub>5</sub> not seen);  ${}^{19}F$  NMR,  $\delta$  82.4 (p,  ${}^{2}J_{FF} = 160$  Hz, 1F), 77.1 (d,  ${}^{2}J_{FF} = 160$  Hz, 4F), -111.2 (s, 1F); HRMS (+ESI-DART): m/z Calcd. for [C<sub>16</sub>H<sub>12</sub>F<sub>6</sub>NOS]<sup>+</sup>: 396.0487. Found: 396.0485.

4.5. General procedure for preparation of 4-pentafluorosulfanyl-2,3,5-triarylsubstituted-4-isoxazolines (8a-c).

To a solution of the SF<sub>5</sub>-acetylene (0.785 mmol) in THF (4 mL) was added the corresponding N-benzylidineaniline N-oxide (1.57 mmol, 2 equiv). The reaction mixture was stirred for 20 hours at room temperature. The solvent was removed under reduced pressure to give a residue which was then purified by silica gel column chromatography (elution with hexanes-CHCl<sub>3</sub>; 65:35), obtaining the corresponding SF<sub>5</sub>-isoxazolidines as light yellow solids.

### 4.5.1. 4-Pentafluorosulfanyl-2,3,5-triphenyl-4-isoxazoline (8a). [24]

0.30 g (90%); mp = 100-101 °C; <sup>1</sup>H NMR,  $\delta$  7.78 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 3H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 8.2 Hz, 3H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 5.84 (s, 1H); <sup>19</sup>F NMR,  $\delta$  85.1 (p, <sup>2</sup>*J*<sub>FF</sub> = 161 Hz, 1F), 74.8 (d, <sup>2</sup>*J*<sub>FF</sub> = 161 Hz, 4F); <sup>13</sup>C NMR,  $\delta$  157.2, 151.2, 140.4, 131.7, 129.8, 129.6, 129.4, 129.1, 128.9, 127.7, 127.2, 125.0, 116.3, 78.5 (SF<sub>5</sub>-C not observed); Anal.Calcd. for C<sub>21</sub>H<sub>16</sub>F<sub>5</sub>NOS: C, 59.29; H, 3.79; N, 3.29. Found: C, 58.97; H, 3.59; N, 3.17.

4.5.2. 4-Pentafluorosulfanyl-2-(4-methylphenyl)-3-(4-methoxyphenyl)-5-phenyl-4-isoxazoline (**8b**). 0.24 g (65%); mp = 96-97 °C; <sup>1</sup>H NMR,  $\delta$  7.75 (dd, J = 7.5, 2.0 Hz, 2H), 7.35-7.60 (m, 10H), 7.24 (d, J = 7.3 Hz, 2H), 7.21 (t, J = 7.2 Hz, 2H), 5.80 (s, 1H); <sup>19</sup>F NMR,  $\delta$  85.1 (p, <sup>2</sup> $J_{FF}$  = 161 Hz, 1F), 74.8 (d, <sup>2</sup> $J_{FF}$  = 161 Hz, 4F); <sup>13</sup>C NMR,  $\delta$  160.2, 157.0, 151.0, 141.8, 132.4, 129.5, 129.3, 128.7, 124.6, 124.0, 116.1, 114.5, 55.4, 21.7 (SF<sub>5</sub>-C not observed, isoxazoline C-H obscured by CDCl<sub>3</sub> signal, one Ar-C signal not observed); HRMS (+ESI-DART): m/z Calcd. For [C<sub>23</sub>H<sub>21</sub>F<sub>5</sub>NO<sub>2</sub>S]<sup>+</sup>: 470.1208. Found: 470.1231.

#### 4.5.3. 4-Pentafluorosulfanyl-2-phenyl-3-(4-fluorophenyl)-5-phenyl-4-isoxazoline (8c).

0.21 g (60%); mp = 98-100 °C; <sup>1</sup>H NMR (500 MHz),  $\delta$  7.76 (d, J = 6.0 Hz, 2H), 7.58 (m, 1H), 7.55 (m, 2H), 7.54 (m, 2H) 7.41 (m, 2H), 7.24 (m, 2H), 7.19 (m, 1H), 7.16 (m, 2H), 5.83 (s, 1H); <sup>19</sup>F NMR (470 MHz),  $\delta$  85.6 (p, <sup>2</sup> $J_{FF}$  = 155 Hz, 1F), 75.4 (d, <sup>2</sup> $J_{FF}$  = 155 Hz, 4F), -113.1 (s, 1F); <sup>13</sup>C NMR (125.8 MHz),  $\delta$  162.9, 157.0, 150.6, 136.0, 131.4 129.4, 129.3, 129.2, 128.6, 126.7, 126.7, 124.8, 116.1, 116.0, 77.4 (isoxazoline CH); HRMS (+ESI-DART): m/z Calcd. f.6, or [C<sub>21</sub>H<sub>16</sub>F<sub>6</sub>NOS]<sup>+</sup>: 444.0851, Found: 444.0859.

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