Reaction of Benzohydroximinoyl Chlorides and β-(Trifluoromethyl)-acetylenic Esters: Synthesis of Regioisomeric (Trifluoromethyl)-isoxazolecarboxylate Esters and Oxime Addition Products

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The triethylamine induced reaction of benzohydroximinoyl chlorides, precursors of nitrile oxides, with β-trifluoromethylacetylenic esters gives rise to three products: 5-trifluoromethyl-4-isoxozolecarboxylate esters, regioisomeric 4-trifluoromethyl-5-isoxazolecarboxylate esters and an unexpected oxime 1,4-addition adduct. Product distribution is rationalized in terms of two competing reaction modes, either 1,4 addition of the oxime anion to the acetylenic ester or formation of the nitrile oxide followed by 1,3-dipolar cycloaddition. Anionic 1,4-addition of the oximinoyl chloride to the acetylenic ester is preferred at low temperatures, while nitrile oxide formation followed by cycloaddition is preferred at temperatures above 0 °C. Regioisomeric products from addition of nitrile oxides to various perfluoroalkylacetylenes are compared and assigned by ^{13}C NMR.

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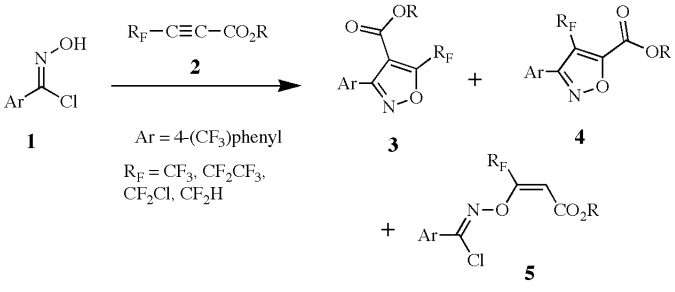
Introduction.

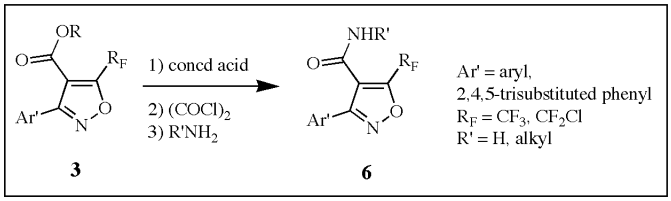
Haloalkyl and trifluoromethyl isoxazoles have been reported as antiviral agents [1], anti-inflammatory agents [2,3], tissue factor Xa inhibitors [4], immunosuppressents [5], herbicides [6] and antifungal agents [7]. Often the trifluoromethyl substituted isoxazoles are included along with non-fluorinated analogs as patent examples of biologically active compounds. However, in some cases trifluoromethylisoxazoles have been shown to have particularly enhanced activity and/or selectivity compared to non-fluorinated analogs as in the case of anti-inflammatory COX-2 inhibitors [2] and herbicidal protoporphyrin-9 oxidase inhibitors [8].

Trifluoromethylisoxazoles have been prepared by cyclocondensation of hydroxylamine and conjugated ynone [9], β-diketones [10,11] or difluoroalkyl-2-iodoalkenes [12] or by 1,3-dipolar cycloadditions of nitrile oxides and trifluoromethyl substituted dipolarophiles such as pyrrolidinoacrylates [13], β-ketoesters [14] and acetylenic esters [15-17]. The cyclocondensation routes provide 3- and 5-trifluoromethylisoxazoles depending on the conditions employed. Linderman [9] was able to obtain 5-trifluoromethylisoxazole from hydroxylamine and trifluoromethylacetylenic ketones under basic conditions, and the corresponding 3-trifluoromethyl isomer under acidic conditions. While the cyclocondensations typically provide 3,5-disubstituted isoxazoles, these products have been substituted in the four position by alkylation of the lithium anion to provide trisubstituted 5-trifluoromethylisoxaozles [10]. Trisubstituted isoxazoles can be prepared directly by dipolar cycloadditions, which give 5-trifluoromethyl isomers as the major product from addition of nitrile oxides to perfluoroalkyl substituted β-ketoesters, acetylenes and acrylates. Small amounts (5 – 10%) of the regioisomeric 4-trifluoromethylisoxazoles have been proposed based on the analysis of crude reaction mixtures, however these minor products have not been previously isolated or characterized [15,18]. A notable exception is the addition of 1-aryl-3-trifluoromethylacetylenes to nitrile oxides which gives 4-trifluoromethylisoxazoles as the major product [19].

In the course of investigating the biological activity of isoxazolecarboxamides **6** [8], we needed to obtain various isomers of the isoxazolecarboxylate ester precursors **3** for preparation of regioisomeric analogs for structure-activity relationship studies (Scheme 1). Carboxamide derivatives **6** of 3-aryl-5-perhaloalkyl-4-isoxazolecarboxylic acids have been found to be potent inhibitors of protoporphyrin IX oxidase [20]; the putative cause of herbicidal activity observed in whole plant studies [21]. A detailed investigation of the reaction of benzohydroximinoyl chlorides **1** and β-perfluoroalkylacetylenic esters **2** led to the identification of both regioisomeric products **3** and **4**, and the unexpected observation of 'Michael type' or 1,4-addition product **5**.

Scheme 1





This is to our knowledge the first report of nucleophilic addition of the intermediate oxime to the dipolarophile in a 1,3-dipolar cycloaddition reaction.

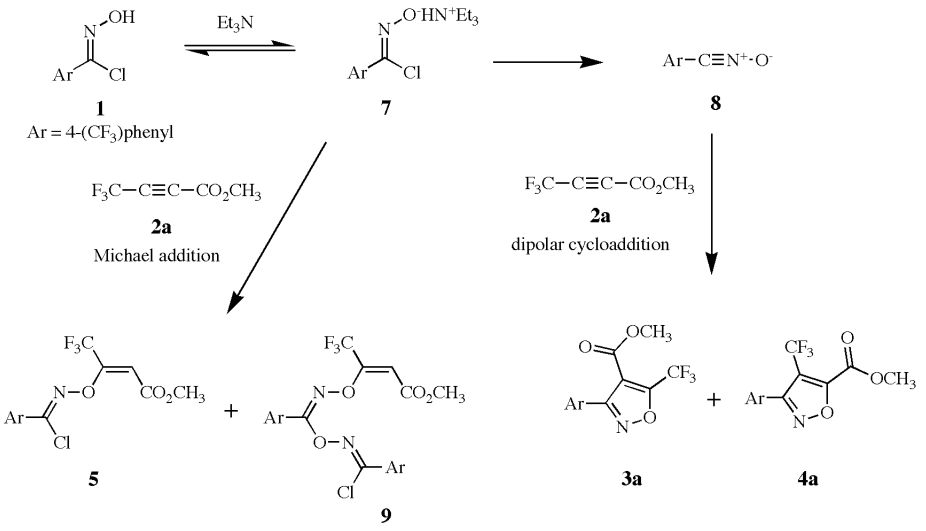
Results and Discussion.

Our initial investigation of the reaction of benzohydroximinoyl chloride **1** and acetylenic ester **2a** in the presence of triethylamine gave rise to three isolable products: the 5-(trifluoromethyl)isoxazole **3a**, its expected regioisomer **4a** and oxime addition adduct **5** (Scheme 2). The 5- and 4-position CF_3 groups of **3a** and **4a** have distinctive ^{19}F NMR resonances at -62.8 and -54.7 ppm, respectively, which are consistent with the downfield shift previously reported for 4-CF_3 isoxazoles [19]. The corresponding CF_3 group of **5** appears at -69.6 ppm, which is significantly upfield of the isoxazole isomers and makes identification of the oxime addition product straightforward in the reaction mixtures. All three components were separated by silica chromatography from a multigram scale reaction to give regioisomeric isoxazoles **3a** (49%) and **4a** (3%) and the oxime **5** (8%). Mass spectral analysis demonstrated that product **5** contains one chlorine atom and has a mass of 375 amu. Structural assignment is consistent with the acyclic product, having a vinyl proton (6.03 ppm) in the ^1H NMR. The ^{13}C NMR spectrum of **5** shows the olefinic carbons C2 and C3 at 105.9 ppm (q, J = 4 Hz) and 150.5 ppm (q, J = 35 Hz), respectively, and the oxime carbon at 144.8 ppm.

At –70 °C (entry e) the formation of nitrile oxide is almost completely suppressed and the oxime addition product **5** is obtained as the major product. In a preparative run at slightly higher temperature (entry d), oxime **5** was isolated in 51% yield and chloro-displacement product **9** in 5% yield. Presumably, compound **9** arises from nucleophilic addition of **1** to the hydroxyiminoyl chloride **5**. The use of the soluble base triethylamine is critical for formation of the oxime addition products, since either two phase aqueous hydroxide or the absence of base (entries f, g) gave only the dipolar cycloaddition products. Since hydroximinoyl chlorides are known to form nitrile oxides by thermal decomposition even in the absence of base [22], we investigated neutral conditions in methylene chloride (entry g). Although it required 5 days for 50% conversion, only the expected isoxazole products were obtained. In practice, the two phase aqueous hydroxide conditions (entry f), which provided nearly instantaneous conversion to the nitrile oxide intermediate, gave the best preparative route towards the isoxazoles **3a** and **4a** without any measureable amount of the oxime addition product.

The results obtained for formation of both isoxazoles and acyclic addition products are consistent with the deprotonation of hydroximinoyl chloride **1** to give ion pair **7** which can either add to acetylenic ester **2a** to give a Michael addition adduct **5** or can lose HCl to give the nitrile oxide **8** followed by the usual 1,3-dipolar

Scheme 2



At room temperature and at 0 °C, the reaction of hydroximinoylchloride with acetylene **2a** in the presence of triethylamine gave mixtures of the isoxazole regioisomers **3a** and **4a** and oxime adduct **5** (Table 1, entries a,b). Attempts to obtain more of the minor isomer **4a** by lowering the reaction temperature afforded increasingly greater amounts of oxime addition products **5** and **9** (entries b-e). cycloaddition products **3a** and **4a**. All three products are stable to the reaction conditions and do not decompose or interconvert in the presence of triethylamine. Temperature studies indicate that in the absence of nitrile oxides, which can react with the electron deficient acetylene **2a**, only Michael addition adducts would be obtained. To test this idea, we considered investigating the addition of

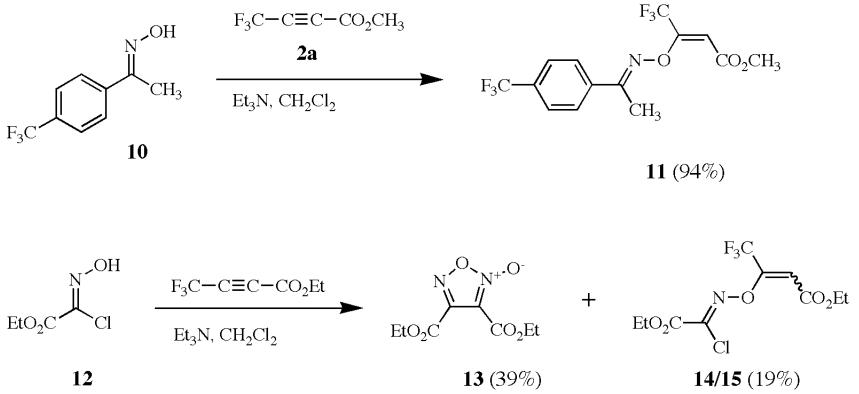
Table 1

Effect of Reaction Conditions on the Ratio of Regioisomeric Isoxazoles and Oxime Addition Products

Entry	Reaction Conditions[a]	Product Composition (%)[b]			
		3a	**4a**	**5**	**9**
a	Et_3N, 30 °C, 18 h	72	20	8	-
b	Et_3N, 0 °C, 18 h	58(49)	15(3)	25(8)	2
c	Et_3N, -17 °C, 18 h	29	6	61	4
d	Et_3N, -45 °C, 18 h	19	2	75(51)	4(5)
e	Et_3N, -70 °C, 18 h	10	1	87	2
f	aq. NaOH, 0 °C, 1 h	78(65)	22	-	-
g	no base, RT, 5 days[c]	92	8	-	-

[a] All reactions were run in methylene chloride using the listed base, time and temperature; [b] Percent composition was determined by a combination of HPLC and integration of ^1H and ^{19}F NMR product resonances. Isolated yields are given in parenthesis; [c] 50% complete as determined by ^{19}F NMR.

Scheme 3

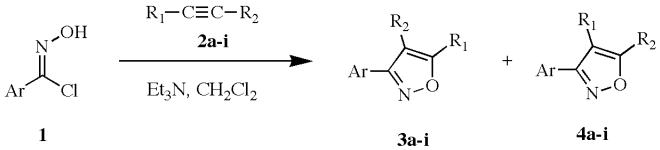


benzaldoxime to acetylene in the presence of base. The non-chlorinated oxime precursor would not be able to form nitrile oxides and would be limited to the anionic 1,4-addition reactions. However in agreement with reported results [23], only benzonitrile was obtained on treatment of benzaldoxime with base. Therefore we prepared acetophenone derivative **10**, which on treatment of **2a** gave nearly quantitative yield of the oxime addition product **11** (Scheme 3). Similar results have been observed in the addition of acetophenone oxime to dimethyl acetylenedicarboxylate and, under certain conditions, addition of benzaldoxime to acetylenic esters [23,24]. In the presence of base, carbethoxyhydroxyiminoyl chloride **12** gives an electron deficient nitrile oxide, which does not react with **2a**. The only products observed upon treatment of **12** with the ethyl ester derivative of acetylene **2a** are the furoxan **13** (from dimerization of the nitrile oxide) and Michael addition adducts **14** and **15**. The nitrile oxide from **12** undergoes cycloaddition under conditions of reverse electron demand and requires an electron rich dipolarophile. Bravo, *et. al.* [14] has reported the cycloaddition of **12** with CF_3 substituted ketoesters as a route towards 5-trifluoromethylisoxazoles.

The reaction of acetylenic esters **2a-d** with **1** gave the 5-perhaloalkylisoxazoles **3a-d** as the major product and

Table 2

Ratio of 1,3-Dipolar Cycloaddition Products Obtained from Acetylenes **2** and Hydroximinoyl Chloride **1**



Compd.	R_1	R_2	Product Ratio (%)[a]		Reaction Temp
			3	**4**	
a	CF_3	CO_2CH_3	80(49)	20(3)	0 °C
b	CF_2CF_3	CO_2Et	79(38)	21(18)	0 °C
c	CF_2Cl	CO_2CH_3	87(68)	13(5)	RT[b]
d	CF_2H	CO_2Et	85(76)	15(2)	RT
e	CF_3	H	77(41)	23	0 °C
f	CF_3	CF_3	(60)		RT
g	CF_3	Ph	-	33(11)[c]	40 °C
h	CH_3	CO_2CH_3	99(83)[d]	1	0 °C
i	H	CO_2CH_3	28(9)[d]	72(61)[d]	0 °C

[a] Product ratios were determined by a combination of HPLC and integration of product resonances by ^1H and ^{19}F NMR. Isolated yields are given in parenthesis. Unless otherwise stated, Ar = 4-(trifluoromethyl)phenyl; [b] Aqueous 50% NaOH was used as the base; [c] Furoxan **16** and oxadiazole **17** were 66% of the reaction product; [d] For entries h and i: Ar = phenyl. Product composition and yields were obtained from ref. 27.

small amounts (2-18%) of the 4-perhaloisoxazoles **4a-d**, which were isolated and fully characterized (Table 2). As seen previously with acetylene **2a**, minor amounts of the Michael addition adducts were also obtained for the reactions with **2b-d**; however, the reaction temperature was controlled to suppress their formation. Other electron deficient acetylenes **2e-g**, which lack the ester functionality, did not give rise to oxime addition products and the isoxazoles **3e**, **3f** and **4g** were isolated as the major products [25]. The more sterically hindered phenylacetylene **2g** afforded isoxazole **4g** in only 33% yield and appreciable amounts of furoxan **16** and oxadiazole **17** were obtained (Scheme 4) [19]. Oxadiazoles have been previously observed in the dimerization of nitrile oxides and are suggested to be the product of a disproportionation reaction between the initially formed oxadiazole-oxide and excess nitrile oxide [26]. To eliminate any possible role of the acetylene or its intermediates in the formation of oxadiazole **17**, the reaction of hydroximinoyl chloride **1** with triethylamine was carried out in the absence of acetylene **2g**. In this case a nearly 1:1 ratio of furoxan **16** and oxadiazole **17** was obtained, which eliminates the possibility of the acetylene playing a role in the formation of **17** and supports the previously reported disproportionation reaction. The selectivity for formation of **3h** and **4h** observed with non-fluorinated acetylene **2h** under nearly identical conditions to ours has been reported by Huisgen, *et. al.* [27] and provides almost exclusive formation of the 4-isoxazolecarboxylate ester **3h** over the regioisomer **4h** (99:1), whereas addition to methyl propiolate **2i** affords primarily the 5-isoxazolecarboxylate **4i** (72%).

Analysis of ^{13}C NMR is particularly useful for unambiguous assignment of the regiochemistry of perfluoroalkylisoxazoles **3** and **4** and can be effectively used even in the absence of one of the two isomers (Table 3) [28]. The CF_3 substituted carbon of the isoxazole ring is readily apparent in the ^{13}C NMR due to the strong carbon-fluorine two bond coupling ($^2J_{CF}$ is 26-44 Hz). In a comparison of the ^{13}C NMR spectra of the two regioisomers, the CF_3 substituted carbon (C5, 160.9 ppm) of **3a** appears downfield of the CF_3 substituted carbon (C4, 113.4 ppm) of regioisomer **4a**. Chemical shift in the range of 140-160 ppm is characteristic of the C3 and C5 ring carbons of isoxazoles, while the C4 carbon appears in the olefin region (105-120 ppm) [14]. Therefore, all of the 4-perfluoroalkylisoxazoles **4a-d,g** have C4 chemical shift of 106.5 - 119.0 ppm and $^2J_{CF}$ of 29-40 Hz. Likewise, the 5-perfluoroalkylisoxazoles **3a-f** have C5 chemical shifts of 158.8-166.7 ppm and $^2J_{CF}$ of 26-44 Hz. The characteristic chemical shifts of the C4 versus C5 carbon, along with the strong 2 bond C-F coupling, allows unambiguous assignment of isoxazoles **3** and **4**. This is particularly useful for

Scheme 4

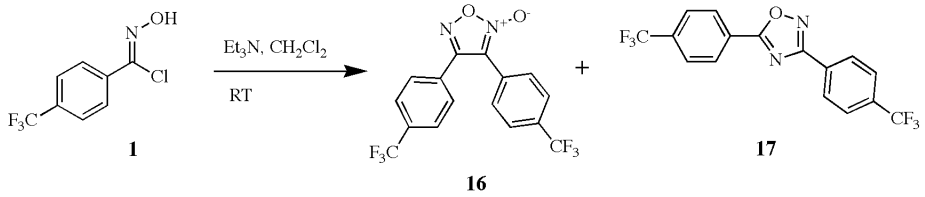


Table 3

Selected ^{13}C, ^{19}F and ^1H NMR Resonances for Regioisomeric Isoxazoles **3** and **4** [a]

Compound	^{13}C NMR[b] C3	C4	C5	^{19}F NMR[c]	^1H NMR[d]
3a	159.7	112.6 (q, 2.5 Hz)	160.9 (q, 40 Hz)	-62.8	3.89[e]
4a	155.9	113.4 (q, 40 Hz)	160.7 (q, 3 Hz)	-54.7	4.07[e]
3b	159.4	115.5	158.8 (t, 32 Hz)	-113.0 (q, 2F, 3 Hz)	4.34 (q, 2H, 7 Hz)[f]
4b	155.4	111.1 (t, 30 Hz)	161.8	-105.9 (q, 2F, 3 Hz)	4.52 (q, 2H, 7 Hz)[f]
3c	159.9	111.0	163.8 (t, 36 Hz)	-51.6	3.89[e]
4c	159.8	119.0 (t, 33 Hz)	158.6 (t, 3 Hz)	-45.6	4.07[e]
3d	159.8	112.3 (t, 3 Hz)	166.7 (t, 26 Hz)	-124.7	4.33 (q, 2H, 7 Hz)[f]
4d	156.1	117.4 (t, 29 Hz)	159.4 (t, 9 Hz)	-115.2	4.53 (q, 2H, 7 Hz)[f]
3e	161.7	103.6 (q, 2 Hz)	160.1 (q, 43 Hz)	-67.9	
3f	161.1 (q, 1.3 Hz)	111.6 (qq, 41 Hz, 2 Hz)	159.6 (qq, 44 Hz, 3 Hz)	-62,0 -55.0	
4g	171.9 (q, 8 Hz)	106.5 (q, 38 Hz)	160.7	-53.2	

[a] Chemical shifts are expressed in ppm relative to TMS (^{13}C and ^1H nmr) and trichlorofluoromethane (^{19}F nmr); [b] The ^{13}C nmr resonances of the three isoxazole ring carbon atoms. Two and/or three bond carbon-fluorine coupling along with the multiplet pattern is listed in parentheses; [c] ^{19}F nmr resonance of the isoxazole substituted perfluoroalkyl group. For compounds **3b** and **4b**, the $^3J_{FF}$ coupling is shown in parentheses; [d] ^1H nmr resonance of the α-protons of the alkyl ester; [e] Methyl ester (R=H); [f] Ethyl ester ($R=CH_3$).

the assignments of **3f** and **4g** in which only one isomer was isolated from the reaction mixtures. As previously reported by Meazza [19], an upfield ^{19}F NMR shift was observed for the fluorine resonances of 4-fluoroalkyl isoxozoles compared with 5-fluoroalkyl isomers with each pair of regioisomers **3a-d** and **4a-d**. The ^{1}H NMR spectra of the isoxazolecarboxylate esters exhibited a downfield shift for the ester protons of 5-isoxazolecarboxylates (either the methyl protons of **4a** and **4c** or the methylene protons of **4b** and **4d**) compared to the regioisomers **3a-d**.

In summary, the reaction of benzohydroximinoyl chlorides with β-perfluoroalkylacetylenic esters in the presence of base gives rise to a mixture of products including trisubstituted isoxazole **3**, its expected regioisomer **4**, and 'Michael type'addition adducts **5** and **9**. At low temperatures using triethylamine as a base, the O-substituted oxime **5** is the preferred product, whereas, at higher temperatures isoxazole **3** is the major product. The observed products can be rationalized by two competing mechanistic pathways invoking a Michael addition for the formation of the oxime and the more usual nitrile oxide intermediate for the formation of isoxazoles. Unambiguous assignment of the isoxazole regioisomers **3** and **4** can be determined by analysis of the ^{13}C NMR and the two bond carbon-fluorine coupling.

EXPERIMENTAL

General Procedures.

All melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained on a Bruker 360 MHz, a Varian EM-360, a Varian XL-400 or an IBM-360. Proton and ^{13}C resonances are reported relative to internal tetramethylsilane in parts per million, whereas ^{19}F resonances are reported relative to trichlorofluoromethane using trifluorotoluene (-63.79 ppm) as an external coaxial standard. Electron impact and chemical ionization mass spectra were recorded on a Finnigan 4535 spectrometer. Elemental analyses were preformed by Analytical Microlabs, Inc. or by Midwest Microlab. Reverse-phase HPLC analysis was performed with 250 mm X 0.46 mm i.d. columns containing a 5-um C18 ODS bonded phase, using 0.1% aqueous TFA/acetonitrile mixtures as the mobile phase. The 4-(trifluoromethyl)benzo-hydroximinoyl chloride **1** was prepared from the benzaldehyde by a modification of the known two-step procedure via the isolated oxime [8,29]. The acetylenic esters **2a-d** and (3,3,3-trifluoro-1-propynyl)benzene **2g** were prepared by thermolysis of the corresponding acylated phosphorane [30,31]. *p*-Trifluoromethylacetophenone oxime **10** was prepared by the literature method [32].

(3,3,3-Trifluoro-1-propynyl)benzene (**2g**).

By employing a previously described vacuum distillation apparatus [30] equipped with a dry ice-acetone trap, 19.4 g (43.2 mmol) of 1,1,1-trifluoro-3-phenyl-3-(triphenylphosphoranylidene)-2-propanone [31] was thermolyzed under reduced pressure (2 Torr). Once the distillation pot reached 190 °C, the solid phosphorane melted and formation of the acetylene began. The mixture was heated to 250 °C to complete the thermolysis and the acetylene collected in the dry ice trap. Vacuum distillation of the product afforded 6.22 g (84.6%) of a clear, colorless oil: bp_{19} 55-57 °C (lit.[33] bp_{40} 60-62 °C); ^{1}H NMR ($CDCl_3$): δ 7.41 (t, 2H, *J*=8 Hz); 7.50 (t, 1H, *J*=8 Hz), 7.57 (d, 2H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$): δ 75.8 (q, C2, $^{2}J_{CF}$=52 Hz), 86.7 (q, C3, $^{3}J_{CF}$=7 Hz), 115.0 (q, CF_3, $^{1}J_{CF}$=257 Hz), 118.6 (q, C4, $^{4}J_{CF}$=3 Hz), 128.7, 131.0, 132.5 (q, *J*=1.6 Hz); ^{19}F NMR ($CDCl_3$): δ -49.4 (s, 3F); IR (neat) 3010 (CH, str), 2200, 1290, 1130.

Anal. Calcd. for $C_9H_5F_3$: C, 63.54; H, 2.96. Found: C, 63.47, H, 2.98.

Formation of Dipolar Cycloaddition Products: Methyl 5-(Trifluoromethyl)-3-[4-(trifluoromethyl)phenyl]-4-isoxazolecarboxylate (**3a**).

A solution of **1** (44.9 g, 0.20 mol) in 300 mL of CH_2Cl_2 was cooled in a wet ice-acetone bath to –7 °C and treated at once with **2a** (31.5 g, 0.21 mol). The stirred solution was treated dropwise with triethylamine (29.5 mL, 0.21 mol) such that the reaction temperature was maintained below –2 °C. After 90 minutes, addition was complete and the reaction allowed to stir overnight. The reaction mixture was washed with 1 *N* HCl and the organic layer dried and concentrated *in vacuo* to afford 66.2 g of an orange-yellow liquid. The reaction mixture was purified by silica chromatography (10% CH_2Cl_2 in hexanes) to afford three fractions; 33.4 g (49%) of **3a** (k'=1.35), 6.2 g (8.3%) of **5** (k'=4.0) and 2.1 g (3.1%) of **4a** (k'=4.8). The major component (first eluted fraction) **3a** crystallized on standing and was recrystallized from cold pentane to afford a white, crystalline solid **3a**: mp 49-50 °C; ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 7.74 (d, 2H, *J*=8 Hz), 7.82 (d, 2H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$): δ 53.1, 112.6 (C4, $^{3}J_{CF}$ = 2.5 Hz), 117.7 (CF_3, $^{1}J_{CF}$ = 273 Hz), 124.0 (CF_3, $^{1}J_{CF}$ = 273 Hz), 125.8 ($^{3}J_{CF}$ = 4 Hz), 129.9, 130.3, 133.0 (C4', $^{2}J_{CF}$ = 34 Hz), 159.7 (C3), 160.9 (C5, $^{2}J_{CF}$ = 40 Hz), 162.3; ^{19}F NMR ($CDCl_3$): δ -62.8 (s), -63.0 (s); MS(EI) 339 (M^+, 87), 320 (-F, 18), 308 (-OCH_3, 27), 270 (-CF_3, 100), 258 (30), 211 (40), 145 ($CF_3C_6H_4$, 53), 59 (CO_2CH_3, 46); MS(CI) 340 (M+1, 100).

Anal. Calcd. for $C_{13}H_7F_6NO_3$: C, 46.03; H, 2.08; N, 4.13. Found: C, 46.15; H, 2.10; N, 4.12.

Methyl 4-(Trifluoromethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolecarboxylate (**4a**).

The most chromatographically retained material **4a** was crystallized from cold pentane to afford a white, crystalline solid **4a**: mp 34.0-34.5 °C; ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 3H), 7.73 (d, 2H, *J* = 8 Hz), 7.77 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 54.0, 113.4 (C4, $^{2}J_{CF}$ = 40 Hz), 120.5 (CF_3, $^{1}J_{CF}$ = 269 Hz), 123.9 (CF_3, $^{1}J_{CF}$ = 273 Hz), 125.9 (J_{CF} = 4 Hz), 129.8 (J_{CF}=3 Hz), 130.3, 133.0 (C4',$^{2}J_{CF}$=34 Hz), 155.9 (C3), 160.7 (C5, $^{3}J_{CF}$= 3 Hz), 160.9; ^{19}F NMR ($CDCl_3$) δ -54.7, -63.0; MS(EI) 339 (M^+, 31), 320 (-F, 6), 308 (-OCH_3, 2), 280 (-CO_2CH_3, 100), 145 ($CF_3C_6H_4$, 38).

Anal. Calcd. for $C_{13}H_7F_6NO_3$: C, 46.03; H, 2.08; N, 4.13. Found: C, 46.13; H, 2.09; N, 4.08.

Oxime Addition Products: Methyl 3-(((4-(trifluoromethyl)-phenyl)chloromethylene)-amino)oxy-(4,4,4-trifluoro)butenoate (**5**).

To a solution of 5.61 g (25.1 mmol) of **1** in 40 mL of CH_2Cl_2 was added 3.2 mL (25.3 mmol) of acetylene **2a**. The mixture was cooled in an acetonitrile/dry ice bath to -55°C and treated dropwise with 3.5 mL (25.1 mmol) of triethylamine such that the

temperature was maintained below -45°C. The mixture was allowed to stir overnight, washed with 1N HCl and the acid wash extracted twice with CH_2Cl_2. The combined extracts were dried and conc. in *vacuo* to afford a crude oil. Chromatographic purification (silica, 2" x 22", 30% CH_2Cl_2 in hexanes) afforded 4.83 g (51.2%) of **5** and 0.75 g (5.3%) of **9** as a crystalline solid. The first eluted chromatographic fraction **5** was obtained as an oil which could be crystallized in cold pentane to afford a white crystalline solid **5**: mp 30-33°C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s,3H), 6.03 (s,1H), 7.69 (d,2H, *J*=8 Hz), 7.98 (d,2H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$) δ 52.4, 105.9 (q, *J* = 4 Hz), 119.4 (CF_3, *J* = 276 Hz), 123.8 (CF_3, *J* = 271 Hz), 125.9 (q, *J* = 4 Hz), 128.3, 133.9 (q, $^2J_{CF}$ = 32 Hz), 134.5, 144.8, 150.5 (q, $^2J_{CF}$ = 35 Hz), 163.6; ^{19}F NMR ($CDCl_3$) δ -63.0(3F), -69.6(3F); MS(EI) 375(M^+,6), 206($CF_3C_6H_4CNCl$,100), 145($CF_3C_6H_4$,75); MS(CI) 376 (M+1,100), 377 (12), 378 (28), 379 (4).

Anal. Calcd. for $C_{13}H_8F_6ClNO_3$: C, 41.57; H, 2.08; N, 3.73. Found: C, 41.74; H, 2.17; N, 3.74.

Methyl 3-(((4-(Trifluoromethyl)phenyl)(((4-(trifluoromethyl)-phenyl)chloromethylene)-amino)methylene)amino)oxy-(4,4,4-trifluoro)butenoate (**9**).

Recrystallization of **9** from hexanes afforded a white, crystalline solid: mp 90.5-91.5 °C; ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 6.36 (s, 1H), 7.66-8.11 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 52.2 (CH_3), 101.3 (C4), 119.0 (CF_3, $^1J_{CF}$ = 276 Hz), 123.6 (CF_3, $^1J_{CF}$ = 273 Hz), 123.7 (CF_3, $^1J_{CF}$ = 273 Hz), 125.7, 125.9, 128.3, 129.2, 131.1, 133.9 (q, $^2J_{CF}$ = 33 Hz), 134.0 (q, $^2J_{CF}$ = 33 Hz), 134.1, 145.8, 152.7 (q, $^2J_{CF}$ = 37 Hz), 159.1, 164.2; ^{19}F NMR ($CDCl_3$): δ -65.51 (s, 3F), -62.78 (s, 3F), -62.69 (s, 3F); MS(EI) 208 (32), 206 ($CF_3C_6H_4CNCl^+$, 100), 187 (19), 173 (35), 145 ($CF_3C_6H_4^+$, 61); MS(CI) 563 (M+1, 100).

Anal. Calcd. for $C_{21}H_{12}N_2O_4ClF_9$: C, 44.82; H, 2.15; N, 4.98. Found: C, 44.86; H, 2.16; N, 4.93.

Methyl 3-(((4-(Trifluoromethyl)phenyl)chloroethylene)amino)-oxy-(4,4,4-trifluoro)butenoate (**11**).

A solution of 2.12 g (10.4 mmol) of oxime **10** in 20 mL of methylene chloride was cooled in wet ice-acetone to –10 °C and treated with 1.7 mL (1.98 g, 11.9 mmol) of **2a** followed by 1.6 mL (1.16 g, 11.5 mmol) of triethylamine. After stirring for a few minutes, the ice bath was removed and the mixture allowed to stir overnight. The reaction mixture was treated with 1 *N* HCl, extracted three times with CH_2Cl_2 and the combined extracts dried and concentrated to afford 4.1 g of orange oil. The oil solidified on standing and was recrystallized from methanol-water to give 3.46 g (93.6%) of a slightly yellow, crystalline solid: mp 59 °C; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H), 3.69 (s, 3H), 5.89 (s, 1H), 7.66 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 13.5, 52.0, 103.0 (q, *J* = 4.0 Hz), 119.4 (q, CF_3, $^1J_{CF}$ = 276 Hz), 123.9 (q, $^1J_{CF}$ = 272 Hz), 125.7 (q, *J* = 3.8 Hz), 127.1, 132.4 (q, $^2J_{CF}$ = 32.8 Hz), 137.8, 150.7 (q, $^2J_{CF}$ = 34.3 Hz), 160.0, 164.4; ^{19}F NMR ($CDCl_3$): δ -64.0 (s, 3F), -70.5 (s, 3F).

Anal. Calcd. for $C_{14}H_{11}NO_3F_6$: C, 47.34; H, 3.12; N, 3.94. Found: C, 47.46; H, 3.09; N, 3.97.

Ethyl (*Z,Z*)-3-(((Carbethoxy)chloromethylene)amino)oxy-4,4,4-trifluorobutenoate (**14**) and Ethyl (*E,Z*)-3-(((Carbethoxy)-chloromethylene)amino)oxy-4,4,4-trifluorobutenoate (**15**).

To a solution of 7.6 g (50 mmol) of ethyl chlorooximidoacetate and 7.3 mL (8.32 g, 50 mmol) of ethyl 4,4,4-trifluoro-2-butynoate in 75 mL of CH_2Cl_2 at 30 °C was added dropwise 7.7 mL (55 mmol) of triethylamine. After stirring overnight, the mixture was washed with 1 *N* HCl, dried and the solvent removed to afford 14.2 g of a reddish oil. Chromatographic purification (silica, 2" x 22", 5% ethyl acetate in hexanes) afforded 3.0 g (18.9 %) of a mixture (k', 3) of the two syn and anti isomers which were not separable by silica gel chromatography and 2.23 g (38.7 %) (k', 4.8) of diethyl furoxandicarboxylate **13** [34]. The mixture of isomers was purified by reverse phase chromatography (C18, 21.2 mm i.d. x 30 cm, 50% CH_3CN/H_2O) to afford 0.81 g (k', 20) of the *cis* isomer. Bulb to bulb distillation (60 °C, 0.1 Torr) afforded **14** as a clear, colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, *J* = 7 Hz), 1.39 (t, 3H, *J* = 7 Hz), 4.24 (q, 2H, *J* = 7 Hz), 4.41 (q, 2H, *J* = 7Hz), 6.14 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.5, 13.5, 61.2, 63.7, 108.8 (q, C4, $^3J_{CF}$ = 3.5 Hz), 118.6 (CF_3, $^1J_{CF}$ = 275 Hz), 137.7 (C3), 149.1 (q, C5, $^2J_{CF}$ = 36 Hz), 157.0, 161.8; ^{19}F NMR ($CDCl_3$): δ -75.4; MS(EI) 317 (M^+, 0.7), 272 (-OEt, 23), 139 (28), 115 (29), 87 (34), 69 (93), 62 (100); MS(CI) 318 (M+1, 100), 320 (A+2, 35).

Anal. Calcd. for $C_{10}H_{11}O_5NClF_3$: C, 37.81; H, 3.49; N, 4.41. Found: C, 37.75; H, 3.50; N, 4.35.

The more retained *trans* isomer (k', 26) was concentrated and distilled bulb to bulb (60 °C, 0.1 Torr) to afford 0.27 g of **15** as a clear, colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.32 (t,3H, 7 Hz), 1.41 (t,3H, 7 Hz), 4.26 (q 2H, 7 Hz), 4.43 (q,2H, 7Hz), 6.37 (s,1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.0, 61.7, 64.4, 105.4 (q,C4, $^3J_{CF}$ = 2.0 Hz), 118.5 (CF_3, $^1J_{CF}$ = 273 Hz), 139.8 (C3), 150.6 (q,C5, $^2J_{CF}$ = 38 Hz), 157.4 (C=O), 162.9 (C=O); ^{19}F NMR ($CDCl_3$): δ -76.5; MS(EI) 317 (M^+, 1), 272 (-OEt, 20), 139 (23), 115 (23), 87 (24), 69 (80), 62 (100); MS(CI) 318 (M+1, 100), 320 (A+2, 44).

Anal. Calcd. for $C_{10}H_{11}O_5NClF_3$: C, 37.81; H, 3.49; N, 4.41. Found: C, 37.96; H, 3.54; N, 4.37.

Ethyl 5-(Pentafluoroethyl)-3-[4-(trifluoromethyl)phenyl]-4-isox-azolecarboxylate (**3b**) and Ethyl 4-(Pentafluoroethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolecarboxylate (**4b**).

A solution of **1** (13.1 g, 58.6 mmol) in 100 mL of CH_2Cl_2 was cooled in a wet ice-acetone bath and treated with **2b** (13.4 g, 62.0 mmol). To the cooled solution was subsequently added triethylamine (9.0 mL, 64.6 mmol) dropwise and the solution stirred overnight. The reaction was washed with 1 *N* HCl, dried and concentrated *in vacuo* to afford a clear, orange-yellow oil. The oil was purified by preparative chromatography (20% CH_2Cl_2 in hexanes, 2" x 22" silica column) to yield two components; 8.93 g (37.8%) of **3b** (chromatographically unretained component) and 4.2 g (17.8%) of **4b** (chromatographically retained component). The major, less chromatographically retained component **3b** was evaporatively distilled and a small portion purified by chromatography (20% CH_2Cl_2 in hexanes) to afford an analytical sample **3b**: $bp_{0.08}$ 55-60 °C; HPLC(reverse phase a) t_r=12.2 min; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, *J* = 7 Hz), 4.34 (q, 2H, *J* = 7 Hz), 7.76 (d, 2H, *J* = 8 Hz), 7.82 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 13.7, 63.0, 108.6 (tq, CF_2, $^1J_{CF}$ = 258 Hz, $^2J_{CF}$ = 42 Hz), 115.5 (C4), 118.2 (qt, CF_3, $^1J_{CF}$ = 287 Hz, $^2J_{CF}$ = 36 Hz), 123.9 (CF_3, $^1J_{CF}$ = 273 Hz), 125.8 (q, J_{CF} = 4 Hz), 129.6, 130.2(C1), 133.0 (C4', $^2J_{CF}$ = 32 Hz), 158.8 (t, C5, $^2J_{CF}$ = 32 Hz), 159.4 (C3), 161.8; ^{19}F NMR ($CDCl_3$): δ -62.8 (s, 3F), -83.0 (t, 3F, *J* = 3 Hz), -113.4 (q, 2F, *J* = 3 Hz); MS(EI) 403 (M^+, 61), 375 (15), 358 (-OEt, 45), 284 (-CF_2CF_3, 42), 212 (100), 145 ($CF_3C_6H_4$, 36); MS(CI) 404 (M+1, 100).

Anal. Calcd. for $C_{15}H_9F_8NO_3$: C, 44.68; H, 2.25; N, 3.56. Found: C, 44.78; H, 2.23; N, 3.47.

The minor component **4b** was evaporatively distilled (55-70 °C, 60 mTorr) and the resultant oil dissoved in cold pentane to afford a white, crystalline solid **4b**: mp 35-36 °C; HPLC(reverse phase a) t_r=11.4 min; ^{1}H NMR ($CDCl_3$): δ 1.44 (t, 3H, *J*=7 Hz), 4.52 (q, 2H, *J*=7 Hz), 7.64 (d, 2H, *J*=8 Hz), 7.75 (d, 2H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$): δ 13.9, 63.8, 110.7(tq, CF_2, $^1J_{CF}$ = 255 Hz, $^2J_{CF}$ = 42 Hz), 111.1 (t, C4, $^2J_{CF}$ = 30 Hz), 118.8 (qt, CF_3, $^1J_{CF}$ = 286 Hz, $^2J_{CF}$ = 38 Hz), 123.9 (q, CF_3, $^1J_{CF}$ = 273 Hz), 125.6 (q, $^3J_{CF}$ = 4 Hz), 130.2, 130.6, 132.8 (q, C4', $^2J_{CF}$ = 32 Hz), 155.4(C3), 161.8(two overlapping resonances, C5 and C=O); ^{19}F NMR ($CDCl_3$): δ -62.8 (s, 3F), -83.8 (t, 3F, *J* = 3 Hz), -105.9 (q, 2F, *J* = 3 Hz); MS(EI) 403 (M^+, 27), 330 (-CO_2Et, 100), 145 ($CF_3C_6H_4$, 33); MS(CI) 404 (M+1, 100).

Anal. Calcd. for $C_{15}H_9NO_3F_8$: C, 44.68; H, 2.25; N, 3.47. Found: C, 44.58; H, 2.30; N, 3.44.

Methyl 5-(Chlorodifluoromethyl)-3-[4-(trifluoromethyl)phenyl]-4-isoxazolecarboxylate (**3c**).

Purification by preparative chromatography (20% CH_2Cl_2 in hexanes, 2" x 22" silica column) gave 14.42 g (68%) of a clear oil. An analytical sample was prepared by crystallizing the oil in a cold pentane solution. The crystalline solid was collected and promptly melted upon reaching room temperature to afford a clear, colorless oil: ^{1}H NMR ($CDCl_3$): δ 3.89 (s,3H), 7.75 (d, 2H, *J* = 8 Hz), 7.81 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 53.1, 111.0 (C4), 118.7 (-CF_2Cl, $^1J_{CF}$ = 290 Hz), 123.9 (-CF_3, $^1J_{CF}$ = 272 Hz), 125.7 (q, J_{CF} = 4 Hz), 129.7, 130.3, 132.9 (C4', $^2J_{CF}$ = 33 Hz), 159.9 (C3), 162.0 (C=O), 163.8 (C5, $^2J_{CF}$ = 36 Hz); ^{19}F NMR ($CDCl_3$): δ -51.6 (2F), -62.9 (3F); MS(EI) 355 (M^+, 51, Cl_1 cluster), 320 (-Cl, 16), 270 (-CF_2Cl, 100), 211 (-CF_2Cl, -CO_2CH_3, 37), 145 (38), 59 (45); MS(CI) 356 (M+1, 100, Cl_1 cluster).

Anal. Calcd. for $C_{13}H_7O_3ClF_5N$: C, 43.90; H, 1.98; N, 3.94. Found: C, 44.01; H, 1.99; N, 3.94.

Methyl 4-(Chlorodifluoromethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolecarboxylate (**4c**).

The more retained chromatographic fraction was concentrated to afford 1.3 g (5%) of **4c** as a clear, colorless oil: n^{22}_D 1.4834; ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 3H), 7.70 -7.80 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 53.8, 119.0 (t, $^2J_{CF}$ = 33 Hz), 120.7 (t, $^1J_{CF}$ = 290 Hz), 123.7 (q, $^1J_{CF}$ = 273 Hz), 125.6 (q, *J* = 4 Hz), 129.7, 129.7, 130.3, 132.7 (q, $^2J_{CF}$ = 33 Hz), 155.8, 158.6 (t, *J* = 3 Hz), 159.8; ^{19}F NMR ($CDCl_3$): δ -45.6(s, 2F), -65.0 (s, 3F); MS(EI) 355 (M^+, 43, Cl_1 cluster), 296 (100), 206 (91), 145 (60).

Anal. Calcd. for $C_{13}H_7O_3ClF_5N$: C, 43.90; H, 1.98; N, 3.94. Found: C, 44.00; H, 2.02; N, 3.98.

5-(Difluoromethyl)-3-[4-(trifluoromethyl)phenyl]-4-isoxazolecarboxylic Acid, Ethyl Ester (**3d**) and 4-(Difluoromethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolecarboxylic Acid, Ethyl Ester (**4d**).

To a solution of **1** (16.8 g, 75 mmol) in 100 mL of methylene chloride warmed to 30 °C was added **2d** (11.2 g, 76 mmol). The stirred mixture was treated dropwise with triethylamine (11.5 mL, 83 mmol) and the temperature kept between 32-42 °C with the aid of a cold water bath. After 2 hours, the mixture was washed with 1 *N* HCl, dried and concentrated *in vacuo* to afford a crude orange oil. The oil was dissolved in 50 mL of warm hexanes and cooled to afford 19.0 g (76%) of **3d** as a yellow, crystalline solid. A small sample was further recrystallized to give off-white crystals **3d**: mp 53-53.5 °C; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, *J* = 7 Hz), 4.33 (q, 2H, *J* = 7 Hz), 7.25 (t, 1H, $^2J_{HF}$ = 52 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 7.81 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 13.9, 62.4, 106.4 (t, CF_2H, $^1J_{CF}$ = 241 Hz), 112.3 (t, C4, $^3J_{CF}$ = 5 Hz), 124.0 (q, CF_3, $^1J_{CF}$ = 272 Hz), 125.4 (q, $^3J_{CF}$ = 4 Hz), 130.3, 130.8, 132.6 (q, C4', $^3J_{CF}$ = 33 Hz), 159.8 (C3), 161.8 (C=O), 166.7 (t, C5, $^2J_{CF}$ = 26 Hz); ^{19}F NMR ($CDCl_3$): δ -67.8 (s, 3F), -124.7 (d, 2H, $^2J_{FH}$ = 52 Hz).

Anal. Calcd. for $C_{14}H_{10}NO_3F_5$: C, 50.16; H, 3.01; N, 4.18. Found: C, 50.27; H, 3.06; N, 4.17.

The combined mother liquors from crystallization of the above product were concentrated *in vacuo* and purified by chromatography. Chromatographic separation of the regioisomers (silica, 21.2 mm i.d., 1% ethyl acetate in hexanes) afforded an additional 0.28 g of **3d** and 0.56 g (2%) of **4d**. Recrystallization from cold hexanes gave a white, crystalline solid **4d**: mp 51-52 °C; ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, *J* = 7 Hz), 4.53 (q, 2H, *J* = 7 Hz), 7.43 (t, 1H, $^2J_{HF}$ = 54 Hz), 7.76 (d, 2H, *J* = 8 Hz), 7.94 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 63.4, 108.8 (t, CF_2H, $^1J_{CF}$ = 235 Hz), 117.4 (t, C4, $^2J_{CF}$ = 29 Hz), 123.8 (q, CF_3, $^1J_{CF}$ = 272 Hz), 125.7 (q, $^3J_{CF}$ = 4 Hz), 129.5 (t, C5, $^3J_{CF}$ = 2 Hz),130.7, 132.6 (q, C4', $^3J_{CF}$ = 33 Hz), 156.1 (C4'), 159.4 (t, C3, $^3J_{CF}$ = 9 Hz), 161.0 (C=O); ^{19}F NMR ($CDCl_3$): δ -67.8 (s, 3F), -115.2 (d, 2H, $^2J_{FH}$ = 53 Hz); MS(EI) 335 (M^+, 24), 262 (-CO_2Et, 100), 145 ($CF_3C_6H_4^+$, 49); MS(DP/CI) 336 (M+1, 100).

Anal. Calcd. for $C_{14}H_{10}NO_3F_5$: C, 50.16; H, 3.01; N, 4.18. Found: C, 50.12; H, 3.02; N, 4.10.

5-(Trifluoromethyl-3-[4-(trifluoromethyl)phenyl]isoxazole (**3e**).

To a round bottom flask equipped with a dry ice condensor was added 100 mL of methylene chloride. The liquid was cooled to -10 °C, the condensor charged with dry ice-acetone and a gas inlet tube was used to add 8.24 g (87.7 mmol) of trifluoropropyne. The ice bath was removed and the solution reached 10 °C at which time the trifluoropropyne began to reflux. To this solution was added 13.6 g (60.7 mmol) of **1** and the nearly homogeneous solution treated with 8.5 mL (61 mmol) of triethylamine. After stirring overnight at room temperature, the mixture was washed with 1 *N* HCl, dried and the solvent removed to give a crude oil which crystallized overnight. By ^{1}H NMR, the crude material appears to contain 23% of the 4-CF_3 isomer and 77% of the desired 5-CF_3 isomer. Recrystallization from cold methanol afforded 7.0 g (41%) of **3e** as a white solid: mp 49-54 °C; ^{1}H NMR ($CDCl_3$): δ 7.06 (q, 1H, $^4J_{HF}$ = 0.9 Hz), 7.74 (d, 2H, *J* = 8 Hz), 7.93 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 103.6 (q, C4, $^2J_{CF}$ = 2 Hz), 118.0 (CF_3, $^1J_{CF}$ = 270 Hz), 123.9 (CF_3, $^1J_{CF}$ = 272 Hz), 126.4 (q, $^3J_{CF}$ = 4 Hz), 127.5, 131.0, 133.0 (q, $^2J_{CF}$ = 33 Hz), 160.1 (C5, $^2J_{CF}$ = 43 Hz), 161.7 (C3); ^{19}F NMR ($CDCl_3$): δ -67.9, -69.1.

Anal. Calcd. for $C_{11}H_5NOF_6$: C, 46.99; H, 1.79; N, 4.98. Found: C, 47.27; H, 1.86; N, 5.19.

4,5-Bis(trifluoromethyl)-3-(4-trifluoromethyl)phenylisoxazole (**3f**).

A solution of 7.31 g (45 mmol) of hexafluoro-2-butyne in 100 mL of CH_2Cl_2 was prepared in a vessel cooled with a dry ice-acetone bath and equipped with a dry ice-acetone condensor. The cold solution was treated with 10.1 g (45 mmol) of **1**, allowed to warm to room temperature and treated dropwise with 6.3 mL

(45 mmol) of triethylamine. Total addition time was 15 minutes. After addition was complete, the acetylene no longer refluxed in the apparatus. The mixture was washed with 1 *N* HCl, dried and the solvent removed to afford 13.3 g of a crude oil. Bulb to bulb distillation (45-60 °C, 0.1 Torr) afforded 9.44 g (60%) of **3f** as a clear, colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.78 (m); ^{13}C NMR ($CDCl_3$): δ 111.6 (qq, C4, $^2J_{CF}$ = 41 Hz, $^3J_{CF}$ = 2 Hz), 117.3 (CF_3, $^1J_{CF}$ = 274 Hz), 120.0 (CF_3, $^1J_{CF}$ = 269 Hz), 123.8 (CF_3, $^1J_{CF}$ = 272 Hz), 126.2 (q, $^3J_{CF}$ = 4 Hz), 129.4, 129.7, 133.6 (q, $^2J_{CF}$ = 33 Hz), 159.6 (qq, C5, $^2J_{CF}$ = 44 Hz, $^3J_{CF}$ = 3 Hz), 161.1 (q, C3, J_{CF} = 1.3 Hz); ^{19}F NMR ($CDCl_3$): δ -54.96 (q, 7 Hz), -62.02 (q, 7Hz), -63.14 (s); MS(CI) 350 (M+1, 100); MS(EI) 349 (M^+,49), 330 (-F,28), 280 (-CF_3,100), 145 (72).

Anal. Calcd. for $C_{12}H_4ONF_9$: C, 41.28; H, 1.15; N, 4.01. Found: C, 41.37; H, 1.15; N, 4.00.

5-Phenyl-4-trifluoromethyl-3-(4-trifluoromethyl)phenylisoxazole (**4g**).

To a solution of 4.5 g (20 mmol) of **1** and 2.37 g (22.1 mmol) of (3,3,3-trifluoro-1-propynyl)benzene **2g** in 40 mL of methylene chloride at room temperature was added 3.1 mL (22.2 mmol) of triethylamine. After stirring overnight, the mixture was washed with 1 *N* HCl, dried and the solvent removed to afford 5.4 g of an oily, brownish solid. Analysis by ^{19}F NMR shows a mixture of nearly equimolar amounts of oxadiazole **17**, furoxan **16** and a desired isoxazole product. Removal of the furoxan was achieved by chromatography (silica, 2" x 22", 20% CH_2Cl_2 in hexanes) to afford 1.66 g (k', 1.1) of a mixture of products and 0.82 g (k', 3.5) of furoxan. The less retained material was further purified (C-18, 21.2 mmi.d. x 30 cm, 80% CH_3CN/H_2O) to give 0.78 g of oxadiazole (k', 8.5) and 0.77 g (11%) of **4g** (k', 4.1). Recrystallization from cold hexanes afforded **4g** as a white, crystalline solid: mp 86.5 °C; ^{1}H NMR ($CDCl_3$): δ 7.53 (m, 3H), 7.77 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 106.5 (C4, $^2J_{CF}$ = 38 Hz), 121.8 (CF_3, $^1J_{CF}$ = 268 Hz), 124.0 (CF_3, $^1J_{CF}$ = 282 Hz), 125.7 (q, $^3J_{CF}$ = 4 Hz), 128.8, 128.9, 129.0, 129.4, 131.4, 131.9, 132.5 (q, C1', $^2J_{CF}$ = 33 Hz), 160.7 (C3), 171.9 (q, C5, $^3J_{CF}$ = 3 Hz); ^{19}F NMR ($CDCl_3$): δ -53.21 (s), -62.63 (s).

Anal. Calcd. for $C_{17}H_9ONF_6$: C, 57.15; H, 2.54; N, 3.92. Found: C, 57.23; H, 2.57; N, 3.88.

3,5-Bis[4-(trifluoromethyl)phenyl-1,2,4-oxadiazole (**17**) and 3,4-Bis[4-(trifluoromethyl)phenyl]furoxan (**16**).

A solution of 4.8 g (25 mmol) of 4-trifluoromethylbenzaldehyde oxime in 75 mL of methylene chloride was heated to reflux and treated with 7.6 mL (54 mmol) of triethylamine. After two hours, the mixture was cooled and washed with 1 *N* HCl, dried and concentrated *in vacuo* to afford 10.1 g of a crude brownish residue. The residue was triturated with cold methanol to give a white, crystalline solid. Recrystallization from methanol afforded 1.5 g of **17** as analytical material: mp 121-122 °C; ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 2H, 8 Hz), 7.80 (d, 2H, 8 Hz), 8.25 (d, 2H, 8 Hz), 8.29 (d, 2H, 8 Hz); ^{13}C NMR ($CDCl_3$): δ 123.6 (q, CF_3, $^1J_{CF}$ = 273 Hz), 123.8 (CF_3, $^1J_{CF}$ = 273 Hz), 126.0 (q, $^3J_{CF}$ = 4 Hz), 126.3 (q, $^3J_{CF}$ = 4 Hz), 127.2, 127.9, 128.6, 130.0, 133.2 (C1', $^2J_{CF}$ = 33 Hz), 134.6 (C1', $^2J_{CF}$ = 33 Hz), 168.3 (C4), 174.9 (C5); ^{19}F NMR ($CDCl_3$): δ -68.0, -68.2; MS(EI) 358 (M^+, 43), 187 ($CF_3C_6H_4CNO^+$, 100); MS(CI) 359 (M+1, 100).

Anal. Calcd. for $C_{16}H_8N_2OF_6$: C, 53.64; H, 2.25; N, 7.82. Found: C, 53.50; H, 2.29; N, 7.77.

The concentrated mother liquors from crystallization of **17** were purified by chromatography (2" x 22", silica, 20% CH_2Cl_2) to afford an additional 0.75 g of **17** (k' = 1.7, total yield of 26%) and 2.58 g (k' = 5.0) of **16** (28%). Recrystallization from hexanes gave an analytical sample of **16** as a white, crystalline solid: mp 114.0-114.5 °C (lit.[35] 114-116 °C); ^{1}H NMR ($CDCl_3$): δ 7.64-7.70 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 113.2, 123.6 (q, CF_3, $^1J_{CF}$ = 273 Hz), 123.6 (CF_3, $^1J_{CF}$ = 273 Hz), 126.3 (q, $^3J_{CF}$ = 4 Hz), 126.4 (q, $^3J_{CF}$ = 4 Hz), 129.0, 129.2, 129.9, 129.9, 130.0, 132.8 ($^2J_{CF}$ = 33 Hz), 133.3 ($^2J_{CF}$ = 33 Hz), 155.0; ^{19}F NMR ($CDCl_3$): δ -68.0, -68.1; MS(EI) 374 (M^+, 7), 314 (-N_2O_2, 100); MS(CI) 375 (M+1, 100).

Anal. Calcd. for $C_{16}H_8N_2O_2F_6$: C, 51.35; H, 2.15; N, 7.49. Found: C, 51.41; H, 2.16; N, 7.43.

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