Synthesis and Herbicidal Activity of 3-Aryl-5-(haloalkyl)-4-isoxazolecarboxamides and Their Derivatives†

Bruce C. Hamper,* Kindrick L. Leschinsky, Steven S. Massey, Crystal L. Bell, Lawrence H. Brannigan, and S. Douglas Prosch

New Products Division, The Agricultural Group of Monsanto Company, 800 North Lindbergh Boulevard, St. Louis, Missouri 63167

A series of unique 3-aryl-5-(haloalkyl)-4-isoxazolecarboxamides have been prepared which exhibit, in both greenhouse and field studies, significant preemergent and postemergent herbicidal activity in the grams per hectare range against broadleaf and narrowleaf weeds. The key step in the formation of the fully substituted isoxazole ring **2** is 1,3-dipolar cycloaddition of a haloalkyl-substituted acetylenic ester and a nitrile oxide intermediate. The 3-aryl-5-(haloalkyl)-4-isoxazolecarboxylate esters **2** are converted to isoxazole-4-carboxamide herbicides **5** and **6**, secondary amides **7**, and amino acid derivatives **8**. Greatest activity was observed with compounds having a combination of three substituents: a substituted phenyl ring in the 3-position, a primary or secondary carboxamide in the 4-position, and a difluorochloromethyl group in the 5-position of the isoxazole ring.

Keywords: *Isoxazole; isoxazolecarboxamide; herbicide; fluoroalkyl; cycloaddition*

INTRODUCTION

Derivatives of aryl-substituted isoxazolecarboxylic acids have provided a rich source of candidates for development as agrochemical and pharmaceutical products. Various ester and amide derivatives have been reported as plant growth regulators (Franz and Howe, 1979) and agents for control of endoparasites (Jeschke et al., 1993) as well as a series of commercial isoxazole penicillins (Doyle and Nayler, 1961; Essery and Van Harken, 1970). Recently, fluoroalkyl-substituted isoxazoles have been prepared as intermediates for urea-type herbicides and analogs of other biologically active materials (Sumimoto et al., 1986). In connection with our continuing studies of biologically active perhaloalkyl-substituted heterocycles (Hamper et al., 1992), we targeted the synthesis of 3-arylisoxazoles having both carboxylate and haloalkyl substituents. Using this approach, we have found a unique series of 3-aryl-5-(haloalkyl)-4-isoxazolecarboxamides having significant herbicidal activity.

The synthesis of trifunctionalized 3-aryl-5-alkyl-4-isoxazolecarboxylates has been investigated for the preparation of isoxazole penicillins by cycloaddition of nitrile oxides and keto esters (Essery and Van Harken, 1970) and acetylenes (Cristl et al., 1973). Disubstituted 3-phenyl-5-(trifluoromethyl)isoxazoles have been obtained by cyclocondensation of a diketone and hydroxylamine (Carr et al., 1977); however, to our knowledge, the analogous trisubstituted 4-isoxazolecarboxylates have not been prepared by cyclocondensation. A few 3-aryl-5-(trifluoromethyl)-4-isoxazolecarboxylate esters had been previously prepared by 1,3-dipolar cycloadditions (Shen et al., 1985); however, none of the carboxamide derivatives were prepared, and the herbicidal activity was not described.

Herein, we report the first synthesis of 3-aryl-5-(perhaloalkyl)-4-isoxazolecarboxamides, preparation of a variety of trisubstituted isoxazoles by cycloaddition with acetylenic esters, and a comparision of the relative herbicidal activity of compounds in this series.

EXPERIMENTAL PROCEDURES

Synthesis. 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 (^{1}H NMR and ^{13}C NMR), a Varian EM-360 (60 MHz ^{1}H or 56.5 MHz ^{19}F), a Varian XL-400 (^{1}H NMR and ^{13}C NMR), or an IBM-360 (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR). 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 (−63.76 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 Atlantic Microlabs, Inc., or by Midwest Microlab. Preparative liquid chromatographic separations were preformed on Dynamax columns (21.2 mm i.d.) or Waters Prep 500 LC columns (2 in. i.d.) using either a Waters Prep 500 LC or a Rainin chromatography system. Smaller scale normal phase separations were carried out on a centrifugally accelerated, radial, thin-layer chromatograph (Chromatotron 7924, 4 mm silica gel plate).

Unless otherwise indicated, all of the benzaldehydes were obtained from commercial sources. 2-Fluoro-4-chloro-5-methoxybenzaldehyde was prepared from 2-chloro-4-fluoroanisole (Woodard et al., 1994) and 2-fluoro-4-chlorobenzaldehyde was obtained from 2-fluoro-4-chlorobenzoic acid (Brown et al., 1979). Ethyl 4,4,4-trifluoro-2-butynoate was prepared by thermolysis of an acylated phosphorane (Hamper, 1991). Other acetylenic esters, methyl 4,4-difluoro-4-chloro-2-butynoate, ethyl pentafluoro-2-pentynoate, and methyl 4-methyl-2-pentynoate, were prepared as previously described (Hamper et al., 1992). The benzohydroximinoyl chlorides were prepared from the benzaldehydes by a modification of a known two-step procedure via the isolated oxime (Liu et al., 1980). All new compounds reported herein have been fully characterized by NMR spectral analysis and elemental analysis. A complete listing of all compounds can be found in the supplementary material.

4-Chloro-2-fluorobenzohydroximinoyl Chloride (1a). General Procedure. A solution of 4-chloro-2-fluorobenzaldehyde (54.7 g, 0.345 mol) in 150 mL of ethanol was prepared

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in a 2 L beaker equipped with a magnetic stirring bar. The stirred solution was treated with 225 mL of ice water and 25.6 g (0.365 mol) of hydroxylamine hydrochloride followed by addition of 70 g (0.875 mol) of 50% aqueous NaOH. The temperature was kept between 30 and 35 °C by addition of more ice. After stirring for 1 h, the mixture was extracted with 300 mL of diethyl ether to remove neutral impurities, acidified with concentrated HCl, and extracted with two 300 mL portions of ether. The combined extracts were dried with $MgSO_4$ and concentrated in vacuo to give a solid residue. Hexanes were added to the residue and the resulting solid was filtered and air dried to afford 46.6 g (78%) of 4-chloro-2-fluorobenzaldehyde oxime as a white solid: mp 121–123 °C. To a stirred solution of 44.8 g (0.26 mol) of the 4-chloro-2-fluorobenzaldehyde oxime in 200 mL of DMF was added approximately 10 g of *N*-chlorosuccinimide, and the flask was heated with a heat gun until an exothermic reaction occurred (40 °C). A cooling bath was applied and the rest of the *N*-chlorosuccinimide (total of 34.4 g, 0.258 mol) was added portionwise to maintain the temperature between 50 and 60 °C. After the addition was complete, the reaction was allowed to cool and stand at room temperature overnight. Water and ether were added and the layers separated. The aqueous layer was washed with ether, and the combined organic layers were washed with 2% HCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting solid was recrystallized from ether/hexanes to give 45.2 g (84%) of 4-chloro-2-fluorobenzohydroximinoyl chloride as a white solid: mp 124–126 °C; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 159.2 (d, J = 259 Hz), 136.2 (d, J = 10 Hz), 131.2 (d, J = 2 Hz), 130.9 (d, J = 6 Hz), 124.2 (d, J = 4 Hz), 120.4 (d, J = 12 Hz), 116.7 (d, J = 25 Hz); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 11.55 (s, very broad, 1H), 7.49 (t, J = 8 Hz, 1H), 7.02–7.11 (m, 2H); ^{19}F NMR ($CDCl_3$ + DMSO-d_6) δ −111.1 (t, J = 9 Hz).

Anal. Calcd for $C_7H_4N_1O_1F_1Cl_2$: C, 40.42; H, 1.94; N, 6.73; Cl, 34.09. Found: C, 40.36; H, 1.97; N, 6.70; Cl, 34.00.

Ethyl 3-(4-Chlorophenyl)-4-isoxazolecarboxylate (2a). General Procedure. A solution of 7.1 g (75 mmol) of ethyl propiolate in 60 mL of diethyl ether was cooled in an ice water bath and stirred while a solution of 6.3 mL (75 mmol) of pyrrolidine in 60 mL of diethyl ether was added dropwise over 30 min. The yellow solution was stirred at room temperature for 45 min and subsequently treated with 10.5 mL of triethylamine. After the reaction cooled to 0 °C, the stirred mixture was treated dropwise with a solution of 14.3 g (75 mmol) of 4-chlorobenzohydroximinoyl chloride in 100 mL of diethyl ether over a period of 45 min. The reaction mixture was allowed to warm to room temperature and filtered, and the ether solution was washed with 1 N HCl and water. The aqueous washes were back extracted with diethyl ether, and the ether extracts were combined, dried with $MgSO_4$, and concentrated in vacuo. Treatment of the resultant oil with hexanes afforded a crystalline solid which was collected and air-dried to give 14.3 g (75.7%) of yellow, finely divided needles; mp 47 °C [lit. mp 43–45 °C (Franz and Howe, 1980)]; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H), 4.15 (q, 2H), 7.20–7.70 (m, 4H), 8.85 (s, 1H).

Anal. Calcd for $C_{12}H_{10}NO_3Cl$: C, 57.27; H, 4.01; N, 5.57; Cl, 14.09. Found: C, 57.29; H, 3.88; N, 5.35; Cl, 14.04.

5-(Chlorodifluoromethyl)-3-(4-chlorophenyl)-4-isoxazolecarboxylic Acid, Methyl Ester (2m). General Procedure. A solution of 19.0 g (0.10 mol) 4-chlorobenzohydroximinoyl chloride and 16.9 g (0.10 mol) of methyl 4-chloro-4,4-difluoro-2-butynoate in 200 mL of methylene chloride was chilled to −5 °C in a saltwater/ice bath and treated portionwise with 100 mL of 5% aqueous NaOH over a 15 min period with vigorous stirring such that the temperature did not exceed 5 °C. The reaction was stirred cold for an additional 15 min, water was added, and the layers were separated. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with 5% HCl, dried with $MgSO_4$, filtered and concentrated in vacuo to give 29.8 g of a yellow oil which was completely soluble in hexanes. The oil was purified by chromatography (2 in. × 22 in. silica column) using 2% ethyl acetate/hexanes as the eluent. The main peak was concentrated to afford 21.8 g (68%) of methyl 5-(chlorodifluoromethyl)-3-(4-chlorophenyl)-4-isoxazolecarboxylate as a colorless oil. A 3.0 g sample of a heart cut of the main chromatographic peak was distilled bulb-to-bulb (75–85 °C at 0.03 Torr) to afford 2.64 g of a colorless oil: η^{23}_D 1.5284; ^{13}C NMR ($CDCl_3$) δ 163.3 (t, J = 36 Hz), 161.9, 159.9, 137.2, 130.2, 129.0, 125.0, 118.6 (t, J = 290 Hz), 110.8, 53.0; ^1H NMR ($CDCl_3$) δ 7.62 and 7.46 (abq, J = 9 Hz, 4H), 3.88 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −53.3 (s).

Anal. Calcd for $C_{12}H_7NO_3F_2Cl_2$: C, 44.75; H, 2.19; N, 4.35; Cl, 22.02. Found: C, 44.81; H, 2.16; N, 4.33; Cl, 21.95.

5-(Chlorodifluoromethyl)-3-(4-chlorophenyl)-4-isoxazolecarboxylic Acid (3m). General Procedure. A solution of 19.0 g (59 mmol) of **2m** in a mixture of 190 mL of acetic acid was treated with 85 mL of concentrated HCl and heated to reflux. After 3 h, the mixture was treated with an additional 25 mL of concentrated HCl and heated at reflux for 3 days. The reaction was cooled to room temperature and the bulk of the solvent removed in vacuo. Water was added to the solid residue, and the mixture was filtered. The solid was partially dried, dissolved in ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was slurried in ether/hexanes, filtered, and air-dried to afford 11.7 g (64%) of a white solid: mp 110–112 °C; ^{13}C NMR ($CDCl_3$) δ 165.1 (t, J = 36 Hz), 164.7, 162.5, 137.4, 130.6, 129.0, 124.5, 118.4 (t, J = 291 Hz), 109.7; ^1H NMR ($CDCl_3$) δ 11.54 (s, br, 1H), 7.61 and 7.48 (abq, J = 8 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ −53.5 (s).

Anal. Calcd for $C_{11}H_5NO_3F_2Cl_2$: C, 42.89; H, 1.64; N, 4.55; Cl, 23.02. Found: C, 42.87; H, 1.65; N, 4.51; Cl, 22.98.

5-(Chlorodifluoromethyl)-3-(4-chlorophenyl)-4-isoxazolecarbonyl Chloride (4m). General Procedure. To a solution of 10.2 g (33.1 mmol) of **3m** in 40 mL of methylene chloride was added 10 mL of oxalyl chloride followed by 2 drops of dimethylformamide. The mixture was heated to reflux for 1 h and the resulting clear solution concentrated in vacuo. The residue was Kugelrohr distilled (70–80 °C at 0.08 Torr) to afford 8.2 g (80%) of a colorless oil: $\eta_D^{23.0}$ 1.5438; ^{13}C NMR ($CDCl_3$) δ 162.0 (t, J = 37 Hz), 160.4, 159.3, 137.9, 130.0, 129.5, 123.9, 118.1 (t, J = 290 Hz), 115.8; ^1H NMR ($CDCl_3$) δ 7.60–7.54 (m, 2H), 7.54–7.48 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −53.3 (s).

Anal. Calcd for $C_{11}H_4NO_2F_2Cl_3$: C, 40.64; H, 1.23; N, 4.29; Cl, 32.57. Found: C, 40.49; H, 1.22; N, 4.26; Cl, 32.54.

5-(Chlorodifluoromethyl)-3-(4-chlorophenyl)-4-isoxazolecarboxamide (6b). General Procedure. The freshly distilled **4m** (2.0 g, 6.1 mmol) was dissolved in 20 mL of methylene chloride, and 20 mL of 10% sodium carbonate was added. Concentrated ammonium hydroxide (5 mL) was added, and the mixture was stirred for 15 min. Water was added, and the layers were separated. The aqueous layer was washed with methylene chloride, and the combined organic layers were washed with 2.5% aqueous HCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. The solid residue was recrystallized from ether/hexanes to afford 1.48 g (79%) of a white solid: mp 161–162 °C; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 161.1, 159.7, 158.4 (t, J = 36 Hz), 136.8, 129.08, 129.06, 125.2, 118.6 (t, J = 288 Hz), 115.0; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.60 (s, br, 1H), 7.50–7.45 (m, 2H), 7.19–7.13 (m, 2H), 7.10 (s, br, 1H); ^{19}F NMR ($CDCl_3$ + DMSO-d_6) δ −53.6 (s).

Anal. Calcd for $C_{11}H_6N_2O_2F_3Cl_1$: C, 43.02; H, 1.97; N, 9.12; Cl, 23.09. Found: C, 43.15; H, 1.97; N, 9.09; Cl, 22.99.

***N*-[[5-(Chlorodifluoromethyl)-3-[4-chlorophenyl]-4-isoxazolyl]carbonyl]methionine, Ethyl Ester (8a).** The crude white crystals were recrystallized from ethyl acetate/hexanes to afford 1.16 g (83%) of a white solid: mp 106–108 °C; ^1H NMR($CDCl_3$) δ 7.62 (d, 2H, J = 8 Hz), 7.36 (d, 2H, J = 8 Hz), 6.71 (d, 1H), 4.75 (q, 1H), 4.13 (q, 2H, J = 7 Hz), 2.37 (t, 2H), 2.11 (m, 2H), 1.97 (s, 3H) 1.20 (t, 3H, J = 7 Hz).

Anal. Calcd for $C_{18}H_{18}N_2O_4Cl_2F_2S$: C, 46.26; H, 3.88; N, 5.99. Found: C, 46.40; H, 3.87; N, 5.84.

3-(4-Chlorophenyl)-5-(trichloromethyl)-4-isoxazolecarboxamide (5l). To a stirred suspension of 2.0 g (6.5 mmol) of **6b** in 40 mL of CH_2Cl_2 cooled in an ice water–acetone bath to 0 °C was added 2.2 g (16.5 mmol) of $AlCl_3$ at once. The mixture was stirred for 90 min, the ice bath removed, and the mixture heated to reflux overnight. The reaction mixture was diluted with 1 N HCl and extracted three times with CH_2Cl_2;

the combined extracts were dried with $MgSO_4$ and concentrated in vacuo to afford 1.3 g of a purple-white solid. Chromatographic purification (silica, CH_2Cl_2) gave 1.3 g (58.8%) of a white, crystalline solid: mp 201.5–203 °C; ^{1}HNMR (acetone-d_6) δ 7.47 (bs, 1H), 7.59 (m, 2H), 7.81 (bs, 1H), 7.85 (m, 2H); ^{13}CNMR (acetone-d_6) δ 85.3, 115.1 (C4), 127.0, 130.0, 130.1, 137.3, 161.1, 162.5, 163.8.

Anal. Calcd for $C_{11}H_6N_2OCl_4$: C, 38.86; H, 1.78; N, 8.24. Found: C, 39.05; H, 1.86; N, 8.27.

5-(Chlorodifluoromethyl)-3-(4-chloro-2-fluoro-5-methoxyphenyl)-4-isoxazolecarboxylic Acid (3cc). A solution of 11.0 g (29.7 mmol) of **2cc** in 110 mL of concentrated acetic acid was treated with 60 mL of concentrated HCl and heated to reflux. After 6 h, the mixture was treated with an additional 25 mL of concentrated HCl and heated to reflux for 3 days. The reaction mixture was concentrated in vacuo to remove most of the acetic acid and treated with water; the resultant solid was collected by filtration and air-dried to give a white solid. Recrystallization was from diethyl ether/hexanes to give 7.5 g (71%) of a white, crystalline solid: mp 143–146 °C; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 163.6 (t, J = 36 Hz), 161.5, 159.6, 154.7 (d, J = 247 Hz), 152.8 (d, J = 3 Hz), 126.8 (d, J = 10 Hz), 119.7 (t, J = 290 Hz), 119.1 (d, J = 28 Hz), 115.1 (d, J = 16 Hz), 114.3 (d, J = 3 Hz), 57.8; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.0 (s, very broad, 1H), 6.96 (d of d, J = 9 Hz, J' = 1 Hz, 1H), 6.86 (d, J = 6 Hz, 1H), 3.62 (d, J = 1 Hz, 3H); ^{19}F NMR ($CDCl_3$ + DMSO-d_6) δ −51.5 (s, 2F), −121.2 (m, appears as a triplet, 1F).

Anal. Calcd for $C_{12}H_6NO_4F_3Cl_2$: C, 40.48; H, 1.70; N, 3.93; Cl, 19.91. Found: C, 40.53; H, 1.75; N, 3.90; Cl, 19.98.

5-(Chlorodifluoromethyl)-3-(4-chloro-2-fluoro-5-methoxyphenyl)-4-isoxazolecarbonyl Chloride (4cc). A slurry of 4.5 g (12.6 mmol) of **3cc** in 30 mL of methylene chloride was treated with 3.3 mL (37.9 mmol) of oxalyl chloride followed by 2 drops of dimethylformamide. The mixture was refluxed for 1 h, and the resulting solution was concentrated in vacuo. The residue was Kugelrohr distilled (110–120 °C at 0.2 Torr) to afford 4.5 g (86%) of a yellow oil which crystallized on standing to afford a white solid: mp 55–57 °C; ^{13}C NMR ($CDCl_3$) δ 166.1, 163.5 (t, J = 37 Hz), 159.2, 158.2, 154.5 (d, J = 247 Hz), 153.5 (d, J = 2 Hz), 128.5 (d, J = 10 Hz), 119.6 (d, J = 26 Hz), 119.2 (t, J = 290 Hz), 117.4, 113.6 (m, not fully resolved), 58.0; ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 9 Hz, 1H), 7.08 (d, J = 6 Hz, 1H), 3.84 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −56.8 (s, 2F), −125.6 (m, appears as a triplet, 1F).

Anal. Calcd for $C_{12}H_5NO_3F_3Cl_3$: C, 38.48; H, 1.35; N, 3.74; Cl, 28.40. Found: C, 38.58; H, 1.39; N, 3.71; Cl, 28.34.

5-(Chlorodifluoromethyl)-3-(4-chloro-2-fluoro-5-methoxyphenyl)-4-isoxazolecarboxamide (6t). A solution of 1.87 g (5 mmol) of **4cc** in 20 mL of diethyl ether was chilled in an ice/water bath and treated with 20 mL of 10% aqueous sodium carbonate, and the resulting two-phase mixture was vigorously stirred as 2–3 mL of ammonium hydroxide was added all at once. The cooling bath was removed, more ether added to aid stirring, and the mixture stirred at ambient temperature. After stirring for 15–30 min, water and ether were added and the layers were separated. The organic layer was washed with 5% aqueous HCl, dried, filtered, and concentrated in vacuo. The solid residue was triturated with ether/hexanes, filtered, washed with hexanes, and air-dried to afford 1.5 g (85%) of a white solid: mp 191–193 °C; ^{13}C NMR (DMSO-d_6) δ 160.7, 158.6 (t , J = 36 Hz), 158.0, 154.0 (d, J = 248 Hz), 152.5 (d, J = 2 Hz), 125.9 (d, J = 10 Hz), 119.7 (t, J = 287 Hz), 119.4 (d, J = 26 Hz), 118.2, 114.8 (d, J = 3 Hz), 114.5 (d, J = 16 Hz), 57.9; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, slightly broad, 1H), 7.94 (s, slightly broad, 1H), 7.65 (d, J = 10 Hz, 1H), 7.34 (d, J = 6 Hz, 1H), 3.83 (s, 3H); ^{19}F NMR (DMSO-d_6) δ −50.6 (s, 2F), −121.3 (m, appears as a triplet, 1F).

Anal. Calcd for $C_{12}H_7N_2O_3F_3Cl_2$: C, 40.59; H, 1.99; N, 7.89; Cl, 19.97. Found: C, 40.65; H, 2.03; N, 7.84; Cl, 20.03.

5-(Chlorodifluoromethyl)-3-(4-chloro-2-fluoro-5-hydroxyphenyl)-4-isoxazolecarboxamide (6u). A slurry of 5.56 g (15.8 mmol) of **6t** in 25 mL of methylene chloride was cooled in an ice/water bath and treated with 50 mL (50 mmol) of 1 M boron tribromide in methylene chloride. The resulting solution was allowed to stand overnight at room temperature. The solution was poured into 600 mL of ice water and stirred for 30 min. The resulting solid was collected by filtration, the filter cake slurried in 25 mL of 50% ether/hexanes, filtered, and washed with ether/hexanes, and the solid air-dried to afford 3.5 g (66%) of a white solid: mp 173–175 °C; ^{13}C NMR (DMSO-d_6) δ 160.6, 158.6 (t , J = 36 Hz), 157.9 (d, J = 2 Hz), 153.0 (d, J = 246 Hz), 151.2 (d, J = 3 Hz), 124.4 (d, J = 10 Hz), 119.7 (t, J = 287 Hz), 119.0 (d, J = 25 Hz), 118.1, 117.9 (d, J = 2 Hz), 114.5 (d, J = 16 Hz); ^{1}H NMR (DMSO-d_6) δ 10.64 (s, br, 1H), 8.09 (s, slightly broad, 1H), 7.88 (s, slightly broad, 1H), 7.51 (d, J = 10 Hz, 1H), 7.17 (d, J = 7 Hz, 1H); ^{19}F NMR (DMSO-d_6) δ −50.8 (s, 2F), −123.3 (m, 1F).

Anal. Calcd for $C_{11}H_5N_2O_3F_3Cl_2$ + 0.5H_2O: C, 37.74; H, 1.73; N, 8.00. Found: C, 37.76; H, 1.72; N, 7.98.

5-(Chlorodifluoromethyl)-3-[4-chloro-2-fluoro-5-(2-propynyloxy)phenyl]-4-isoxazolecarboxamide (6v). To a mixture of 1.8 g (5.3 mmol) of **6u** and 0.89 g (6 mmol) of 80% propargyl bromide in 25 mL of dimethyl sulfoxide was added 0.83 g (6 mmol) of potassium carbonate. The mixture was stirred and heated in a 40–45 °C oil bath for 1.5 h. The mixture was allowed to cool, treated with ice water, and stirred, and the resulting solid was filtered. The solid was purified by chromatography (silica, 35% ethyl acetate/hexanes) to afford 1.5 g (75%) of a white solid: mp 198–199 °C; ^{13}C NMR (DMSO-d_6) δ 160.5, 158.7 (t, J = 36 Hz), 157.9 (m), 154.5 (d, J = 248 Hz), 150.6 (d, J = 3 Hz), 126.8 (d, J = 10 Hz), 119.7 (t, J = 288 Hz), 119.6 (d, J = 27 Hz), 118.2, 116.8 (m), 114.5 (d, J = 16 Hz), 80.5, 79.1, 58.5; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, slightly broad, 1H), 7.89 (s, slightly broad, 1H), 7.70 (d, J = 9 Hz, 1H), 7.45 (d, J = 6 Hz, 1H), 4.89 (d, J = 2 Hz, 2H), 3.58 (t, J = 2 Hz, 1H); ^{19}F NMR (DMSO-d_6) δ −47.9 (s, 2F), −116.7 (m, appears as a triplet, 1F).

Anal. Calcd for $C_{14}H_7N_2O_3F_3Cl_2$: C, 44.35; H, 1.86; N, 7.39. Found: C, 44.39; H, 1.88; N, 7.34.

2-[5-[4-(Aminocarbonyl)-5-(chlorodifluoromethyl)-3-isoxazolyl]-2-chloro-4-fluorophenoxy]propionic Acid, Ethyl Ester (6w). To a mixture of **6u** (1.8 g, 5.3 mmol) and ethyl 2-bromopropionate (1.09 g, 6 mmol) in 25 mL of dimethyl sulfoxide was added 0.83 g of potassium carbonate (6 mmol). The mixture was stirred and heated in a 40–45 °C oil bath for 0.5 h. The mixture was allowed to cool, treated with ice water, and stirred and the resulting solid filtered. The solid was dissolved in ether, dried, filtered, and concentrated in vacuo. The residue was slurried in ether, treated with hexanes, filtered, and air-dried to afford 1.8 g (77%) of **6w** as a white solid: mp 126–127 °C; ^{13}C NMR (DMSO-d_6) δ 171.5, 160.5, 158.7 (t , J = 36 Hz), 157.8, 154.5 (d, J = 249 Hz), 150.9 (d, J = 3 Hz), 127.1 (d, J = 11 Hz), 119.7 (t, J = 288 Hz), 119.6 (d, J = 26 Hz), 118.2, 117.3 (d, J = 2 Hz), 114.5 (d, J = 16 Hz), 74.9, 62.3, 19.1, 15.0; ^{1}H NMR (DMSO-d_6) δ 8.08 (s, slightly broad, 1H), 7.89 (s, slightly broad, 1H), 7.69 (d, J = 9 Hz, 1H), 7.25 (d, J = 6 Hz, 1H), 5.00 (q, J = 7 Hz, 1H), 4.12 (q, J = 7 Hz, 2H), 1.51 (d, J = 7 Hz, 3H), 1.13 (t, J = 7 Hz, 3H); ^{19}F NMR (DMSO-d_6) δ −47.9 (d, J = 7 Hz, 2F), −116.8 (m, appears as a triplet, 1F).

Anal. Calcd for $C_{14}H_7N_2O_3F_3Cl_2$: C, 44.35; H, 1.86; N, 7.39. Found: C, 44.39; H, 1.88; N, 7.34.

5-[4-(Aminocarbonyl)-5-(chlorodifluoromethyl)-3-isoxazolyl]-2-chloro-4-fluorophenoxyacetic Acid, 1-Methylethyl Ester (6x). To a solution of 2.5 g (7.0 mmol) of **6u** and 1.08 mL (8.4 mmol) of isopropyl bromoacetate in 25 mL of acetone was added 1.35 g (9.7 mmol) of potassium carbonate. The slurry was heated to reflux overnight and treated with water, and the resulting solid was filtered. The wet solid was dissolved in ether, dried with $MgSO_4$, filtered, and partially concentrated. Hexanes were added to the slurry, and the solid was filtered and air-dried overnight to afford 2.8 g (91%) of a white solid. Recrystallization from ethanol/water gave a crystalline, white solid: mp 146–148 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (s, slightly broad, 1H), 6.93 (d, J = 9 Hz, 1H), 6.86 (d, J = 6 Hz, 1H), 6.77 (s, slightly broad, 1H), 4.74 (m, 1H), 4.32 (s, 2H), 0.90 (d, J = 6 Hz, 6H).

Anal. Calcd for $C_{16}H_{13}N_2O_5F_3Cl_2$: C, 43.56; H, 2.97; N, 6.35. Found: C, 43.64; H, 3.01; N, 6.33.

Methyl 5-(Chlorodifluoromethyl)-3-(2,4-difluoro-5-nitrophenyl)-4-isoxazolecarboxylate (9). To 21.5 g (66.4 mmol) of methyl 5-(chlorodifluoromethyl)-3-(2,4-difluorophenyl)-4-isoxazolecarboxylate (**2p**) in a 500 mL flask equipped with magnetic stirring was added 150 mL of 90% nitric acid. A slight exotherm occurred, and the reaction was allowed to stir at ambient temperature overnight. The reaction was poured onto ice water, and ether was added. The layers were separated, and the organic layer was dried, filtered through silica gel, and concentrated in vacuo. The residue was recrystallized from hexanes to afford 19.7 g (80%) of an off-white solid: mp 68–70 °C; ^{13}C NMR ($CDCl_3$) δ 165.4 (t, J = 36 Hz), 164.3 (d of d, J = 264, J' = 12 Hz), 160.0, 159.2 (d of d, J = 272, J' = 13 Hz), 158.1, 135.4 (m, small and broad), 130.5 (d of d, J = 5 Hz, J' = 2 Hz), 119.5 (t, J = 291 Hz), 114.1 (d of d, J = 16, J' = 4 Hz), 112.6, 108.6 (d of d, J = 27, J' = 25 Hz), 54.3; ^{1}H NMR ($CDCl_3$) δ 8.35 (d of d, appears as a triplet, $J = J'$ = 7 Hz, 1H), 7.15 (d of d, appears as a triplet, $J = J'$ = 10 Hz, 1H), 3.81 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −53.7 (s, 2F), −98.9 (m, 1F), −108.6 (m, 1F).

Anal. Calcd for $C_{12}H_5N_2O_5F_4Cl_1$: C, 39.10; H, 1.37; N, 7.60. Found: C, 39.19; H, 1.43; N, 7.51.

Methyl 5-(Chlorodifluoromethyl)-3-(5-fluoro-2-nitrophenyl)-4-isoxazolecarboxylate (10). To 9.0 g (29 mmol) of methyl 5-(chlorodifluoromethyl)-3-(3-fluorophenyl)-4-isoxazolecarboxylate (**2v**) chilled to 10 °C was carefully added 2–3 mL of 90% nitric acid. An exotherm was evident as the temperature rose to 20 °C. The solution was chilled to 12 °C, and the rest of the nitric acid (25 mL total) was added portionwise with no further rise in temperature. The bath was removed, and the reaction was allowed to stir at ambient temperature for 1 h. The reaction was poured onto ice water and extracted twice with ether, and the combined ether extracts were washed with water and 10% sodium bicarbonate, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography (silica, 9% ethyl acetate/hexanes) to give an oil which crystallized on standing. Recrystallization from ether/hexanes gave 7.9 g (77%) of an off-white solid: mp 42–43 °C; ^{13}C NMR ($CDCl_3$) δ 167.2, 165.0 (t, J = 36 Hz), 164.6, 161.4 (d, J = 267 Hz), 145.5 (d, weak and broad, J = 3 Hz), 129.1 (d, J = 10 Hz), 127.0 (d, J = 10 Hz), 121.1 (d, J = 26 Hz), 119.7 (t, J = 291 Hz), 119.6 (d, J = 23 Hz), 112.0, 54.1; ^{1}H NMR ($CDCl_3$) δ 8.29 (d of d, J = 9 Hz, J' = 5 Hz, 1H), 7.31–7.37 (m, 1H), 7.21 (d of d, J = 8 Hz, J' = 3 Hz, 1H), 3.69 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −53.6 (s, 2F), −103.4 (m 1F).

Anal. Calcd for $C_{12}H_6N_2O_5F_3Cl$: C, 41.11; H, 1.72; N, 7.99; Cl, 10.11. Found: C, 41.19; H, 1.77; N, 7.94; Cl, 10.20.

5-(Chlorodifluoromethyl)-3-(2-fluoro-4-methoxy-5-nitrophenyl)-4-isoxazolecarboxylic Acid, Methyl Ester (11). A slurry of **9** (3.7 g, 10 mmol) and 1.4 g (10 mmol) of potassium carbonate in methanol was stirred overnight, added to cold water, and extracted twice with ethyl acetate. The combined organic layers were dried, filtered, and concentrated. The yellow solid residue was recrystallized from ethanol to afford 3.0 g (79%) of **11** as a yellow solid: mp 113–115 °C; ^{13}C NMR ($CDCl_3$) δ 164.1 (t, J = 36 Hz), 163.5 (d, J = 260 Hz), 159.6, 157.7, 157.5 (d, J = 12 Hz), 136.4, 129.4 (d, J = 6 Hz), 118.9 (t, J = 290 Hz), 111.9, 107.8 (d, J = 17 Hz), 102.4 (d, J = 27 Hz), 57.8, 53.4; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 7 Hz, 1H), 7.06 (d, J = 11 Hz, 1H), 4.15 (s, 3H), 3.97 (s, 3H).

Anal. Calcd for $C_{13}H_8N_2O_6F_3Cl$: C, 41.02; H, 2.12; N, 7.36. Found: C, 41.18; H, 2.14; N, 7.31.

5-(Chlorodifluoromethyl)-3-(2-fluoro-4-methoxy-5-nitrophenyl)-4-isoxazolecarboxylic Acid. A mixture of **11** (14.3 g, 37.6 mmol), 140 mL of acetic acid, and 70 mL of concentrated HCl was refluxed overnight. Another 50 mL of concentrated HCl was added, and the reaction was refluxed for another 24 h. The reaction was cooled to room temperature and concentrated in vacuo, water was added, and the resulting solid was filtered and air-dried. The solid was dissolved in ether, dried over $MgSO_4$, and concentrated. The solid residue was recrystallized from ether/hexanes to afford 11.2 g (81%) of a yellow solid: mp 159–163 °C; ^{1}H NMR ($CDCl_3$) δ 12.0 (s, very broad, 1H), 8.29 (d, J = 7 Hz, 1H), 7.01 (d, J = 11 Hz, 1H), 4.10 (s, 3H).

Anal. Calcd for $C_{12}H_6N_2O_6F_3Cl$: C, 39.31; H, 1.65; N, 7.64. Found: C, 39.40; H, 1.71; N, 7.63.

5-(Chlorodifluoromethyl)-3-(2-fluoro-4-methoxy-5-nitrophenyl)-4-isoxazolecarboxamide (12). A slurry of 5-(chlorodifluoromethyl)-3-(2-fluoro-4-methoxy-5-nitrophenyl)-4-isoxazolecarboxylic acid (10.6 g, 28.9 mmol) in 50 mL of methylene chloride was treated with 5.1 mL (57.8 mmol) of oxalyl chloride followed by 2 drops of dimethylformamide. The mixture was refluxed for 1 h, and the resulting solution was concentrated. The residue was dissolved in hot hexanes and decanted from the insoluble material. The acid chloride crystallized on cooling of the hexane solution, and the crystalline material was filtered and dissolved in ether. To this solution was added 40 mL of 10% sodium carbonate followed by 10 mL of ammonium hydroxide. This mixture was stirred rapidly for 5 min and treated with ethyl acetate and water, and the layers were separated. The organic layer was washed with water, dried, filtered, and partially concentrated. Hexanes were added to the concentrated solution, and the resulting slurry was filtered and air-dried to afford 7.4 g (70%) of a white solid: mp 181–183 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 7 Hz, 1H), 8.41 (s, slightly broad, 1H), 8.14 (s, slightly broad, 1H), 7.73 (d, J = 12 Hz, 1H), 4.16 (s, 3H).

Anal. Calcd for $C_{12}H_7N_3O_5F_3Cl$: C, 39.42; H, 1.93; N, 11.49. Found: C, 39.50; H, 1.99; N, 11.44.

5-(Chlorodifluoromethyl)-3-(2-fluoro-4-hydroxy-5-nitrophenyl)-4-isoxazolecarboxamide (13). A mixture of **12** (6.8 g, 18.6 mmol) was prepared in 150 mL of methylene chloride under nitrogen and cooled in an ice bath. Boron tribromide (55.8 mmol, 56 mL of a 1 M solution in methylene chloride) was added and the mixture stirred for 2–3 h in the ice bath. The mixture was poured into cold water and stirred for 30 min. The mixture was filtered, the filtrate was refiltered to obtain more product, and the combined solids were air-dried overnight, washed with 25% ethanol/hexanes, and air-dried to afford 5.75 g (70%) of **13** as a yellow solid: mp 175–178 °C; ^{1}H NMR (DMSO-d_6) δ 12.4 (s, broad, 1H), 8.40 (d, J = 8 Hz, 1H), 8.28 (s, slightly broad, 1H), 8.13 (s, slightly broad, 1H), 7.25 (d, J = 12 Hz, 1H).

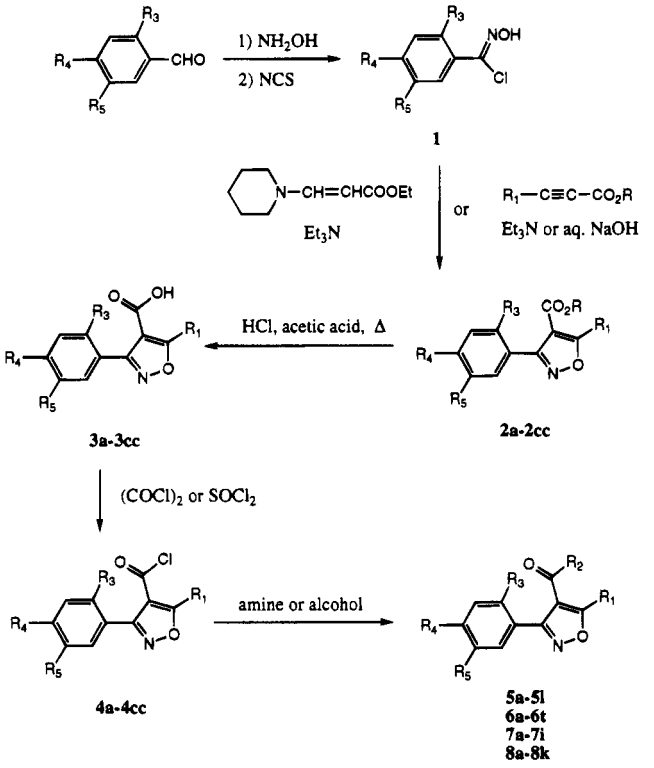
Anal. Calcd for $C_{11}H_5N_3O_5F_3Cl + 0.2H_2O$: C, 37.19; H, 1.53; N, 11.83. Found: C, 37.12; H, 1.52; N, 11.71.

4-[4-(Aminocarbonyl)-5-(chlorodifluoromethyl)-3-isoxazolyl]-5-fluoro-2-nitrophenoxyacetic Acid, Ethyl Ester (14). A mixture of **13** (5.2 g, 14.8 mmol), potassium carbonate (2.13 g, 15.4 mmol), and ethyl bromoacetate (1.78 mL, 16 mmol) in 20 mL of acetone was heated in an oil bath at 40 °C. Additional acetone was added to the heavy slurry, and the mixture was heated overnight. Additional ethyl bromoacetate and DMSO were added to give an easily stirred, hazy mixture. The reaction was heated at 40 °C for 8 h and allowed to stand at room temperature for 60 h. The mixture was poured into cold 5% aqueous HCl, stirred for 15 min, and filtered, and the resulting solid was air-dried. Analytical HPLC (reversed-phase ODS, acetonitrile/water) showed the presence of two products (a mixture of **14** and **15**) which were separated by preparative reversed-phase chromatography. This major product **14** was eluted first (reversed-phase C_{18}, 60% acetonitrile/water), the eluant concentrated and filtered, and the resultant solid was air-dried to afford 4.4 g (68%) of **14** as a white solid: mp 183–185 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (d, J = 7 Hz, 1H), 8.29 (s, slightly broad, 1H), 8.14 (s, slightly broad, 1H), 7.76 (d, J = 12 Hz, 1H), 5.27 (s, 2H), 4.31 (q, J = 7 Hz, 2H), 1.34 (t, J = 7 Hz, 3H).

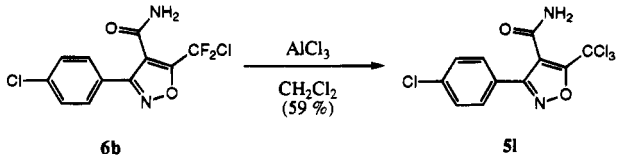
Anal. Calcd for $C_{15}H_{11}N_3O_7F_3Cl$: C, 41.16; H, 2.53; N, 9.60. Found: C, 41.26; H, 2.55; N, 9.55.

2,2′-[[3-(Chlorodifluoromethyl)-8-nitroisoxazolo[4,3-*c*]quinoline-4,7-diyl]bis(oxy)]bis(acetic acid), Diethyl Ester (15). The minor product obtained from alkylation of **13** (see preparation of **14** above) was obtained by preparative chromatography using a stronger elution solvent mixture (reversed-phase C_{18}, 80% acetonitrile/water). The eluant was partially concentrated and the resultant crystalline solid collected by filtration and air-dried to afford 0.5 g (7%) of **15** as a white solid: mp 189–191 °C; ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H), 7.29 (s, 1H), 5.38 (s, 2H), 5.31 (s, 2H), 4.29 (m, 2 q, 4H), 1.35 (t, J = 7 Hz, 3H), 1.32 (t, J = 7 Hz, 3H).

Scheme 1



Scheme 2



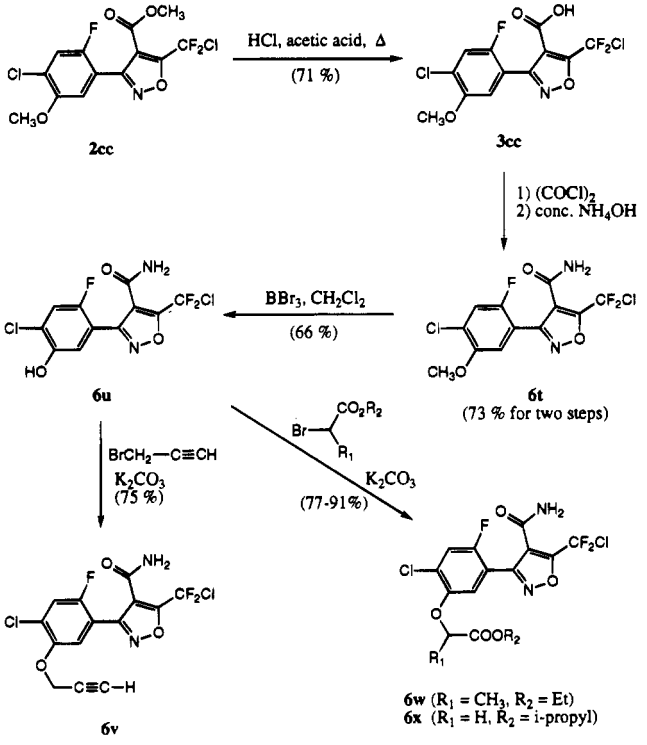
Anal. Calcd for $C_{19}H_{16}N_3O_9F_2Cl$: C, 45.30; H, 3.20; N, 8.34. Found: C, 45.42; H, 3.23; N, 8.34.

5-(Chlorodifluoromethyl)-3-(7-fluoro-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-6-yl)-4-isoxazolecarboxamide (16). In a 500 mL flask equipped with a mechanical stirrer was prepared a mixture of **14** (3.9 g, 8.9 mmol) in 125 mL of acetic acid. The reaction mixture was heated to 75–80 °C. Iron powder (1.54 g, 27.6 mmol) was added portionwise to maintain the temperature at 75–85 °C. After stirring for 2 h, the reaction was allowed to cool to 50 °C and filtered. Ice and water were added to the filtrate, and the solution was partially concentrated. The crude product crystallized and was collected by filtration and air-dried to afford 2.7 g (84%) of **16** as a white solid: mp 248–255 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.09 (s, slightly broad, 1H), 8.22 (s, slightly broad, 1H), 8.01 (s, slightly broad, 1H), 7.27 (d, J = 7 Hz, 1H), 7.24 (d, J = 11 Hz, 1H), 4,82 (s, 2H).

Anal. Calcd for $C_{13}H_7N_3O_4F_3Cl$: C, 43.17; H, 1.95; N, 11.62. Found: C, 43.29; H, 2.02; N, 11.55.

5-(Chlorodifluoromethyl)-3-[7-fluoro-3,4-dihydro-3-oxo-1-(2-propynyl)-2*H*-1,4-benzoxazin-6-yl]-4-isoxazolecarboxamide (17). A mixture of **16** (1.1 g, 3 mmol), potassium carbonate (0.44 g, 3.2 mmol), and propargyl bromide (80% in toluene solution) (0.36 mL, 3.2 mmol) in 25 mL of DMSO was stirred and heated in a 45–50 °C oil bath. The reaction mixture was diluted with water and extracted with ethyl acetate. Combined organic extracts were dried, concentrated and purified by chromatography (silica, 50% ethyl acetate/hexanes). Concentration of the major chromatographic fraction and recrystallization from ethyl acetate/hexanes yielded 0.54 g (44%) of **17** as a white solid: mp 235–238 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.30 (s, slightly broad, 1H), 8.04 (s, slightly broad, 1H), 7.63 (d, J = 6 Hz, 1H), 7.37 (d, J = 10 Hz, 1H), 4.98 (s, 2H), 4.84 (d, J = 2 Hz, 2H), 3.41 (t, J = 2 Hz, 1H).

Scheme 3



Anal. Calcd for $C_{16}H_9N_3O_4F_3Cl$: C, 48.08; H, 2.27; N, 10.51. Found: C, 48.15; H, 2.30; N, 10.49.

Preemergent Herbicide Tests. A topsoil mixture was placed in an aluminum pan and compacted to a depth of 0.95–1.27 cm from the top of the pan. On the top of the soil was placed a predetermined number of seeds of each of several moncotyledonous and dicotyledonous annual plant species including morning glory, velvetleaf, and barnyard grass. A known amount of the test compound was dissolved or suspended in 50% acetone/water such that a 0.1–1% solution was obtained and applied directly to the soil surface. The amount of applied herbicide corresponded to application rates that ranged from 0.004 to 10 lb/acre in multiples of 2. These applications were made in a spray chamber, utilizing an 8001E nozzle and a spray pressure of 170 kPa. After treatment, the pans were placed on a greenhouse bench where 0.25 in. of overhead irrigation was applied. Subsequent watering was applied by subirrigation. Approximately 10–14 days (usually 11) after seeding and treating, the pans were observed and the results recorded. Herbicidal activity is expressed as a GR_{80} (pounds per acre) for the particular species, which is the amount of herbicide required to inhibit 80% of weed growth relative to that of the untreated control.

Postemergent Herbicide Tests. Untreated aluminum pans containing a predetermined number of seeds and prepared in an identical manner as those for the preemergent test were placed on a bench in a greenhouse and watered from below as needed. After the plants reached the desired age (approximately 2 weeks), each pan was removed individually to a spraying chamber and sprayed by means of an 8001E nozzle, operating at a spray pressure of 170 kPa at the appropriate application rate. The amount of herbicide applied corresponded to rates that ranged from 0.004 to 5 lb/acre. The pans were returned to the greenhouse and watered as before, and the injury to the plants as compared to controls was observed at approximately 10–14 days. The postemergent herbicidal activity was recorded and is expressed as a GR_{80} in pounds per acre for the particular weed species.

RESULTS AND DISCUSSION

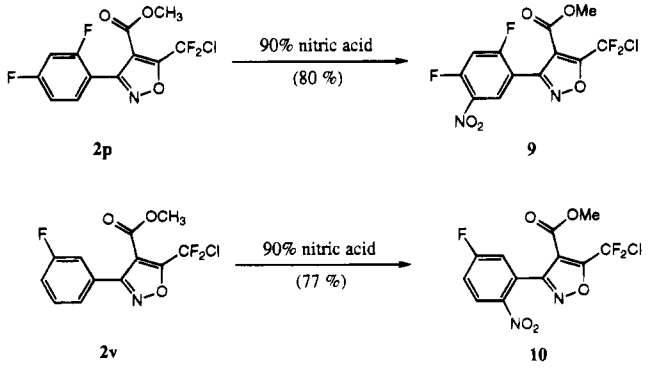
Synthesis. All of the compounds of interest were prepared by a multistep sequence which began with construction of isoxazoles **2a–2cc** by a 1,3-dipolar

Table 1. Physical Properties of 3-Aryl-4-isoxazolecarboxylate Esters 2

compd[a]	R_1	R_2	R_3	R_4	R_5	mp/η^{23}_D	yield, %
2a	H	OEt	H	Cl	H	47 °C[b]	76
2b	H	OEt	H	CF_3	H	38–39 °C	76
2c	H	OEt	H	F	H	54–55 °C	38
2d	CH_3	OEt	H	CF_3	H	43–46 °C	28
2e	CH_3	OCH_3	H	F	H	55–57 °C	38
2f	CF_3	OEt	H	CF_3	H	clear oil	66.3
2g	CF_3	OMe	H	Cl	H	38.5–40 °C[c]	
2h	CF_3	OMe	Cl	Cl	H	27–29 °C	49
2i	CF_2H	OEt	H	CF_3	H	53–53.5 °C	76
2j	CF_2CF_3	OEt	H	CF_3	H	clear oil	38
2k	$CH(CH_3)_2$	OMe	H	CF_3	H	50.5–51.5 °C	20.2
2l	CF_2Cl	OMe	H	CF_3	H	clear oil	68
2m	CF_2Cl	OMe	H	Cl	H	1.5284	68
2n	CF_2Cl	OEt	F	Cl	H	1.5085	71
wo	CF_2Cl	OMe	H	Br	H	1.5447	39
2p	CF_2Cl	OMe	F	F	H	53–54 °C	67
2q	CF_2Cl	OMe	Cl	Cl	H	1.5357	68
2r	CF_2Cl	OMe	H	CH_3	H	1.5147	44
2s	CF_2Cl	OMe	H	Cl	Cl	1.5363	52
2t	CF_2Cl	OMe	H	Cl	NO_2	62–64 °C	41
2u	CF_2Cl	OMe	H	F	H	1.5023	26
2v	CF_2Cl	OMe	H	H	F	1.5017	67
2w	CF_2Cl	OMe	H	NO_2	H	66–68 °C	48
2x	CF_2Cl	OMe	H	NO_2	OCH_3	58–60 °C	32
2y	CF_2Cl	OMe	H	OCH_3	H	1.5262	53
2z	CF_2Cl	OMe	F	CF_3	H	1.4659	67
2aa	CF_2Cl	OMe	F	H	F	1.4919	57
2bb	CF_2Cl	OMe		5-nitrofuranyl		57–59 °C	26
2cc	CF_2Cl	OMe	F	Cl	OMe	1.5245	67

[a] Compounds **2a**, **2b**, and **2c** were prepared from β-pyrrolidinyl acylate. All other compounds were prepared from acetylenic esters. The physical properties are reported as melting point (mp) or refractive index (η). [b] Lit. mp 43–45 °C (Franz and Howe, 1980). [c] Lit. mp 41–42 °C (Shen et al., 1985).

Scheme 4



2p 9 2v 10

cycloaddition (Scheme 1; Table 1). Nitrile oxides required for the cycloaddition were derived from benzohydroximinoyl chlorides by treatment with base in the presence of either acetylenic or olefinic dipolarophiles. Three 5-hydroisoxazoles, **2a**, **2b**, and **2c** (R_1 = H), were obtained as previously described (Franz and Howe, 1980) by reaction of the intermediate nitrile oxide with ethyl β-pyrrolidinylacrylate. The 5-alkylisoxazoles **2d**, **2e**, and **2k** were prepared from the corresponding acetylenic esters (Christl et al., 1973). Cycloaddition of methyl 4,4,4-trifluoro-2-butynoate with *p*-chlorophenylnitrile oxide using triethylamine as a base to give **2g** (R_1 = CF_3) has been reported (Shen et al., 1985); however, in our hands mixtures of cycloadducts were obtained. We obtained good to excellent yields of cycloadducts **2f-2cc** (where R_1 was CF_3 or CF_2Cl) with a minimum of side products using a two-phase reaction mixture of the substrate benzohydroximinoyl chloride and the acetylenic ester in methylene choride and 5% aqueous sodium hydroxide. Short reaction times of 15 min or less gave the best yields and avoided potential decomposition of the isoxazole ring. The carboxylic acids **3** were obtained by acid hydrolysis of **2** with a mixture of acetic acid and concentrated HCl. Conversion of **3** to acid chloride **4** provided a convenient intermediate for preparation of a wide variety of isoxazolecarboxamide derivatives **5**–**8** by treatment with ammonia or substituted amines.

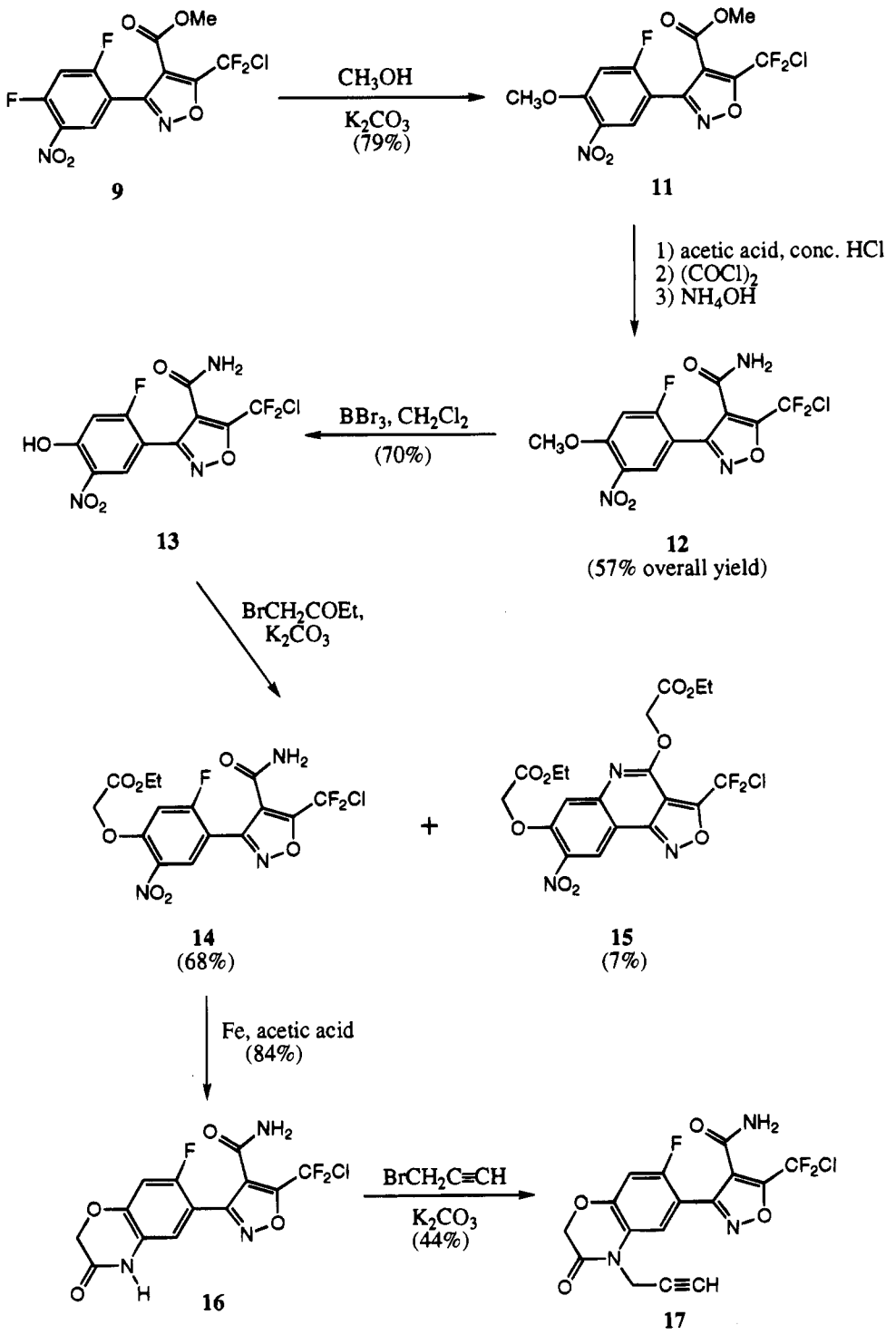
Isoxazolecarboxamide **5l** could not be obtained directly due to the lack of availability of a trichloroacetylenic ester precursor for preparation of the initial cycloadduct **2**. In addition, we were concerned that a trichloro group would not withstand the harsh hydrolysis conditions required to obtain the corresponding acid **3**. The direct replacement of fluorine for chlorine has been demonstrated (Chupp and Smith, 1988) for conversion of a difluorochloropyridine to a trichloropyridine using aluminum chloride, and it seemed likely that such

Table 2. Preemergent Herbicidal Activity of 3-Aryl-4-isoxazolecarboxamides 5 (R_2 = NH_2; R_5 = H)

				GR_{80}[a]		
compd	R_1	R_3	R_4	MG	VL	BG
5a	H	H	Cl			
5b	H	H	CF_3			
5c	H	H	F			
5d	CH_3	H	CF_3			
5e	CH_3	H	F			
5f	CF_3	H	CF_3	0.75	0.20	0.88
5g	CF_3	H	Cl	0.85	0.21	0.77
5h	CF_3	Cl	Cl	0.22	0.40	0.95
6a	CF_2Cl	H	CF_3	0.46	0.065	0.273
5i	CF_2H	H	CF_3	3.7	0.83	4.3
5j	CF_2CF_3	H	CF_3	6.7	4.3	5.7
5k	$CH(CH_3)_2$	H	CF_3	5.3	0.85	4.1
5l	CCl_3	H	Cl	10	4.0	16

[a] Herbicidal activity is expressed as a GR_{80} value, in pounds per acre, which is the amount of herbicide required to inhibit 80% of weed growth relative to that of an untreated control. MG, morning glory; VL, velvetleaf; BG, barnyard grass. No value indicates a GR_{80} value greater than 10 lb/acre.

Scheme 5



a reaction could be employed for direct conversion of a 5-(difluorochloromethyl)-4-isoxazolecarboxamide to the desired product. We found that treatment of difluorochloro **6b** with aluminum chloride gave the trichloromethylisoxazole **5l** in 59% yield with the amide functionality intact (Scheme 2). Derivatives of the 2-fluoro-4-chloro-5-methoxyphenylisoxazole (**6t**), prepared in the usual manner from **2cc**, were obtained by cleavage of the methyl ether to give **6u** and subsequent alkylation with propargyl bromide or a bromoacetate to afford **6v**–**6x** (Scheme 3).

The ester functionality of the 5-(fluoroalkyl)isoxazolecarboxylates (**2**, where R_1 is fluoroalkyl) is remarkably stable to acid hydrolysis, requiring treatment with mixed acids at elevated temperatures for conversion to **3**. As a result of this behavior, we were able to nitrate isoxazolecarboxylate esters **2p** and **2v** in concentrated acids at room temperature to give **9** and **10**, respectively, without hydrolysis of the ester group (Scheme 4). The regiochemistry of nitration is influenced by the phenyl ring substituents, rather than the isoxazole ring. Thus, nitration occurs almost exclusively ortho and para to the fluorine substituents of the phenyl ring irrespective of the isoxazole ring position. The activated fluorine of nitrophenylisoxazole **9** was displaced with methanol in potassium carbonate to give *p*-methoxyphenylisoxazole **11** which was converted to benzoxazinylisoxazole **17** by a multistep route (Scheme 5). Alkylation of carboxam-

Table 3. Preemergent Herbicidal Activity of 3-Aryl-5-(difluorochloromethyl)-4-isoxazolecarboxamides 6 ($R_1 = CF_2Cl$; $R_2 = NH_2$)

compd	R_3	R_4	R_5	GR_{80}[a] MG	VL	BG
6a	H	CF_3	H	0.46	0.065	2.73
6b	H	Cl	H	0.146	0.057	0.149
6c	F	Cl	H	0.095	0.080	0.060
6d	H	Br	H	0.41	0.063	0.21
6e	F	F	H	0.25	0.050	0.053
6f	Cl	Cl	H	0.44	0.63	0.21
6g	H	CH_3	H	99	0.40	0.41
6h	H	Cl	Cl	0.25	0.063	1.8
6i	H	Cl	NO_2	32	11	16
6j	H	F	H	0.10	0.050	0.13
6k	H	H	F	3.0	0.77	3.5
6l	H	NO_2	H	0.70	0.25	2.0
6m	H	NO_2	OCH_3	5.0	0.10	2.4
6n	H	OCH_3	H	4.1	0.16	0.50
6o	F	CF_3	H	0.21	0.047	0.18
6p	F	H	F	1.9	0.40	5.0
6q		5-nitrofuranyl				
6r	F	H	NO_2			
6s	F	F	NO_2			
6t	F	Cl	OCH_3	0.18	0.055	0.19
6u	F	Cl	OH	1.2	0.50	0.81
6v	F	Cl	$OCH_2C{\equiv}CH$	0.054	0.004	0.054
6w	F	Cl	$OCH(CH_3)CO_2Et$	0.68	0.25	0.83
6x	F	Cl	$OCH_2CO_2CHMe_2$	3.6	0.89	2.4
16	NH-benzoxazinone			7.1	0.15	2.4
17	*N*-propargylbenzoxazinone			1.4	0.18	0.76

[a] See Table 2 for explanation of GR_{80} values.

ide **13** gave a mixture of two products: the expected ether **14** and tricyclic isoxazoloquinoline **15**. Unexpected product **15** arises from displacement of the *o*-fluorine substituent by nitrogen under basic conditions. This ring system has been previously prepared by an intramolecular aza-Wittig reaction (Purwono et al., 1992). The benzoxazine ring was obtained by reduction of **14** to give **16** in 84% yield and subsequently treated with propargyl bromide to afford the target benzoxazinone **17**.

Herbicidal Activity. In general, the 3-aryl-(5-perhaloalkyl)-4-isoxazolecarboxamides exhibited moderate to excellent herbicidal activity, particularly in preemergent tests on broadleaf weeds. Substituents in the 5-position of the isoxazole ring had the most pronounced effect on activity with the greatest activity observed for perhaloalkyl groups CF_2Cl and CF_3 (Table 2). Surprisingly, isoxazoles with other R_1 substitutents with electron withdrawing properties (such as **5j**, $R_1 = CF_2CF_3$) or steric size (**5k**, $R_1 = CHMe_2$) similar to that of the CF_2Cl group did not provide the same levels of herbicidal activity. Even small changes in the number or type of halogen atoms on the R_1 group, such as **5i** ($R_1 = CF_2H$) or **5l** ($R_1 = CCl_3$), provided compounds which were significantly less active in these tests. In comparisons of a large number of CF_2Cl- and CF_3-substituted 4-isoxazolecarboxamides, the CF_2Cl group afforded greater activity in nearly every case; however, the degree of difference between these two substituents varied greatly.

Aromatic phenyl ring substituents also played a role in activity, and a variety of substituents maintain good herbicidal activity (Table 3). The most active compounds had a substituent in the para position (R_4), particularly a halogen or electron withdrawing group such as CF_3. Thus, **6k**, **6p**, and **6r** ($R_4 = H$) which have no para substituent are much weaker than most of the para substituted compounds. Compound **6j**, which has a single fluorine atom in the para position, is at least 10 times more active than *o*-fluoro **6k**. The nitro compounds are also weaker regardless of the position of the nitro group. While *p*-chloro **6b** and 2,4-difluoro **6e** have excellent activity on all three weed species (GR_{80}s < 0.2 lb/acre), the nitro analogs **6i** and **6s**, respectively, have very little preemergent activity. *p*-Nitro compounds **6l** and **6m** are more active than the ortho- or meta-substituted nitro compounds but still weaker than *p*-halophenylisoxazoles **6b**–**6e**. Both *p*-methyl **6g** and *p*-methoxy **6n** provided control, particularly of velvetleaf, but were also less active than the halogen analogs. The furanylisoxazole **6q** was inactive in our tests. For **6h** and **6m**, substituents were tolerated in the 5-position of the phenyl ring (R_5) without having much effect on herbicidal activity compared to **6b** and **6l**, respectively. On the basis of this observation, we investigated the effect of 5-position substitution on the most active halophenylisoxazole, **6c**. Introduction of the methoxy group to give **6t** (R_5 = OMe) did not significantly affect herbicidal activity. Although activity against velvetleaf was good, the morning glory and barnyard grass activity was reduced. However, **6v** (R_5 = propargyloxy) gave excellent activity on all three weed species and was the most active compound of this series. Similar substitution patterns have been reported as preferred candidates in the *N*-phenylimide class of herbicides (Hamada et al., 1989). The benzoxazinyl-isoxazoles **16** and **17** were also prepared but, unlike their *N*-phenylimide counterparts (Yosida et al., 1991), did not provide more active preemergent herbicides.

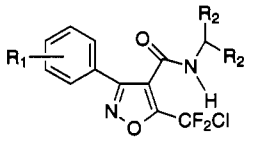
The 4-position of the isoxazole ring was also investigated as a readily accessible means to enhance herbicidal activity (Table 4). A surprisingly great difference was observed for the various carbonyl derivatives, with the primary and secondary carboxamides giving consistently better activity. The ethyl and methyl esters, such as **2m**, were much less active than the corresponding primary amide, and the carboxylic acids **3a**–**3cc** were, with rare exception, completely inactive at test

Table 4. Herbicidal Activity of 3-Aryl-5-(difluorochloromethyl)-4-isoxazolecarboxylic Acid Derivatives 7 (R_1 = CF_2Cl; R_5 = H)

				preemergent GR_{80}[a]			postemergent GR_{80}		
compd	R_2	R_3	R_4	MG	VL	BG	MG	VL	BG
2m	OCH_3	H	Cl	0.77	0.16	1.0	5.0	5.7	80
4m	Cl	H	Cl	5.0	4.2	8.0	5.7	10	16
6b	NH_2	H	Cl	0.146	0.057	0.149	0.135	0.128	2.2
7a	$NHCH_3$	H	Cl	0.25	0.16	0.19	5.0	0.14	4.2
7b	$NHCH_2CH_2CH_2CH_3$	H	Cl	0.45	0.23	0.17	0.41	0.026	0.81
7c	$N(CH_3)_2$	H	Cl	3.7	3.0	4.2			
6c	NH_2	F	Cl	0.095	0.080	0.060	0.085	0.126	1.44
7e	$NHCH_2CH_3$	F	Cl	0.058	0.016	0.050	0.042	0.063	0.85
7f	$NHCH_2CH_2CH_3$	F	Cl	0.051	0.014	0.057	0.16	0.063	1.0
7g	$NHCH_2CH_2CH_2CH_3$	F	Cl	0.10	0.18	0.16	0.13	0.025	3.1
7h	$NHCH_2CH{=}CH_2$	F	Cl	0.055	0.051	0.063	0.047	0.063	0.89
7i	$NHCH_2C{\equiv}CH$	F	Cl	0.29	0.21	0.22			

[a] See Table 2 for explanation of GR_{80} values.

Table 5. Herbicidal Activity of Amino Acid Derivatives of 3-Aryl-5-(difluorochloromethyl)isoxazoles 8



8

				preemergent GR_{80}[a]			postemergent GR_{80}		
compd	R_1	R_2	R_3	MG	VL	BG	MG	VL	BG
8a	4-Cl	$(CH_2)_2SCH_3$	CO_2Et	1.0	0.044	8.0	6.2	0.11	40
8b	4-Cl	CH_3	CO_2Me	1.0	0.20	1.0	0.40	0.039	0.80
8c	4-Cl	H	$(CH_2)_2CO_2Et$	0.65	0.68	0.25	0.016	0.040	0.89
8d	4-Cl	H	CO_2Me	3.0	0.80	0.88	0.40	0.40	0.89
8e	4-Cl	proline	CO_2Et	3.4	3.1	3.1			
8f	2-F,4-Cl	(*R*)-CH_3	CO_2Et	0.063	0.055	0.20	0.18	0.063	0.16
8g	2-F,4-Cl	(*S*)-CH_3	CO_2Et	0.25	2.7	0.41	5.3	0.55	3.1
8h	2-F,4-Cl	H	$(CH_2)_2CO_2Et$	0.22	0.21	0.76	0.044	0.013	16
8i	2-F,4-Cl	H	$CONH_2$	0.13	0.10	0.71	0.13	0.016	0.65
8j	4-Br	H	CH_2CO_2Et	0.72	2.4	0.84	0.053	0.040	3.9
8k	4-Br	H	$(CH_2)_2CO_2Et$	0.50	1.0	0.64	0.016	0.016	1.0

[a] See Table 2 for explanation of GR_{80} values.

rates of 10 lb/acre. The acid chlorides, such as **4m**, were more active than the carboxylic acids but still less active than the corresponding ester or amide derivatives. The postemergent activity against velvetleaf was greater for secondary amides **7b** and **7e**–**7g** compared to the primary amides **6b** and **6c**. In some cases, the secondary amides provided slight enhancements of preemergent activity as seen for **7e** and **7f**.

A number of *N*-acylamino acids **8a**–**8k** were also prepared and found to give good herbicidal activity, particularly in postemergent tests (Table 5). Compounds **8a**–**8e** are derivatives of primary amide **6b** (Table 4). Of these five amino ester derivatives, γ-amino ester **8c** gave the best overall activity and was 10 times more active postemergent than **6b** against morning glory. Three of the four 2-fluoro-4-chlorophenylisoxazoles **8f**–**8i** were more active postemergent than the analogous primary amide **6c**. Again, the γ-amino ester **8h** was the most active against morning glory and velvetleaf. For chiral α-amino acid derivatives, the *R* enantiomer **8f** was more active than its enantiomer **8g** in all tests. This difference was particularly pronounced for velvetleaf, with the *R* enantiomer providing almost 50 times greater preemergent and 9 times greater postemergent activity.

CONCLUSIONS

The results of these studies have demonstrated the herbicidal activity of novel substituted 3-phenyl-5-(haloalkyl)-4-isoxazolecarboxamides. Investigations into the structure–activity requirements show the 4-isoxazolecarboxamides to be the most active of the various possible carbonyl derivatives. The 5-position of the isoxazole ring greatly influenced herbicidal activity, with the difluorochloromethyl group consistently providing the best herbicidal activity. A number of possible phenyl substituents were identified as suitable for good activity; however, the para-substituted and 2,4- and 2,4,5-substituted phenyl rings gave the most active herbicide candidates.

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Supplementary Material Available: The methods of preparation, means of purification, physical constants, percent yield, complete spectral data, and elemental analysis or mass spectral data are provided for all new compounds reported herein (25 pages). Ordering information is given on any current masthead page.

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