Synthesis of Pyrazolecarbonylaminopyridinecarboxamides as Herbicides

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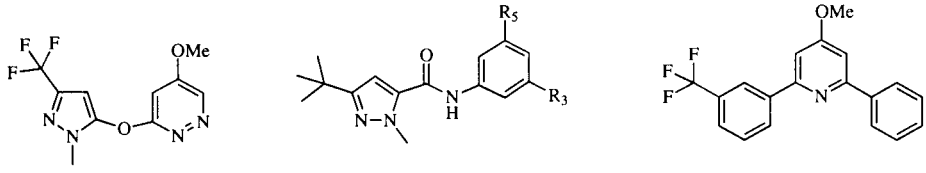
Received November 13, 1997

Target compounds from a herbicide lead area, pyrazolecarboxamides, were selected and synthesized. These targets were chosen based on 1) "structural" similarities of **2a-c** with other known bleaching herbicides, and 2) the structure activity relationship previously established with analogs of the lead compound **2a**. Syntheses of three target compounds were accomplished, two of which involved various transformations and regioselective additions with a pyridine nucleus to afford novel pyridine derivatives. These targets were tested in whole plant assays with the herbicidal data reported.

J. Heterocyclic Chem., **35**, 1493 (1998).

We previously reported the preparation of heterocyclic carboxamides [1,2,3], which in whole plant herbicide assays demonstrated modest preemergent activity against both narrowleaf and broadleaf weeds controlling several weed species at 100 g/ha. The herbicidal activity of the pyrazolecarboxamides exhibited bleaching symptoms which suggest that inhibition of phytoene desaturase may be the mode of action. Preparation of several hundred analogs using a high-speed parallel synthesis approach led to analog **2b**, with a fourfold improvement in unit activity over the initial lead compound **2a** [2]. In an effort to further increase the herbicidal activity, other very specific target analogs were selected on the basis of "structural" similarities of the pyrazolecarboxamides with other classes of bleaching herbicides [4,5,6]. Figure 1 shows pyrazolecarboxamides **2a-c**, with structures **1** and **4** from two other classes of bleachers [4,7,8]. The pyrazolecarboxamides **2a-c** depicted in Figure 1 were selected from the hundreds of analogs prepared and are shown to represent three key compounds with **2a** being the initial lead, **2b** exhibiting an improvement in unit activity, and **2c** having a methoxy substitution on the phenyl ring. In a very simplistic two-dimensional observation, some structural similarities between the pyrazole carboxamides **2a-c** and compounds **1** and **4** were noticed as described by the following: The pyrazolecarboxamides **2a-c** and compound **1** have "structural" similarities in that each has a pyrazole linked to an aromatic ring, and in both compounds, the pyrazoles are linked through the 5-position each having the *N*-methyl, with a 3-trifluoromethyl group on compound **1** and a 3-*t*-butyl group on compounds **2a-c**. Also, the pyrazolecarboxamide **2c** has the 5-methoxy in the same position (*meta* relative to the pyrazole) as the methoxy on compound **1**.

The pyrazolecarboxamides **2a-c** and compound **4** have "structural" similarities in that compound **4** has a *m*-trifluoromethylphenyl linked directly to a pyridine which occupies the same region as the *t*-butylpyrazole of **2a-c**. Compound **4** has a phenyl ring directly linked to the pyridine while compound **2a** has the phenyl ring at the same position linked through a carbonyl. The pyrazolecarboxamide **2c** has the methoxy *meta* to the pyrazole linkage and compound **4** has the methoxy *meta* to the *m*-trifluoromethylphenyl group.



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2a R_3 = COPh, R_5 = H
2b R_3 = $CONEt_2$, R_5 = H
2c R_3 = H, R_5 = OMe

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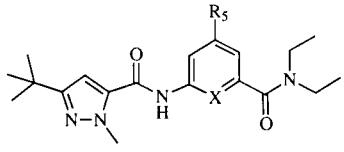
Figure 1.

Based on the discussion above and the structure activity relationship established with the previously prepared pyrazolecarboxamide analogs [2], three target compounds were selected for preparation as shown in Figure 2. Two of these targets have the methoxy group at the 5-position (R_5 = OMe), one with the nitrogen at the 2-position (X = N) and the other with a carbon at the 2-position (X = C) both possessing the diethylamide moiety at the 3-position. The diethylamide was selected based on the fact that the



targets

R_5 = OMe, X = C
R_5 = OMe, X = N
R_5 = H, X = N

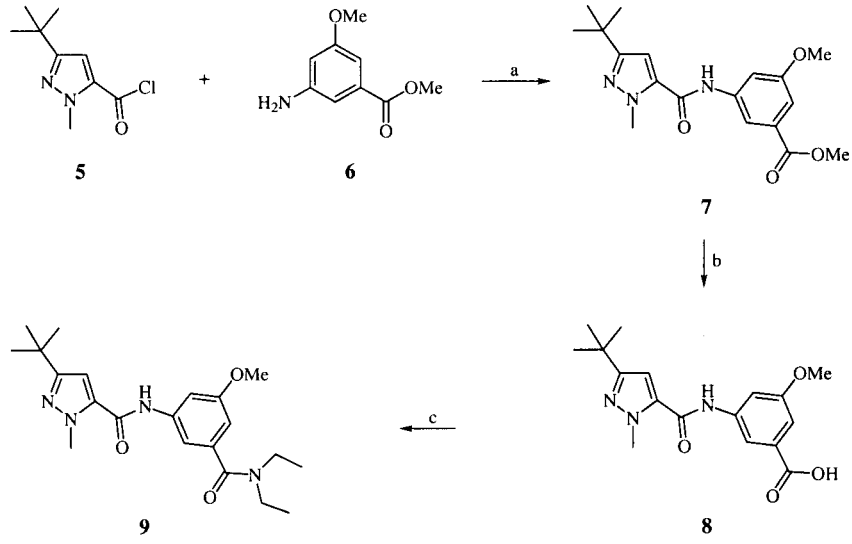
Figure 2.

analogs with this substitution demonstrated the more favorable herbicidal activity. Another target selected contains the nitrogen at the 2-position (X = N) and the diethylamide at the 3-position without the 5-methoxy (R_5 = H). Two of the targets have nitrogen in the 2-position (X = N) which was desirable due to the fact that compounds **1** and **4** have a nitrogen in the same position.

The first synthesis was directed at placing the methoxy at the 5-position on the phenyl ring with the diethylamide at the 3-position. The straightforward synthesis is shown in Scheme 1 in which 3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carbonyl chloride **5** was reacted with methyl 5-amino-3-methoxybenzoate **6** to afford the methyl ester 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methoxybenzoic acid **7**. Compound **7** was hydrolyzed to the carboxylic acid **8** using potassium carbonate in a mixture of methanol and water. The acid **8** was converted to the acid chloride using oxalyl chloride followed by addition of diethylamine to afford the target compound *N*-[3-[(diethylamino)carbonyl]-5-methoxyphenyl]-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxamide **9**.

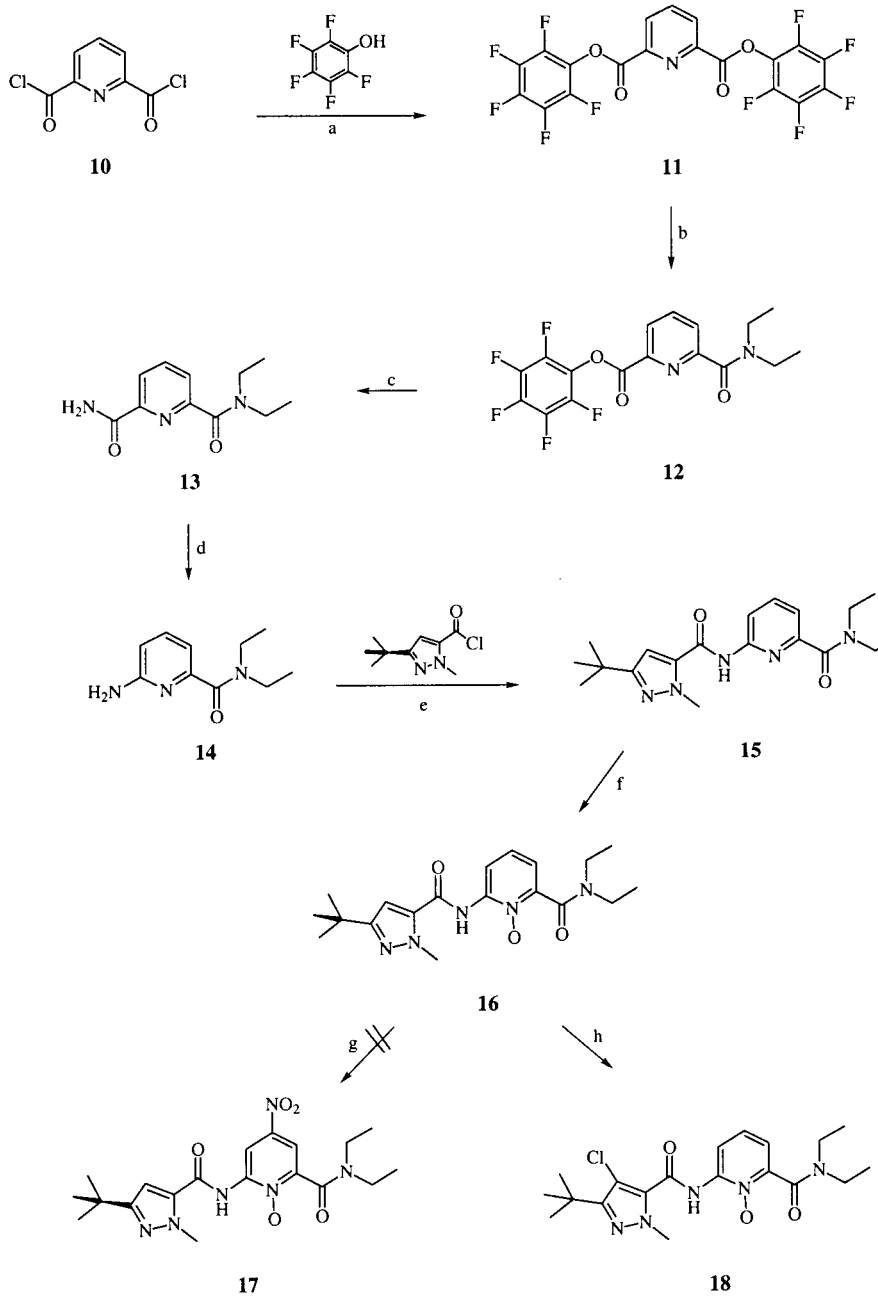
The synthesis in Scheme 2 was directed at preparing the two compounds with nitrogen at the 2-position. 2,6-Pyridinedicarbonyl dichloride **10** was used as the starting material, allowing for the nitrogen to be in place at the start of the synthesis. The pyridine **10** was first reacted with an equimolar solution of diethylamine and ammonium hydroxide with the expectation of producing a possible 50% of the desired product containing both the primary amide and diethylamide. However, less than favorable results were obtained resulting with the bis-diethylamide as the major product. This led to the preparation of a bis-activated ester of the pyridine. The pyridinedicarbonyl dichloride **10** was reacted with pentafluorophenol in dichloromethane to afford bis(pentafluorophenyl) ester 2,6-pyridinedicarboxylic acid **11**. The next step was to prepare the mono-amide/pentafluorophenyl ester pyridine. The choice of amide to prepare first was the diethylamide due to the reactivity and easiblity in measuring precise quantities for the reaction. Using the optimized conditions, the bis(pentafluorophenyl) ester **11** was cooled in tetrahydrofuran to 0° and one half of an equivalent of diethylamine in tetrahydrofuran was added dropwise. After stirring at room temperature for 30 minutes, gc/ms showed a ratio of 85:15 of the mono-diethylamide **12** to bis-diethylamide. It was noted during silica gel isolation that compound **12** was unstable and was used immediately in the

Scheme 1



a) Pyridine, CH_2Cl_2, 17 hours, (61% yield); b) K_2CO_3, MeOH/H_2O, 15 hours, 88%; c) $(COCl)_2$, CH_2Cl_2, $HNEt_2$, Pyridine, 14 hours, 85%.

Scheme 2



a) Triethylamine, CH_2Cl_2, 2 hours, (70% yield); b) Tetrahydrofuran, $HNEt_2$, 0° then r.t. 2 hours, 52%; c) Tetrahydrofuran, NH_4OH, 0.5 hour, 74%; d) NaOH, Br_2, H_2O, 0° then 75° 10 minutes; e) CH_2Cl_2, Pyr., 14 hours (d & e 78%); f) H_2O_2, AcOH, 90° 14 hours, 61%; g) fum. HNO_3 or HNO_3/H_2SO_4, r.t.; h) SO_2Cl_2, CH_2Cl_2, 2 hours, 87%.

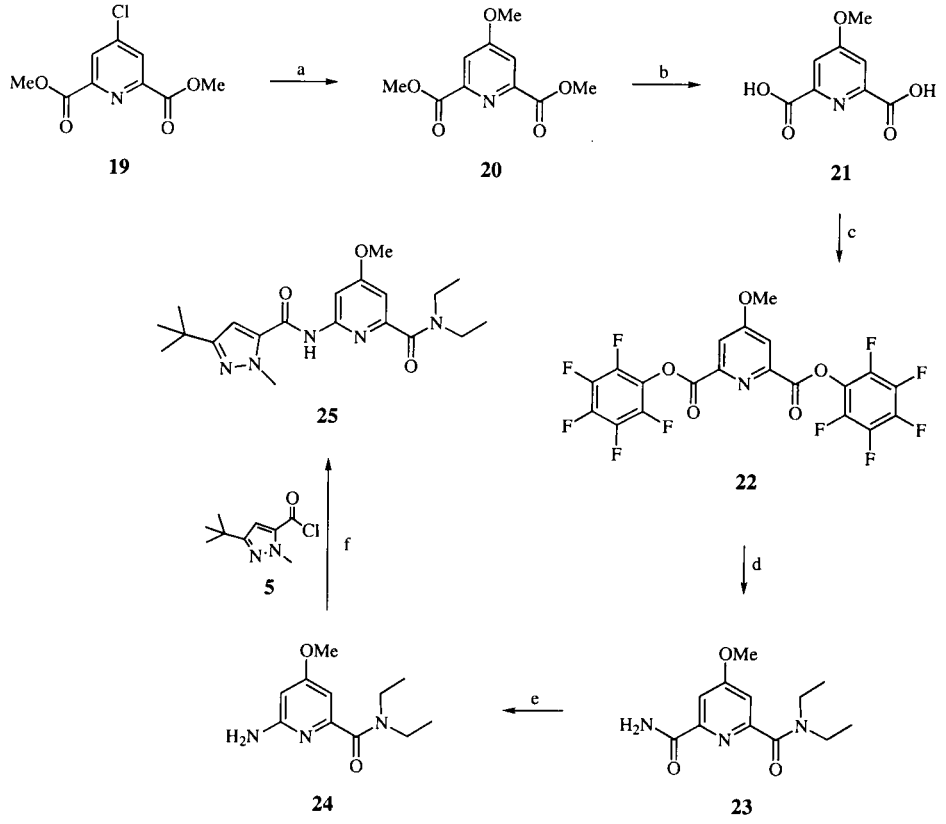
next step. A solution of the pentafluorophenyl ester 6-[(diethylamino)carbonyl]-2-pyridinecarboxylic acid **12** was treated with ammonium hydroxide to afford pyridine **13** containing both the primary amide and diethylamide. It was found that compound **13** is extremely water soluble and was purified by recrystallization from ether. A Hoffman rearrangement [9] was performed on *N,N*-diethyl-2,6-pyridinedicarboxamide **13** to afford the 6-amino-*N,N*-diethyl-2-pyridinecarboxamide **14**. The crude 6-aminopyridine **14** was reacted with the pyrazole acid chloride to afford the desired target compound 6-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]-carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide **15** possessing the nitrogen in the 2-position.

It was thought that activation of the 5-position of the pyrazolecarboxamide followed by displacement with

methoxide would afford the remaining target compound [10]. In an effort to attempt this, compound **15** was reacted with hydrogen peroxide in acetic acid to afford 6-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]-amino]-*N,N*-diethyl-2-pyridinecarboxamide 1-oxide **16**. Nitration of pyridine 1-oxide **16** using fuming nitric acid or a mixture of nitric acid and sulfuric acid failed at room temperature. Chlorination using sulfuryl chloride only resulted in chlorinating the 4-position of the pyrazole ring to afford 6-[[[4-chloro-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide 1-oxide **18.**

The di-acid **22** was not purified and converted to the acid chloride using oxalyl chloride followed by the addition of pentafluorophenol to afford the bis(pentafluorophenyl) ester 4-methoxy-2,6-pyridinedicarboxylic acid **22**. Using the same reaction conditions from the previous synthesis, the bis(pentafluorophenyl) ester **22** was reacted with diethylamine to afford the pentafluorophenyl ester 6-[(diethylamino)carbonyl]-4-methoxy-2-pyridinecarboxylic acid in greater than 95% purity by gc. The diethylamide/ester pyridine was not isolated and directly treated with ammonium hydroxide to afford the *N,N*-diethyl-4-methoxy-2,6-pyridinedicarboxamide **23**. A Hoffman

Scheme 3



a) NaOMe, MeOH, reflux 2 hours, (98% yield); b) K_2CO_3, MeOH/H_2O, 18 hours; c) $(COCl)_2$, CH_2Cl_2, 14 hours, then C_6F_5OH, Triethylamine, Tetrahydrofuran, 6 hours; d) Tetrahydrofuran, $HNEt_2$, 0° then r.t. 1 hour, then Tetrahydrofuran, NH_4OH, 12 hours (22% from **20**); e) NaOH, Br_2, H_2O, 0° then 75° 25 minutes, 100%; f) CH_2Cl_2, Pyr., 14 hours, 70%.

It was decided to place the methoxy on the pyridine ring in the beginning of the synthesis as is shown in Scheme 3. Preparation of dimethyl 4-chloro-2,6-pyridinedicarboxylate **19** was prepared according to Markees *et al.* [11]. Displacement of the chlorine was achieved using sodium methoxide in methanol to afford dimethyl 4-methoxypyridine-2,6-dicarboxylate **20**. Compound **20** was hydrolyzed to 4-methoxy-2,6-pyridinedicarboxylic acid **21** using potassium carbonate in a mixture of methanol and water. rearrangement with **23** yielded 6-amino-*N,N*-diethyl-4-methoxy-2-pyridinecarboxamide **24**, which was reacted with pyrazole acid chloride **5** to afford the desired target compound 6-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-4-methoxy-2-pyridinecarboxamide **25**, which contains the nitrogen in the 2-position and the methoxy at the 5-position.

The three target compounds **9**, **15**, and **25** were tested along with the compounds **2a-c** in an expanded preemer-

Table 1

Preemergent Whole Plant Herbicide Assay Results

Compound	Abuth	Solni	Sorha	Amare	Pandi	Cheal	Sorvu	Conar	Brapp	Porol	Digsa
2a	*	300	*	300		300	*		100	300	100
2b	300	300	*	100	300	30	*	300	*	100	300
2c			*	*	*	*	*			300	*
9	*	*	*	100	*	100				300	*
15		300	*	30		100	*	*			*
25		*		*		300					

gent whole plant herbicide assay and the results are shown in Table 1. The assay contained plant species usually regarded as weeds which were treated at 300, 100, 30, and 10 g/ha. Approximately 14 days after planting and treating, the plants were observed and the results recorded. The number listed is the lowest rate at which 80% weed control was obtained. Where activity was evident but was not 80% control at the highest rate, an * was entered. The plant species are identified by letter headings printed above the columns according to the following legend: Abuth-velvetleaf, Solni-black nightshade, Sorha-seedling johnsongrass, Amare-redroot pigweed, Pandi-fall panicum, Cheal-common lambsquarters, Sorvu-shattercane, Conar-field bindweed, Brapp-broadleaf signalgrass, Porol-common purslane, Digsa-large crabgrass. Of the targets prepared, compounds **9** and **15** were comparable to each other in overall activity while compound **25** was the least active. None of the targets had activity comparable to the lead **2a** or **2b**. As a result, these targets (cores) were not selected for high-speed parallel synthesis for analog preparation.

In summary, the syntheses of target compounds were successfully prepared. Two of the targets, compounds **9** and **15**, were prepared from a multistep synthesis involving various transformations and regioselective additions with a pyridine nucleus to afford novel pyridine derivatives. The three targets were tested in a whole plant assay and some herbicidal activity was observed, but not at the level to warrant further investigation.

EXPERIMENTAL

Melting points were determined with a Mettler PF62 capillary melting point apparatus and are uncorrected. The ^{1}H, ^{13}C, ^{19}F nuclear magnetic resonance spectra were recorded using a Bruker WM-360 and Varian XL-400 NMR spectrometers. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Sample purity was determined by glc analysis on a Varian 3400 gas chromatograph utilizing a capillary column (0.53 mm interdiameter, DB-1 bonded phase, 1.5 micron film thickness, 30 meters). Normally, a temperature program from 100° to 300° at 15°/minutes was employed. Column chromatography was performed on a Waters preparative liquid chromatography Model 500 using silica gel columns. The gc/ms was performed using a 5890 Hewlett Packard gas chromatograph and a Hewlett Packard 5970 Series Mass Selective Detector. Reported yields are unoptimized with emphasis on purity of products rather than quantity.

3-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methoxybenzoic Acid, Methyl Ester (**7**).

Pyridine (0.26 g, 3.28 mmoles) was added to a solution of 3-*t*-butyl-1-methyl-1*H*-pyrazole-5-carbonyl chloride (**5**) (0.67 g, 3.33 mmole) and methyl 5-amino-3-methoxybenzoate (**6**) (0.50 g, 2.75 mmoles) in dichloromethane (15 ml). After stirring at room temperature 17 hours the solvent was removed and the residue was stirred with ether and water. The mixture was washed with water, 3% aqueous hydrochloric acid, water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to afford the crude product. The product was purified by column chromatography (30% ethyl acetate-hexane) to afford 0.70 g (61%) of a yellow solid of **7**, mp 149-150°; ^{1}H nmr (deuteriochloroform): ppm 1.38 (s, 9H), 3.85 (s, 3H), 3.91 (s, 3H), 4.17 (s, 3H), 6.64 (s, 1H), 7.35 (t, 1H), 7.64 (t, 1H), 7.70 (t, 1H), 8.30 (bs, 1H).

Anal. Calcd. for $C_{18}H_{23}O_4N_3$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.50; H, 6.65; N, 12.10.

3-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methoxybenzoic Acid (**8**).

Potassium carbonate (1.6 g, 11.5 mmoles) was added to a solution of methyl ester 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methoxybenzoic acid (**7**) (0.50 g, 1.4 mmoles) in a 2:1 mixture of methanol/water. The solution stirred at room temperature for 15 hours. The solution was poured over ice/hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent was removed to give 0.41 g (88%) of a white solid of **8**, mp >275°; ^{1}H nmr (deuteriochloroform): ppm 1.28 (s, 9H), 3.76 (s, 3H), 4.00 (s, 3H), 6.88 (s, 1H), 7.17 (t, 1H), 7.67 (t, 1H), 7.84 (t, 1H), 8.86 (s, 1H).

Anal. Calcd. for $C_{17}H_{21}O_4N_3$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.54; H, 6.38; N, 12.65.

N-[3-[(Diethylamino)carbonyl]-5-methoxyphenyl]-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxamide (**9**).

To 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methoxybenzoic acid (**8**) (0.10 g, 0.30 mmole) in dichloromethane (20 ml) was added oxalyl chloride (0.19 g, 1.5 mmoles) followed by a drop of dimethylformamide. After stirring at room temperature for 3 hours the solvent was removed to afford the acid chloride. The acid chloride was dissolved into dichloromethane (20 ml) and diethylamine (43.8 mg, 0.60

mmole) was added followed by pyridine (23.7 mg, 0.30 mmole). The solution stirred at room temperature for 14 hours. A polyamine polymer [2] (2.36 meq/g) (254 mg, 0.60 mmole) was added and stirred for 15 minutes. The solution was filtered and the resin was rinsed with dichloromethane, tetrahydrofuran (butylated hydroxytoluene free), and dichloromethane until no more uv activity was seen in the eluent. The solvent was removed to give 0.098 g (85%) of a white solid of **9**, mp 188-189°; ^{1}H nmr (deuteriochloroform): ppm 1.18 (bq, 3H), 1.29 (bq, 3H), 1.39 (s, 9H), 3.33 (bt, 2H), 3.58 (bt, 2H), 3.85 (s, 3H), 4.19 (s, 3H), 6.64 (m, 1H), 6.69 (s, 1H), 6.98 (t, 1H), 7.45 (t, 1H), 8.47 (bs, 1H).

Anal. Calcd. for $C_{21}H_{30}O_3N_4$: C, 65.26; H, 7.82; N, 14.50. Found: C, 65.29; H, 7.75; N, 14.34.

Bis(pentafluorophenyl) Ester of 2,6-Pyridinedicarboxylic Acid (**11**).

Triethylamine (9.9 g, 97.6 mmoles) was added to a solution of 2,6-pyridinedicarbonyl dichloride (**10**) (10.0 g, 49.0 mmoles) and pentafluorophenol (18.0 g, 97.8 mmoles) in dichloromethane at 0° (ice bath). After complete addition, the solution stirred at room temperature for 2 hours. The solvent was removed and the residue was dissolved into ethyl acetate. The resultant organic layer was washed with 2 *N* hydrochloric acid, dried over magnesium sulfate, filtered and the solvent was removed to give 17.2 g (70%) of a white solid of **11**, mp 204-206°; ^{1}H nmr (deuteriochloroform): ppm 8.29 (t, 1H, J = 7.8 Hz), 8.62 (d, 2H, J = 7.8 Hz).

Anal. Calcd. for $C_{19}H_3O_4N_1F_{10}$: C, 45.71; H, 0.61; N, 2.81. Found: C, 45.54; H, 0.65; N, 2.96.

6-[(Diethylamino)carbonyl]-2-pyridinecarboxylic Acid, Pentafluorophenyl Ester (**12**).

A solution of diethylamine (72.8 mg, 10.0 mmoles) in tetrahydrofuran (30 ml) was added to a solution of bis(pentafluorophenyl) ester of 2,6-pyridinedicarboxylic acid (**11**) (5.0 g, 10.0 mmoles) in tetrahydrofuran (75 ml) at 0° (ice bath). Upon complete addition, the solution stirred at room temperature for 30 minutes. The solvent was removed to give the crude product. The product was purified by column chromatagraphy (50% ethyl acetate-hexane) to give 2.0 g (52%) of a white solid of **12**. The product was not stable and carried on immediately.

N,N-Diethyl-2,6-pyridinedicarboxamide (**13**).

A solution of ammonium hydroxide (50.0 mg, 8.5 mmoles) in tetrahydrofuran (30 ml) was added to a solution of the pentafluorophenyl ester 6-[(diethylamino)carbonyl]-2-pyridinecarboxylic acid (**12**) (2.0 g, 5.1 mmoles) in tetrahydrofuran (30 ml). Upon complete addition, the solution stirred at room temperature for 30 minutes. The solvent was removed to give the crude product. The product was purified by recrystallization from ether to give 0.83 g (74%) of a white solid of **13**; ^{1}H nmr (deuteriochloroform): ppm 1.01 (t, 3H), 1.16 (t, 3H), 3.19 (q, 2H), 3.45 (q, 2H), 7.67 (m, 1H), 8.07 (m, 2H), 8.84 (bs, 1H).

6-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide (**15**).

Bromine (68.5 mg, 4.3 mmoles) was added dropwise to a 2.5 *N* sodium hydroxide solution (7.9 ml, 19.7 mmoles) at 0° (ice bath). Upon complete addition, the solution stirred at 0° for 5 minutes followed by addition of *N,N*-diethyl-2,6-pyridinedicarboxamide (**13**) (73.0 mg, 3.3 mmoles) in small portions maintaining a temperature of 0°. The mixture stirred at 0° for 10 minutes, and was heated to 75° for 15 minutes. The solution was cooled to room temperature and acidified with acetic acid, made basic with 2.5 *N* sodium hydroxide, and extracted with dichloromethane. The solvent was removed to give the crude product 6-amino-*N,N*-diethyl-2-pyridinecarboxamide (**14**) (63.6 mg, 3.3 mmoles) which was dissolved into dichloromethane with 3-*t*-butyl-1-methyl-1*H*-pyrazole-5-carbonyl chloride (**5**) (86.0 mg, 4.2 mmoles) followed by addition of pyridine (33.8 mg, 4.2 mmoles). The solution stirred at room temperature for 14 hours. The organic layer was washed with water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to give the crude product. The product was purified by preparative thin layer chromatagraphy (50% ethyl acetate-hexane) to give 82.7 mg (78%) of a white solid of **15**, mp 159-160°; ^{1}H nmr (deuteriochloroform): ppm 1.20 (t, 3H), 1.33 (t, 3H), 1.38 (s, 9H), 3.36 (q, 2H), 3.62 (q, 2H), 4.22 (s, 3H), 6.61 (s, 1H), 7.28 (dd, 1H), 7.87 (t, 1H), 8.34 (dd, 1H), 8.38 (bs, 1H).

Anal. Calcd. for $C_{19}H_{27}O_2N_5$: C, 63.84; H, 7.61; N, 19.59. Found: C, 64.03; H, 7.46; N, 19.84.

6-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide 1-Oxide (**16**).

Hydrogen peroxide 30% (0.35 g, 3.0 mmoles) and 6-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide (**15**) (0.55 g, 1.54 mmoles) were stirred in acetic acid for 14 hours at 90°. The solution was extracted with dichloromethane and the organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was removed to give the crude product. The product was purified by column chromatagraphy (60% ethyl acetate-hexane) to give 0.35 mg (61%) of a yellow solid of **16**; ^{1}H nmr (dimethyl-d_6 sulfoxide); ppm 1.20 (t, 3H), 1.36 (t, 3H), 1.39 (s, 9H), 3.26 (q, 2H), 3.68 (q, 2H), 4.28 (s, 3H), 6.81 (s, 1H), 7.15 (dd, 1H), 7.53 (t, 1H), 8.59 (dd, 1H), 10.73 (bs, 1H).

6-[[[4-Chloro-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide 1-Oxide (**18**).

Sulfuryl chloride (10.9 mg, 0.81 mmole) was added dropwise to a solution of 6-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-2-pyridinecarboxamide 1-oxide (**16**) (27.6 mg, 0.74 mmole) in dichloromethane (20 ml). The solution stirred at room temperature for 2 hours. The solution was poured over ice and extracted with dichloromethane. The organic layer was washed with water, brine, dried over magnesium sulfate, filtered and the solvent was removed to give the crude product. The product was purified preparative thin layer chromotagraphy (60% ethyl acetate-hexane) to give 0.26 g (87%) of a white solid of **18**, mp 154-155°; ^{1}H nmr (deuteriochloroform): ppm 1.18 (t, 3H), 1.33 (t, 3H), 1.45 (s, 9H), 3.26 (q, 2H), 3.66 (q, 2H), 4.20 (s, 3H), 7.12 (dd, 1H), 7.42 (t, 1H), 8.60 (dd, 1H), 11.41 (bs, 1H).

Anal. Calcd. for $C_{19}H_{26}O_3N_5Cl_1$: C, 55.95; H, 6.42; N, 17.17. Found: C, 55.76; H, 6.43; N, 17.08.

Dimethyl 4-Methoxy-2,6-pyridinedicarboxylate (**20**).

A sodium methoxide solution in methanol (25%) (5.5 ml, 24.0 mmoles) was added to a solution of dimethyl 4-chloro-2,6-pyridinedicarboxylate (**19**) (5.0 g, 21.8 mmoles) in methanol (50 ml). The solution stirred under reflux for 2 hours. The solvent was removed and the solid was stirred in ether and filtered to give 4.80 g (98%) of a white solid of **20**, mp 125-126° in agreement

with reported mp 125-127°; [11] ^{1}H nmr (dimethyl-d_6 sulfoxide); ppm 3.89 (s, 6H), 3.96 (s, 3H), 7.72 (s, 2H).

4-Methoxy-2,6-pyridinedicarboxylic Acid (**21**).

Potassium carbonate (20.0 g, 0.145 mole) was added to a solution of dimethyl 4-methoxy-2,6-pyridinedicarboxylate (**20**) (4.9 g, 21.8 mmoles) in a 2:1 mixture of methanol/water. The solution stirred at room temperature for 18 hours. The solution was poured over ice/hydrochloric acid and the solvent was removed to give a white solid of **21** which also contained potassium chloride. This crude product was carried on to the next step; ^{1}H nmr (dimethyl-d_6 sulfoxide); ppm 3.94 (s, 3H), 7.68 (s, 2H).

N,N-Diethyl-4-methoxy-2,6-pyridinedicarboxamide (**23**).

Oxalyl chloride (27.6 g, 218 mmoles) and 4-methoxy-2,6-pyridinedicarboxylic acid (**21**) (21.8 mmoles) are stirred in dichloromethane (20 ml) followed by a drop of dimethylformamide. After stirring at room temperature for 14 hours, the solvent was removed to afford the acid chloride. The acid chloride was dissolved into tetrahydrofuran and pentafluorophenol (8.0 g, 43.4 mmoles) was added followed by triethylamine (4.35 g, 43.0 mmoles). The solution stirred at room temperature for 6 hours. The solution was cooled to 0°, and diethylamine was added in increments of 0.198 mg in tetrahydrofuran (1 ml) (total 1.18 g, 16.1 mmoles). The solution stirred at room temperature for 1 hour, the solvent was removed and the residue was dissolved into ethyl acetate. The resultant organic layer was washed with 2 *N* hydrochloric acid, the solvent was removed and the residue was dissolved into tetrahydrofuran. Ammonium hydroxide (1.5 g, 25.5 mmoles) was added and the solution stirred at room temperature for 12 hours. The solvent was removed to give the crude product. The product was purified by column chromatagraphy (100% ethyl acetate) to give 1.19 g (22%) of a white solid of **23**, mp 184-185°; ^{1}H nmr (deuteriochloroform): ppm 1.29 (bq, 3H), 1.30 (bq, 3H), 3.50 (bt, 2H), 3.50 (bt, 2H), 3.98 (s, 3H), 5.90 (bs, 2H), 7.24 (d, 1H), 7.82 (d, 1H).

Anal. Calcd. for $C_{12}H_{17}O_3N_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.30; H, 6.72; N, 16.46.

6-Amino-*N,N*-diethyl-4-methoxy-2-pyridinecarboxamide (**24**).

Bromine (41.5 mg, 2.6 mmoles) was added dropwise to a 2.5 *N* sodium hydroxide solution (4.8 ml, 12.0 mmoles) at 0° (ice bath). Upon complete addition, the solution stirred at 0° for 5 minutes followed by the addition of *N,N*-diethyl-4-methoxy-2,6-pyridinedicarboxamide (**23**) (500.0 mg, 2.0 mmoles) in small portions maintaining a temperature of 0°. The mixture stirred at 0° for 10 minutes, and was heated to 75° for 25 minutes. The solution was cooled to room temperature and acidified with acetic acid, made basic with 2.5 *N* sodium hydroxide, and extracted with dichloromethane. The solvent was removed to give 0.44 g (100%) of an orange oil of **24**; ^{1}H nmr (deuteriochloroform): ppm 1.20 (bq, 3H), 1.20 (bq, 3H), 3.41 (bt, 2H), 3.59 (bt, 2H), 3.90 (s, 3H), 5.78 (bs, 2H), 6.25 (d, 1H), 6.45 (d, 1H).

6-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]-*N,N*-diethyl-4-methoxy-2-pyridinecarboxamide (**25**).

Following the same procedure described for compound **15**, 3-*t*-butyl-1-methyl-1*H*-pyrazole-5-carbonyl chloride (**5**) (37.0 mg, 1.8 mmoles), compound **24** (6-amino-*N,N*-diethyl-4-methoxy-2-pyridinecarboxamide) (37.0 mg, 1.6 mmoles), and pyridine (145.7 mg, 1.8 mmoles) were used to give 0.45 g (70%) of a yellow solid of **25**, mp 141-142°; ^{1}H nmr (deuteriochloroform): ppm 1.20 (t, 3H), 1.33 (t, 3H), 1.37 (s, 9H), 3.38 (q, 2H), 3.61 (q, 2H), 4.00 (s, 3H), 4.22 (s, 3H), 6.73 (bs, 1H), 6.83 (dd, 1H), 8.01 (d, 1H), 8.81 (bs, 1H).

Anal. Calcd. for $C_{20}H_{29}O_3N_5$: C, 62.00; H, 7.54; N, 18.07. Found: C, 62.15; H, 7.49; N, 18.26.

Acknowledgement.

The author thanks Martin D. Mahoney, Daniel M. Krupa, and Robert L. Merz for the biological evaluation.

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