Organic Process Research & Development **2003**, *7*, 267–271

Process Optimization and Synthesis of 3-(4-Fluorophenyl)-4,5-dihydro-*N*-[4-(trifluoromethyl)phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1*H*-pyrazole-1-carboxamide

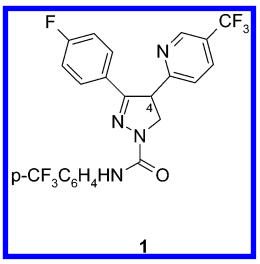
James M. Renga,* Kevin L. McLaren, and Michael J. Ricks

Discovery Process Research, Dow AgroSciences, 9410 Zionsville Road, Indianapolis, Indiana 46268-1053, U.S.A.

A convenient, high-yielding synthesis of the insecticide 3-(4-fluorophenyl)-4,5-dihydro-*N*-[4-(trifluoromethyl)phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1*H*-pyrazole-1-carboxamide is presented. Attempted methenylation of the 2-pyridylacetophenone, obtained from the alkylation of 4-fluoroacetophenone with 2-chloro-5-trifluoromethylpyridine, under standard Mannich conditions resulted in the formation of a methylene-bridged dimer. In addition, the required 2-pyridylpropenone underwent a rearrangement to an acylhydrazine when subjected to hydrazine in a solvent-dependent process. These side reactions were circumvented by the sequential reaction of bis(dimethylamino)methane, trifluoroacetic acid, hydrazine, and arylisocyanate with the 2-pyridylacetophenone in methylene chloride. This one-pot process for preparing the pyrazoline-1-carboxamide enabled rapid and economical scale-up for field and toxicological studies.

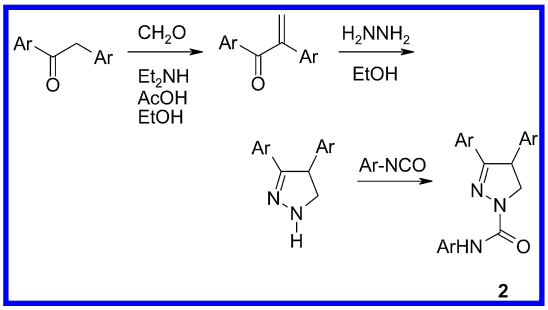
Introduction

3-(4-Fluorophenyl)-4,5-dihydro-*N*-[4-(trifluoromethyl)-phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1*H*-pyrazole-1-carboxamide (**1**) has potent contact and foliar activity against both lepidoptera and orthoptera insects.[1] Extensive SAR studies focused on varying the heterocycle at position 4 resulted in the identification of pyrazoline-1-carboxamide **1** as a potential candidate for commercialization.[2] While the synthesis of 3,4,*N*-tri(substituted)aryl compounds (**2**) is well-documented and proceeds in good yields (Scheme 1),[3,4] the inclusion of a electron-deficient heterocycle in the 4 position brought with it the need to dramatically alter the conditions and reagents used in the diaryl case.[5] Our interest to expand the SAR as well as to scale up active analogues for initial field studies led us to explore in detail the reaction pathway. The results of this process optimization directed toward the large-scale synthesis of **1** are presented.

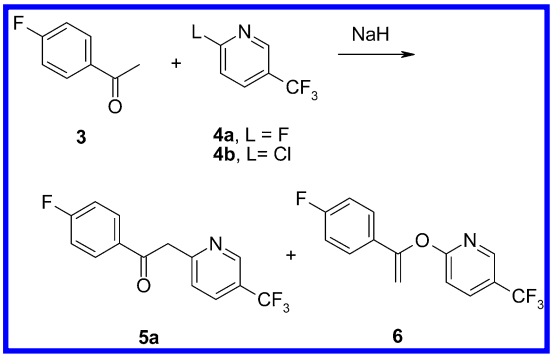


1

Scheme 1



Scheme 2



Results and Discussion

Process Optimization. Alkylation of the enolate of 4-fluoroacetophenone (**3**) with a 2-halopyridine **4** proved to be the route of choice for the synthesis of ethanone **5a** (Scheme 2). We made numerous attempts to minimize the production of the corresponding undesired enol ether **6** by manipulation of the reaction conditions. The impact of changing the rate, the order of addition, the countercation of the enolate, or the temperature had only subtle effects upon the product ratio. However, the choice of solvent had a dramatic effect on the ratio of **5a** to **6** (Table 1). Highly solvating solvents, such as DMSO, promoted reaction at oxygen, while THF enhanced reaction at carbon. Solvents less polar than THF did not offer an advantage due to the substantially longer reaction times required for acceptable

* Author for correspondence. E-mail: jmrenga@dow.com. Telephone: 317-337-3096. Fax: 317-337-3249.

(1) Leonard, P. K.; Hertlein, M. B.; Thompson, G. D.; Paroonagian, D. L. *BCPC Monograph* **1994**, *59*, 67.

(2) (a) McLaren, K. L.; Hertlein, M. B.; Pechacek, J. T.; Ricks, M. J.; Tong, Y. C.; Karr, L. L. Eur. Pat. Appl. 508469; *Chem. Abstr.* **1993**, *118*, 101947. (b) Renga, J. M.; McLaren, K. L.; Pechacek, J. T.; Ricks, M. J.; Tong, Y. C. U.S. Patent 5,324,837; *Chem. Abstr.* **1994**, *121*, 205339. (c) Ricks, M. J.; Tong, Y. C. U.S. Patent 5,338,856; *Chem. Abstr.* **1994**, *121*, 300887.

(3) Neh, H.; Bühmann, U.; Joppien, H.; Giles, D. Ger. Offen. DE 3638631; *Chem. Abstr.* **1988**, *109*, 93002.

(4) Chan, D. M. T.; Stevenson, T. M.; Piotrowski, D. W.; Harrison, C. R.; Fahmy, M. A. H.; Lowe, R. L.; Monaco, K. L.; Reeves, B. M.; Folgar, M. P.; Esrey, E. G *ACS Symp. Ser.* **2002**, *800*(VI), 144.

(5) Fuchs, R.; Gallenkamp, B.; Erdelen, C.; Maurer, F.; Wada, K.; Grosser, R.; Born, L.; Goehrt, A. *Pesticide Science* **1997**, *50*, 333.

10.1021/op025619v CCC: $25.00
Published on Web 04/02/2003

Table 1. **Formation of 5a from 4**

solvent		5a:6[a]
DMSO	**4a**	36:64
THF	**4a**	78:22
THF	**4b**	95:<5
DME	**4b**	98:<2

[a] Determined by GC.

conversion. In general, using DME only improved the yield of **5a** slightly without evidence for substantial reaction at oxygen and proved more useful for the synthesis of analogues.[2]

A change in the leaving group from fluorine to chlorine tended to favor reaction at carbon. Consistent isolated yields of 60−65% of ethanone **5a** were obtained on a 0.1−0.25-mol scale by forming the enolate of **3** prior to adding **4b**. On a 2-mol scale the concurrent addition of **3** and **4b** to a suspension of NaH in THF gave the best results (65% recrystallized yield).

Treatment of **5a** under standard Mannich conditions (Me_2-NH·HCl, $(CH_2O)_n$, EtOH) initially gave the desired Mannich adduct **7a** (Scheme 3). However, this intermediate was highly activated by the presence of the pyridine ring and readily eliminated dimethylamine to form propenone **8a**. The ensuing Michael reaction between **8a** and the enol form of **5a** is more rapid than the Mannich reaction. Essentially only the resulting methylene-bridged dimer **9a** was obtained in 81% yield. This dimerization has not been reported during the formation of diaryl propenones (Scheme 1). While the formation of dimer **9a** is reversible,[6] attempts to regenerate propenone **8a** in situ resulted in a low recovery of material.

Switching to the more reactive formaldehyde equivalent bis(dimethylamino)methane (BDAM)[7] in the presence of acetic anhydride cleanly gave the β-dimethylaminopropanone **7a** at −15 °C. While intermediate **7a** is isolable, adding a second equivalent of acetic anhydride effects elimination in situ to the desired propenone **8a** in 99% crude yield. Unfortunately, the significant amount of dimethylacetamide (DMA) byproduct must be rigorously removed since its presence affects pyrazoline formation in the next step. Attempts to purify **8a** by chromatography resulted in the formation of **9a** presumably from the generation of **5a** via the Michael addition of water followed by a retro Aldol reaction.

Propenones readily react with hydrazine to form pyrazolines (Scheme 1).[3] However, under typical polar conditions (Table 2) the desired pyrazoline **13** was not observed; instead, the major product was the acyl hydrazide **12** (Scheme 3). The selectivity for **12** and **13** was strongly influenced by the properties of the solvent. Polar solvents and basic solvents favored the rearrangement to **12** (Table 2, entries 1−5), while weakly basic solvents (Table 2, entry 6) and acidic solvents (Table 2, entry 10) favored the formation of pyrazoline **13**. While two equivalents of trifluoroacetic acid (TFA) in methylene chloride as a cosolvent were typically sufficient to favor **13a**, neat TFA was required to optimize the formation of **13b**. The analogous rearrangement product was not observed in either ethanol or DMF when a phenyl ring replaced the pyridine ring.

Scheme 3 illustrates a possible explanation for the observed selectivity combined with a proposed mechanism by which the two products are formed. Initially, hydrazine adds in a Michael sense to propenone **8** to give the β-hydrazinopropanone **10**, which readily cyclizes onto the ketone to form the intermediate hydroxypyrazolidine **11**. Under acidic conditions protonation of the hydroxy moiety present on **11** would cause rapid dehydration to the desired pyrazoline **13**. Alternatively, basic conditions would allow the oxygen to undergo a retro aldol-type fragmentation to form the undesired acyl hydrazide **12**. It is believed that polar and highly dielectric solvents favor side-product formation via their ability to separate charge, thereby acting as a general base. It is for this reason that the excessive DMA formed in conjunction with propenone **8** must be thoroughly removed.

Finally, the successful use of TFA as a cosolvent to direct the formation of **13a** arises from the observation that hydroxypyrazolidine **11a** is stable in solution in chlorinated solvents and may be observed by ^{1}H NMR in the absence of TFA.[8] There is no evidence that the two products acyl hydrazide **12a** and pyrazoline **13a** are in equilibrium.[9] Intermediate **13a** was also unstable to ambient conditions[10] and must be acylated immediately with 4-(trifluoromethyl)-phenyl isocyanate to give pyrazoline-1-carboxamide **1**.

One-Pot Synthesis. Although quite functional, the preceding synthesis of pyrazoline-1-carboxamide **1** from ethanone **5a** suffers from several limitations. Isolation and purification of both the unstable propenone **8a** and the pyrazoline **13a** were problematic and resulted in lower overall yields. In addition, a large-scale preparation of pyrazoline-1-carboxamide **1** would require excess reagents to achieve competitive formation of propenone **8a**, the need to remove excess DMA, and the inconvenient use of TFA as a cosolvent. We therefore looked to develop a more efficient sequence that would address these limitations.

We found that the use of acetic anhydride was unnecessary to release the formaldehyde moiety in the Mannich reaction of **5a** with BDAM. Instead the addition of one equivalent of TFA to a solution of **5a** and BDAM in methylene chloride at 0 °C gave β-dimethylaminopropanone **7a**. Anhydrous hydrazine was added, and the reaction was warmed to room temperature to give the pyrazoline **13a**.

The one equivalent of TFA present from the formation of the Mannich adduct **7a** was sufficient to favor the formation of **13a** (Table 2, entry 8). However, the addition of two equivalents of TFA to the TFA salt of **7b** prior to the addition of three equivalents of hydrazine did not fully

(6) A dynamic equilibrium between dimer **9a** and propenone **8a** was demonstrated using a crossover experiment, wherein **9a** was mixed with a differentially substituted ethanone. Scrambling of the substitution under both acid and base conditions was observed by ^{1}H NMR over 24 h.

(7) Takahashi, K.; Shimizu, S.; Ogata, M. *Synth. Commun.* **1987**, *17*, 809.

(8) The NMR of **11a** in either $CDCl_3$ or CD_2Cl_2 was highly complex.

(9) Isolated products **12a** and **13a** were subjected to the reaction conditions which favored formation of the opposite product, (CH_2Cl_2, TFA, H_2NNH_2) and (DMSO, H_2O, H_2NNH_2), respectively. After extended reaction times, neither **12a** nor **13a** showed any interconversion, as determined by ^{1}H NMR.

(10) To avoid oxidative decomposition, the HCl salt can be made and stored at 0 °C.

Scheme 3

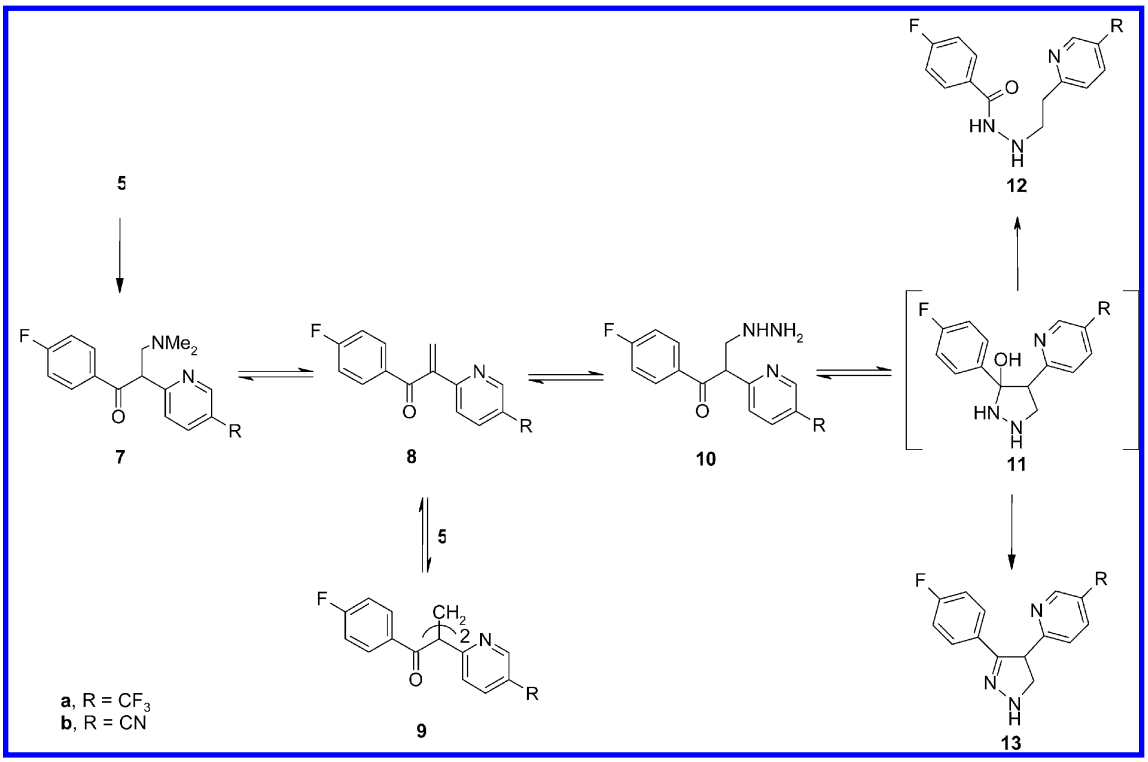


Table 2. **Dependence of 12:13 upon solvent and pK_a**

entry	solvent	pK_a[a]	**12a:13a**[b]	**12b:13b**[b]
1	EtOH	–	95:<5	95:<5
2	DMSO	–	95:<5	95:<5
3	DMF	–	82:18	95:<5
4	Et_3N	11.0	95:<5	–
5	morpholine	8.3	67:33	–
6	pyridine	5.3	8:92	<5:95
7	**7**·AcOH CH_2Cl_2	–	6:94	71:29
8	**7**·TFA CH_2Cl_2	–	2:98	54:46
9	**7**·TFA + 2 equiv TFA CH_2Cl_2	–	–	25:75
10	TFA	0.2	<5:95	<5:95

[a] The listed pK_a values are for those solvents in H_2O. [b] Determined by NMR.

suppress the formation of **12b** (Table 2, compare entries 8 and 9). While the reaction medium was actually basic due to the relatively large amounts of dimethylamine and hydrazine present, sufficient proton transfer occurred to catalyze both the conversion of **7** to β-hydrazinopropanone **10** via propenone **8** and the elimination of water from hydroxypyrazolidine **11**.

On a 1-mol scale, the solution of **13a** was washed, dried, and treated with 4-(trifluoromethyl)phenyl isocyanate to a give a 78% yield of **1** from **5a**.

Conclusions

Through process optimization a high-yielding synthesis of pyrazoline **13a** was achieved without dimerization of ethanone **5a** or significant formation of acylhydrazide **12a**. Five discrete chemical steps were achieved in one pot without the need for isolation of any intermediates. The final carbamoylation step to the pyrazoline-1-carboxamide **1** was accomplished after a simple extraction procedure, again without requiring isolation. The process was used to rapidly and economically prepare samples for field and toxicological studies and to develop the SAR.[2b,c]

Experimental Section

General. All reagents and solvents were used directly as purchased from commercial suppliers. All reactions were conducted under nitrogen. Boiling points and melting points (Pyrex capillary) were uncorrected. ^{1}H NMR spectra were recorded at 200.1 MHz using a Varian XL-200 spectrophotometer or at 400.1 MHz using a Bruker AM-400 spectrophotometer in $CDCl_3$ as solvent, unless otherwise noted. ^{13}C NMR spectroscopy was performed on a Bruker AM-400 operating at 100.6 MHz in $CDCl_3$ as solvent. Elemental analyses and mass spectra (EI 70 meV) were furnished by R. K. Hallberg at the former research facility of the Dow Chemical Company in Walnut Creek, CA.

Preparation of 1-(4-Fluorophenyl)-2-(5-trifluoromethyl-2-pyridyl)ethanone (5a). The mineral oil was removed from 60% NaH/oil (192 g, 4.8 mol) via treatment with hexanes (3 × 400 mL). The resulting solid was slurried with THF (1 L) and heated to 50−55 °C with mechanical stirring. A solution of **3** (304 g, 2.20 mol) and **4b** (363 g, 2.00 mol) in THF (400 mL) was added over 2 h. After an additional 10 h at reflux, the mixture was cooled to 0 °C, and excess NaH was quenched via addition of a solution of MeOH (50 mL) in Et_2O (200 mL) over 1 h. The mixture was partitioned between Et_2O (4 L) and brine (4 L). The organic layer was washed with brine (2 L). The combined aqueous layers were washed with Et_2O (2 × 1 L). The combined Et_2O layers were dried (Na_2SO_4), filtered, and evaporated to a tacky dark

solid (622 g). Kugelrohr (85−95 °C/0.05 mmHg) distillation gave a yellow solid (469 g). Recrystallization (hexane) gave 368 g (65% yield) of **5a** in three crops as yellow needles, mp 82−83 °C. Calcd for $C_{14}H_9F_4NO$: C, 59.37; H, 3.20; N, 4.95. Found: C, 59.43; H, 3.18; N, 4.83.

Ketone: ^{1}H NMR δ 4.53 (s, 2H), 7.13 (dd, 2H, J = 8.5, 8.5), 7.44 (d, 1H, J = 8.0), 7.9 (m, 1H), 8.08 (dd, 2H, J = 5.4, 8.9), 8.8 (m, 1H).

Enol: ^{1}H NMR δ 6.06 (s, 1H), 7.09 (dd, 2H, J = 8.7, 8.7), 7.13 (d, 1H, J = 8.5), 7.79 (dd, 1H, J = 2.4, 7.9), 7.83 (dd, 2H, J = 5.4, 9.0), 8.6 (m, 1H), 14.97 (s, 1H).

2-(5-Cyano-2-pyridyl)-1-(4-fluorophenyl)ethanone (5b). Prepared according to **5a** from **3** (10.0 mL, 11.4 g, 82.4 mmol), 60% NaH (8.2 g, 210 mmol), and 2-chloro-5-cyanopyridine (11.4 g, 82.3 mmol) in THF (90 mL) to give 15.3 g (77%) of **5b** as fine orange needles, mp 166−167 °C. Calcd for $C_{14}H_9FN_2O$: C, 70.00; H, 3.78; N, 11.66. Found: C, 69.62; H, 3.85; N, 11.36.

Enol: ^{1}H NMR δ 6.05 (s, 1H), 7.1 (m, 3H), 7.76 (dd, 1H, J = 2.1, 8.5), 7.82 (dd, 2H, J = 5.4, 8.9), 8.57 (d, 1H, J = 1.8), 10.36 (br s, 1H).

Preparation of 1-(4-Fluorophenyl)-2-(5-trifluoromethyl-2-pyridyl)propenone (8a). A solution of ethanone **5a** (2.7 g, 9.5 mmol) and Ac_2O (2.0 mL, 2.2 g, 21 mmol) in methylene chloride (4 mL) was added to a stirred solution of BDAM (2.2 mL, 1.6 g, 16 mmol) in methylene chloride (4 mL) at −15 °C. After 5 min the mixture was partitioned between 1:1 Et_2O/pentane and H_2O. The organic layer was washed with water (2 × 50 mL), a 5% solution of HCl (50 mL), a saturated NaCl solution (50 mL), and dried ($MgSO_4$) to afford 3.0 g (99% yield) of **8a** as an orange red oil. MS (*m*/*z*) 295(1), 294 (1), 267 (46), 266 (100), 123 (89), 95 (86), 75 (38). ^{1}H NMR δ 5.89 (s, 1H), 6.72 (s, 1H), 7.12 (dd, 2H, J = 8.6, 8.6), 7.62 (d, 1H, J = 8.0), 7.90 (dd, 1H, J = 2.5, 8.3), 7.94 (dd, 2H, J = 5.4, 8.9), 8.8 (m, 1H).

Preparation of 2-(5-Cyano-2-pyridyl)-1-(4-fluorophenyl)propenone (8b). Prepared according to **8a** from ethanone **5b** (3.04 g, 12.7 mmol) to give 2.54 g (80%) of **8b** as a yellow powder, mp 91−92 °C. ^{1}H NMR δ 5.94 (s, 1H), 6.79 (s, 1H), 7.12 (dd, 2H, J = 8.6, 8.6), 7.63 (dd, 1H, J = 0.7, 8.3), 7.9 (m, 3H), 8.82 (dd, 1H, J = 0.7, 2.1). Calcd for $C_{15}H_9FN_2O$: C, 71.42; H, 3.60; N, 11.11. Found: C, 71.79; H, 3.86; N, 11.38. Calcd for $C_{15}H_9F_4NO$: C, 61.02; H, 3.07; N, 4.74. Found: C, 59.99, H, 3.20; N, 4.82.

Preparation of (2*RS*,4*RS*)- and (2*RS*,4*SR*)-1,5-Bis(4-fluorophenyl)-2,4-bis(5-trifluoromethyl-2-pyridyl)-1,5-pentanedione (9a). A solution of ethanone **5a** (2.83 g, 9.99 mmol) in absolute EtOH (20 mL) was treated sequentially with Me_2NH·HCl (0.90 g, 11 mmol) and paraformaldehyde (0.48 g, 15 mmol). The resulting yellow solution was heated at reflux for 1 h causing a colorless solution. Upon cooling a white solid formed. The solid was collected to afford 2.33 g (81% yield) of **9a** as a 1.3:1 mixture of *dl* to *meso* diasteromers. Recrystallization (acetone/hexanes) gave pure *dl* as clear prisms, mp 159−160 °C. ^{1}H NMR δ ***dl***: 2.87 (t, 2H, J = 7.1), 4.97 (t, 2H, J = 7.1), 6.99 (dd, 4H, J_{H-H} = 8.6, J_{H-F} = 8.6), 7.47 (d, 2H, J = 8.2), 7.85 (dd, 2H, J = 2.5, 8.3), 7.89 (dd, 4H, J_{H-H} = 9.0, J_{H-F} = 5.3), 8.7 (m, 2H), ***meso***: 2.60 (ddd, 1H, J = 7.0, 7.4, 14.2), 3.09 (ddd, 1H, J = 7.0, 7.4, 14.2), 4.87 (dd, 2H, J = 7.4, 7.4), 7.05 (dd, 4H, J_{H-H} = 8.6, J_{H-F} = 8.6), 7.36 (d, 2H, J = 8.2), 7.81 (dd, 2H, J = 2.5, 8.3), 7.99 (dd, 4H, J_{H-H} = 8.9, J_{H-F} = 5.4), 8.7 (m, 2H). Calcd for $C_{29}H_{18}F_8N_2O_2$: C, 60.21; H, 3.14; N, 4.84. Found: C, 59.97; H, 3.16; N, 4.90.

Table 2. Entry 3 (Similar Experiments Were Done for Entries 1, 2, 4−6, and 10). To a solution of **8a** (0.55 g, 1.86 mmol) in 3 mL of DMF at room temperature was added hydrazine monohydrate (0.16 mL, 3.3 mmol). After 15 min the mixture was added to 50 mL of EtOAc and was washed with a saturated NaCl solution (3 × 50 mL) and dried ($MgSO_4$) to afford 0.55 g of yellow powder, an 82:18 mixture of **12a**:**13a** by NMR. Recrystallization from EtOAc/hexane gave 0.30 g (49% yield) of **12a** as white plates, mp 101−103 °C. MS (*m*/*z*) 497 (4), 496 (17), 309 (31), 308 (21), 282 (17), 281 (26), 280 (10), 187 (19), 163 (100), 147 (14). ^{1}H NMR δ 3.09 (t, 2H, J = 5.0), 3.38 (t, 2H, J = 5.0), 7.07 (t, 2H, J = 6.5), 7.33 (d, 1H, J = 6.1), 7.72 (m, 2H), 7.82 (dd, 2H, J = 2.1, 6.0), 8.2 (br s, 1H), 8.77 (s, 1H). ^{13}C NMR δ 36.703, 50.869, 115.757, 123.028, 123.872, 124.454, 128.897, 129.186, 133.613, 146.148, 163.929, 164.925, 166.227. Calcd for $C_{15}H_{13}F_4N_3O$: C, 55.05; H, 4.00; N, 12.84. Found: C, 55.15; H, 4.20; N, 12.75.

Table 2. Entry 8 (Similar Experiments Were Done for Entries 7 and 9). To an NMR tube containing **5a** (0.14 g, 0.5 mmol) in 0.6 mL of CD_2Cl_2 cooled in an ice bath was added BDAM (0.068 mL, 0.5 mmol) followed by TFA (0.039 mL, 5 mmol). The tube was warmed to room temperature over 10 min to cleanly give **7a** (^{1}H NMR δ 2.7 (s, 6H), 2.92 (dd, 1H, J = 7.3, 12.6), 3.22 (dd, 1H, J = 7.3, 12.6), 5.27 (t, 1H, J = 6.4), 7.12 (t, 2H, J = 8.5), 7.57 (d, 1H, J = 8.2), 7.9 (d, 1H, J = 8.2), 8.10 (dd, 2H, J = 5.4, 8.8), 8.8 (br s, 1H)). Anhydrous hydrazine (0.047 mL, 1.5 mmol) was added, and after 1.5 h a 2:98 ratio of **12a**:**13a** (^{1}H NMR δ 3.72 (dd, 1H, J = 3.8, 9.8), 4.03 (dd, 1H, J = 9.9, 10.8), 4.80 (dd, 1H, J = 3.7, 10.7), 5.5 (br s, 1H), 6.91 (dd, 2H, J = 8.8, 8.8), 7.39 (dd, 1H, J = 0.9, 8.2), 7.59 (dd, 2H, J = 5.4, 9.0), 7.88 (dd, 1H, J = 2.2, 8.2), 8.75 (dd, 1H, J = 0.9, 2.2)) was observed.

Preparation of 4,5-Dihydro-3-(4-fluorophenyl)-*N*-(4-trifluoromethylphenyl)-4-(5-trifluoromethyl-2-pyridyl)-1*H*-pyrazole-1-carboxamide (1). A solution of TFA (81 mL, 120 g, 1.05 mol) in methylene chloride (400 mL) was added to solution of ethanone **5a** (283 g, 1.00 mol) and of BDAM (143 mL, 107 g, 1.05 mol) in methylene chloride (1 L) at −4 °C over 1 h while maintaining the temperature below 0 °C. After stirring an additional 1 h, anhydrous hydrazine (95.0 mL, 97.0 g, 3.03 mol) was added over 30 min while maintaining the temperature below 10 °C. The mixture was allowed to warm to ambient temperature over 16 h and was added to ice/water (1.2 L). The organic layer was washed with a saturated solution of NH_4Cl (2 × 500 mL), dried ($MgSO_4$), and filtered. A solution of 4-(trifluoromethyl)phenyl isocyanate (187 g, 1.00 mol) in methylene chloride (200 mL) was added to the solution of pyrazoline **13a** over 30 min while maintaining the temperature below 30 °C. After 1 h, the mixture was diluted with Et_2O (1.5 L)

and cooled to 10 °C. The resulting solid was collected by suction filtration to give a total of 389 g (78.4% yield) of white needles, mp 214−215 °C. MS (*m*/*z*) 497 (4), 496 (17), 309 (31), 308 (21), 282 (17), 281 (26), 280 (10), 187 (19), 163 (100), 147 (14). ^{1}H NMR δ 4.24 (dd, 1H, J = 5.3, 11.6), 4.51 (dd, 1H, J = 11.7, 11.7), 5.06 (dd, 1H, J = 5.4, 11.7), 7.02 (dd, 2H, J = 8.6, 8.6), 7.34 (d, 1H, J = 8.2), 7.57 (d, 2H, J = 8.7), 7.6−7.7 (m, 4H), 7.88 (dd, 1H, J = 2.2, 8.2), 8.2 (br s, 1NH), 8.8 (m, 1H). Calcd for $C_{23}H_{15}F_7N_4O$: C, 55.65; H, 3.05; N, 11.29. Found: C, 55.35; H, 3.15; N, 11.34.

Acknowledgment

We thank Virginia W. Miner for conducting the two-dimensional (2-D) NMR analysis and the Analytical Laboratory operated by The University of California, Berkeley for providing the FAB H^+ mass spectrum. We would also like to thank John M. Owen for the optimization of conditions used in the large-scale runs of **1**.

Received for review December 18, 2002.

OP025619V