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A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the Treatment of Cancer

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Abstract:

Urea 3 (BAY 43-9006), a potent Raf kinase inhibitor, was prepared in four steps with an overall yield of 63%. Significant process research enabled isolation of each intermediate and target without chromatographic purification, and overall yield increases >50% were observed compared to those from previous methods. This report focuses on improved synthetic strategies for production of scaled quantities of 3 for preclinical, toxicological studies. These improvements may be useful to assemble other urea targets as potential therapeutic agents to combat cancer.

Introduction

Raf kinase, a downstream effector of *ras*, is a key mediator of signal-transduction pathways from cell surface receptors to the cell nucleus.[1,2] Thus, small-molecule inhibitors of Raf kinase are promising agents for the treatment of hyperproliferative disorders such as cancer. Small-molecule Raf kinase inhibitors that have recently been published in the literature are depicted in Figure 1. Indolinone **1** (GlaxoSmithKline) shows potent and selective Raf kinase inhibition.[3] As part of a medicinal chemistry program directed at selective Raf kinase inhibitors, ureas **2**[4] and **3**[5,6] were identified as potent, orally active inhibitors of Raf kinase, and both showed broad in vivo antitumor activity.

BAY 43-9006 (**3**) is currently undergoing phase I clinical trials. However, the focus of this report is an improved, second-generation synthesis of this excipient that enabled production of scaled quantities of **3** for preclinical, toxicological studies.

Results and Discussion

The retrosynthetic scheme (Scheme 1) details the medicinal-chemistry route, which provided the title compound in 10% overall yield from commercially available **4**.

Many of the steps in this process required chromatographic purification, and it was evident that this route could be streamlined to better support a strategy for scale-up. The development of an improved synthesis afforded urea **3** (**BAY 43-9006**) in four steps without chromatography, and the title compound was delivered cleanly with an overall yield of 63% from **4**.

Starting material **4** was heated in the presence of Vilsmeier reagent[8,9] for 16 h to afford **5** cleanly in 89% yield (Scheme 2). The medicinal-chemistry route allowed this reaction to continue for 21 h, and the extended time induced chlorination of the ring to generate byproduct **5a**[7,8] in 10−15% yield. As a consequence, chromatography was required to isolate **5** in pure form.

Introduction of acid chloride **5** into methanol at room temperature gave ester **6** in 88% yield. A previous protocol generated ester **6** in two separate steps with an overall yield of 46% after recrystallization from hot acetone to remove a dichlorinated impurity (**6a**).[7,8] This sequence was improved by combining the first two steps into a single stage with an overall yield of 78%.

Amidation of **6** with methylamine in tetrahydrofuran (or methanol) proceeded in 97% yield, and “key intermediate” **7** was isolated as pale-yellow crystals after its crystallization from ethyl acetate. Previous batches of this amide were isolated as viscous, brown oils, and chromatography, rather than crystallization from ethyl acetate, was utilized to isolate **7** in pure form. To streamline the procedure further, acid chloride **5** was treated directly with methylamine to generate **7** in good yield (88%) without additional purification (Scheme 2).

An improved synthesis of ether side chain **9** provided access to large quantities of very clean material (Scheme 3). A former method called for >2 equiv of potassium *tert*-butoxide in dimethylacetamide solvent. This much base was unnecessary, and dimethylacetamide was difficult to remove from the product. In addition, varying amounts of bis-addition product (10−20 mol %) were generated when significantly more than 1 equiv of potassium *tert*-butoxide was present. Isolation of very clean material, without

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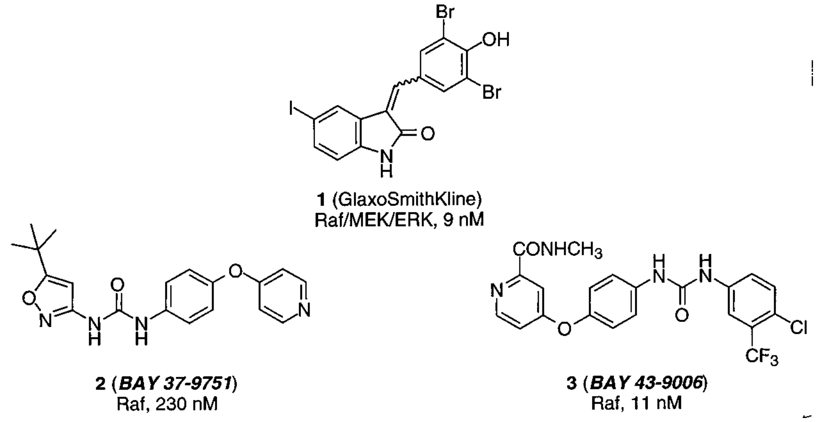
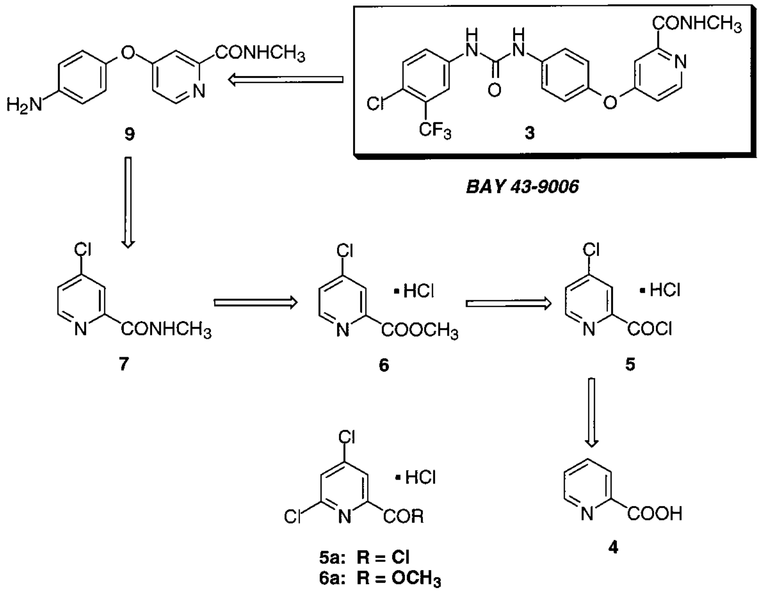
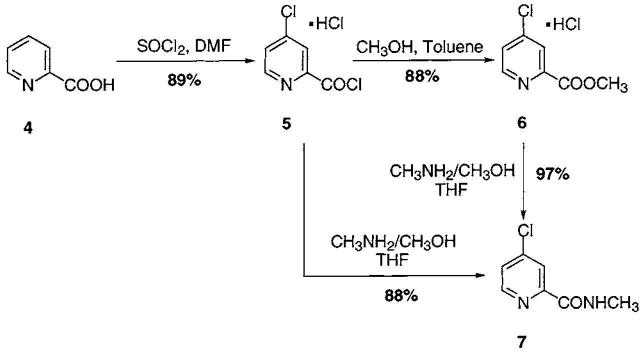


Figure 1. **Small-molecule inhibitors of Raf kinase.**

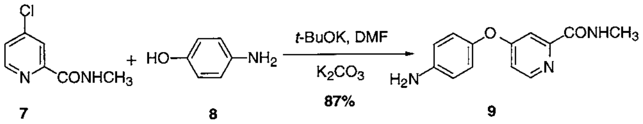
Scheme 1. **Retrosynthesis of BAY 43-9006 (3): medicinal chemistry route**



Scheme 2. **Synthesis of “key intermediate” 7**



Scheme 3. **Synthesis of penultimate intermediate 9**



detection of bis-addition, occurred when this reaction was done in dry *N*,*N*-dimethylformamide in the presence of 1 equiv of potassium *tert*-butoxide and at least 0.5 equiv of potassium carbonate. The yield of this reaction increased under these conditions, and addition of potassium carbonate appeared to accelerate the rate. For instance, without the presence of potassium carbonate, intermediate **9** was produced cleanly in good yield (85%), but at least 16 h were required to achieve complete reaction. On the other hand, addition of 0.5 equiv of potassium carbonate to the reaction mixture increased the rate significantly, so that desired product was rendered in good yield (87%) after 6 h. The rate enhancement and yield remained essentially unchanged when more than 0.5 equiv of that base was added to the system. It is not clearly understood at this time how potassium carbonate affected the rate, but studies indicated that dramatically shorter reaction times were not witnessed when less than 0.5 equiv of this base was part of the protocol.

Since these reactions were conducted under anhydrous conditions, it is not believed that potassium carbonate acted in the capacity of a desiccant.[10] Studies are currently planned to determine if other additives, such as sodium carbonate, provide similar effects.

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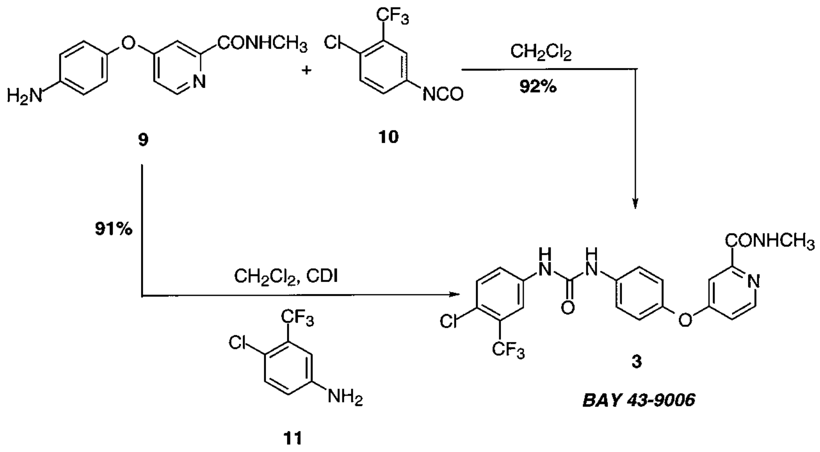
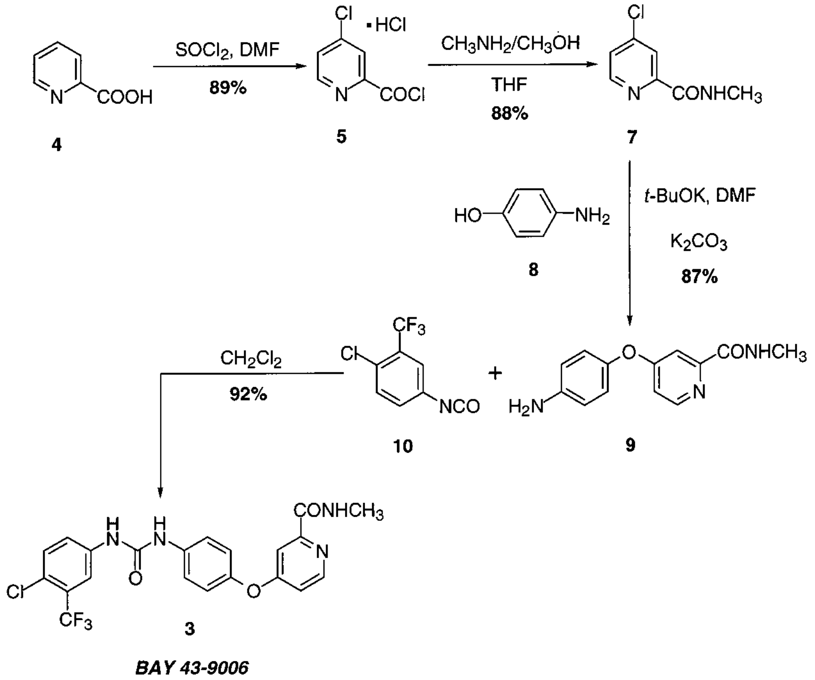
(10) One reviewer suggested that potassium carbonate might act as a desiccant, and for that reason, use of molecular sieves might create a similar result.

Scheme 4. **Synthesis of BAY 43-9006 (3): two different methods**



Scheme 5. **Final synthetic procedure for the scaled synthesis of urea 3**



Reaction of **9** with isocyanate **10** in methylene chloride[11] generated clean urea **3** (**BAY 43-9006**) in 92% yield (Scheme 4). Target **3** was synthesized in similar yield (91%) by coupling aniline **11** with **9** in the presence of *N*,*N*′-carbonyldiimidazole (CDI)[12] without formation of symmetrical byproducts. Earlier experiences with this reaction, as well as others,[13] indicated that concentration was the key to minimizing, or totally eliminating, the production of symmetrical ureas. Generation of symmetrical impurities became a problem when solvent volumes approached 10 or higher. Use of CDI offered a robust alternative if large-scale synthesis of isocyanate **10** became undesirable, although use of this reagent was not considered problematic. Any residual methylene chloride in **3**, regardless of the method chosen, was easily removed by solvent exchange with tetrahydrofuran. Methylene chloride was the solvent of choice in these experiments because urea **3** precipitated as crystalline material from that medium. This outcome did not occur when tetrahydrofuran was utilized as the reaction solvent. The final synthetic protocol for the preparation of **BAY 43-9006** (**3**) is shown in Scheme 5.

Conclusions

An improved, four-step synthesis of ureas provided Raf kinase inhibitor, **BAY 43-9006** (**3**), in 63% overall yield with an HPLC (ELS) purity >98%. An alternative coupling method using *N*,*N*′-carbonyldiimidazole was explored, which

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(11) See, for example: (a) Mayer, P.; Brunel, P.; Chaplain, C.; Piedecoq, C.; Calmel, F.; Scambel, P.; Chopin, P.; Wurch, T.; Pauwels, P.; Marien, M.; Vidaluc, J.; Imbert, T. *J. Med. Chem.* **2000**, *43(20)*, 3653. (b) Miyashita, M.; Matumoto, T.; Matsukubo, H.; Iinuma, F.; Taga, F.; Sekiguchi, H.; Hamada, K.; Okamura, K.; Nishino, K. *J. Med. Chem.* **1992**, *35*, 2446. (c) Gray, A.; Platz, R.; Henderson, T.; Chang, C.; Takahashi, K. *J. Med. Chem.* **1988**, *31(4)*, 807.

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offered additional access to urea **3** in high yield and purity without evidence of a symmetrical urea byproduct. All of the intermediates and final target were isolated cleanly in high yield without a need for chromatographic purification.

Experimental Section

General. All NMR analyses were performed on a GE 300-MHz instrument using hexadeuterated dimethyl sulfoxide. Mass spectra were obtained from a Kratos Concept mass spectrometer. All solvents and reagents were purchased from EM Science, Lancaster, or Aldrich Chemicals and used without further purification. Elemental analyses were obtained from Robertson Microlit Labs. HPLC purities were determined with a Perkin-Elmer Pecosphere 3 × 3C C-18 reversed-phase column (0.46 × 3.3 cm) used in conjunction with a Sedere Sedex model 55 evaporative light scattering (ELS) detector. Eluent gradients ranged from 10 to 90% acetonitrile/0.1% TFA in water; $\lambda = 254$ nm.

Synthesis of 4-Chloropyridine-2-carbonyl Chloride Hydrochloride (5). Anhydrous *N*,*N*-dimethylformamide (6 mL) was slowly added to thionyl chloride (180 mL) at a temperature range of 40−50 °C under argon. The solution was stirred in that temperature range for 10 min prior to portionwise addition of picolinic acid (**4**, 60.00 g, 487.37 mmol) over a 30-min period. The initial green color went to orange and then to purple. The solution was heated to 72 °C, and vigorous SO_2 evolution was observed. A yellow solid precipitated after 16 h. The mixture was then cooled to room temperature, diluted with toluene (500 mL), and concentrated to 200 mL. This process was repeated two additional times before the contents were concentrated to near dryness. The mixture was filtered, washed with toluene (50 mL), and dried under high vacuum for 4 h to afford **5** (92.00 g, 433.02 mmol, 89%) as an off-white solid. The integrity of this material was verified through its subsequent reaction with methanol or methylamine, which led to pure intermediates.

Synthesis of Methyl 4-Chloropyridine-2-carboxylate Hydrodrochloride (6). Anhydrous *N*,*N*-dimethylformamide (10 mL) was slowly added to thionyl chloride (300 mL) at a temperature range of 40−48 °C under argon. The solution was stirred in that temperature range for 10 min prior to portionwise addition of picolinic acid (**4**, 100.00 g, 812.28 mmol) over a 30-min period. The initial green color went to orange and then to purple. The solution was heated to 72 °C and vigorous SO_2 evolution was observed. A yellow solid precipitated after 16 h. The mixture was then cooled to room temperature, diluted with toluene (500 mL), and concentrated to 200 mL. This process was repeated two additional times before the contents were concentrated to near dryness. The mixture was filtered, washed with toluene (50 mL), and dried under high vacuum for 4 h to afford **5** (27.24 g, 128.21 mmol) as an off-white solid. The red filtrate was added to methanol (200 mL) at a rate that kept the internal temperature of the mixture below 55 °C. The contents were stirred at room temperature for 45 min, cooled to 5 °C, and treated with dropwise addition of diethyl ether (200 mL). The material was filtered, washed with ether (200 mL), and dried under high vacuum at 35 °C to provide **6** (110.23 g, 529.85 mmol, 78% based on 683.45 mmol of acid chloride remaining in the filtrate) as a white solid. Mp = 108−112 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.88 (s, 3H, $-CO_2CH_3$); 7.82 (dd, J = 2.2, 5.5 Hz, 1H, aromatic); 8.08 (d, J = 2.2 Hz, 1H, aromatic); 8.68 (d, J = 5.5 Hz, 1H, aromatic); 10.68 (br s, 1H, −NHCl). Mass spectrum (HPLC/ES): $m/e = 172$ (M + 1). Anal. Calcd for $C_7H_7NClO_2 \cdot HCl$: C, 40.41; H, 3.39; N, 6.73. Found: C, 40.34; H, 3.40; N, 6.61.

Synthesis of (4-Chloro(2-pyridyl))-*N*-methylcarboxamide (7) from 6. A suspension of **6** (89.00 g, 427.80 mmol) in methanol (75 mL) was cooled to 0 °C under argon and slowly treated with 2.0 M methylamine in tetrahydrofuran (1000 mL) at a rate that kept the internal temperature below 5 °C. The mixture was stirred at 3 °C for 5 h and concentrated, and the contents were suspended in ethyl acetate (1000 mL) and filtered. The filtrate was washed with brine (500 mL), dried over sodium sulfate, and concentrated to afford **7** (71.15 g, 417.06 mmol, 97%) as pale-yellow crystals (crystallization occurred during the rotary evaporation process). Mp = 41−43 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.81 (s, 3H, $-NHC\mathbf{H}_3$); 7.74 (dd, J = 2.2, 5.1 Hz, 1H, aromatic); 8.00 (d, J = 2.2, 1H, aromatic); 8.61 (d, J = 5.1 Hz, 1H, aromatic); 8.85 (br d, 1H, $-N\mathbf{H}CH_3$). Mass spectrum (CI$^+$): m/e = 171 (M + 1). Anal. Calcd for $C_7H_7N_2ClO$: C, 49.28; H, 4.14; N, 16.42. Found: C, 49.25; H, 4.22; N, 16.42.

Synthesis of (4-Chloro(2-pyridyl))-*N*-methylcarboxamide (7) from 5. Acid chloride **5** (7.00 g, 32.95 mmol) was added portionwise to 2.0 M methylamine in tetrahydrofuran (100 mL) and methanol (20 mL) at 0 °C under argon. The mixture was stirred at 3 °C for 4 h, concentrated to near dryness, and dissolved in ethyl acetate (100 mL). The organics were washed with brine (2 × 100 mL), dried over sodium sulfate, and concentrated to provide **7** (4.95 g, 29.02 mmol, 88%) as a yellow, crystalline solid. Mp = 37−40 °C. NMR data supported product structure (see above experimental data).

Synthesis of [4-(4-Aminophenoxy)(2-pyridyl)]-*N*-methylcarboxamide (9). A solution of 4-aminophenol (9.60 g, 87.98 mmol) in dry *N*,*N*-dimethylformamide (150 mL) was treated with potassium *tert*-butoxide (10.29 g, 91.69 mmol), and the reddish-brown mixture was stirred at room temperature for 2 h. The contents were treated with **7** (15.00 g, 87.92 mmol) and potassium carbonate (6.50 g, 47.03 mmol) and then heated to 80 °C under argon for 6 h. The mixture was cooled to room temperature and poured into ethyl acetate (500 mL) and brine (500 mL). The layers were separated, and the aqueous phase was back-extracted with ethyl acetate (300 mL). The combined organics were washed with brine (4 × 1000 mL), dried over sodium sulfate, and concentrated to afford **9** (18.62 g, 76.54 mmol, 87%) as a light-brown solid after vacuum-drying at 35 °C for 3 h. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.77 (d, J = 4.8 Hz, 3H, $-NHC\mathbf{H}_3$); 5.17 (br s, 2H, $-NH_2$); 6.64, 6.86 (AA′BB′ quartet, J = 8.4 Hz, 4H, aromatic); 7.06 (dd, J = 2.5, 5.5 Hz, 1H, aromatic); 7.33 (d, J = 2.5 Hz, 1H, aromatic); 8.44 (d, J = 5.5 Hz, 1H, aromatic); 8.73 (br d, 1H, $-N\mathbf{H}CH_3$).

Mass spectrum (HPLC/ES): $m/e = 244$ (M + 1). Anal. Calcd for $C_{13}H_{13}N_3O_2 \cdot 0.05\ EtOAc \cdot 0.10\ H_2O$: C, 63.55; H, 5.49; N, 16.84. Found: C, 63.50; H, 5.39; N, 16.85.

Synthesis of *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-({4-[2-(*N*-methyl-carbamoyl)(4-pyridyloxy)]phenyl}amino)-carboxamide (3, BAY 43-9006). A suspension of **9** (67.00 g, 275.43 mmol) in methylene chloride (150 mL) was treated with dropwise addition of a solution of **10** (62.08 g, 280.19 mmol) in methylene chloride (150 mL) at 0 °C under argon. The mixture was stirred at room temperature, and a yellow solid precipitated after 15 min. The mixture was stirred for 16 h and then filtered. The solids were washed with methylene chloride (2 × 50 mL) and dried under vacuum for 4 h at 35 °C to afford **3** (118.19 g, 254.27 mmol, 92%) as an off-white solid. Mp = 210−212 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.77 (d, $J = 4.8$ Hz, 3H, $-NHC\mathbf{H}_3$); 7.16 (m, 3H, aromatic); 7.37 (d, $J = 2.5$ Hz, 1H, aromatic); 7.62 (m, 4H, aromatic); 8.11 (d, $J = 2.5$ Hz, 1H, aromatic); 8.49 (d, $J = 5.5$ Hz, 1H, aromatic); 8.77 (br d, 1H, $-N\mathbf{H}CH_3$); 8.99 (s, 1H, −NHCO−); 9.21 (s, 1H, −NHCO−). Mass spectrum (HPLC/ES): $m/e = 465$ (M + 1). Anal. Calcd for $C_{21}H_{16}N_4ClF_3O_3$: C, 54.26; H, 3.47; N, 12.05. Found: C, 54.11; H, 3.49; N, 12.03. HPLC (ELS) purity >98%: $t_R = 3.5$ min.

Synthesis of *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-({4-[2-(*N*-methyl-carbamoyl)(4-pyridyloxy)]phenyl}amino)-carboxamide (3, BAY 43-9006): Use of CDI. A solution of **11** (1.25 g, 6.39 mmol) in methylene chloride (10 mL) was stirred under argon at room temperature during addition of *N*,*N*′-carbonyldiimidazole (1.10 g, 6.78 mmol). The contents were stirred for 16 h, and then treated with dropwise addition of **9** (1.47 g, 6.04 mmol) in methylene chloride (15 mL). A solution formed, followed by precipitation of an off-white solid. Stirring was continued for 18 h, at which time, the material was filtered, washed with methylene chloride (2 × 15 mL), and dried under high vacuum at 35 °C for 2 h to afford **3** (2.55 g, 5.49 mmol, 91%) as a white solid. Proton NMR and mass-spectral data were consistent with structure. Anal. Calcd for $C_{21}H_{16}N_4ClF_3O_3$: C, 54.26; H, 3.47; N, 12.05; Cl, 7.63. Found: C, 54.24; H, 3.31; N, 12.30; Cl, 7.84. Mp (differential scanning calorimetry, 10 °C/min): 205.6 °C; no polymorphs observed.

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