(19 H, m), 2.51 (1 H, m), 5.93 (1 H, ddd, $J_{H,H_{vic}}$ = 6.0 Hz), 10.7 (1 H); IR (cm^{-1}) 1710 (C=O); high-resolution mass calcd for $C_{12}H_{22}O_2F_2$ 236.302, found 236.415. Anal. Found: C, 60.91; H, 9.73. Calcd for $C_{12}H_{22}O_2F_2$: C, 60.99; H, 9.39.

Preparation of 2-(Difluoromethyl)hexanoic Acid via Fluorinated Acrylic Acid. (a) Reaction of 2-(Trifluoromethyl)propenoic Acid with *n*-Propylmagnesium Bromide. Into a solution of 2-(trifluoromethyl)propenoic acid (2.80 g, 20 mmol) and trimethylsilyl chloride (1.0 g) in tetrahydrofuran (30 mL) was added a solution of *n*-propylmagnesium bromide prepared from *n*-propyl bromide (6.15 g, 50 mmol) and magnesium (1.2 g, 50 mmol) in tetrahydrofuran (70 mL) at -40 °C under an atmosphere of nitrogen. After stirring for 5 h at that temperature, the mixture was quenched with saturated NH_4Cl solution below -20 °C. Oily materials were extracted with diisopropyl ether, and then the ethereal layer was washed with water and dried over anhydrous sodium sulfate. After the solvent was removed, the residue was distilled to give the corresponding fluorinated acrylic acid in 37% yield: bp 94-96 °C (25 mmHg); ^{19}F NMR ($CDCl_3$) δ -7.4, -2.3 (=CF_2); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, $J_{H,H}$ = 6.0 Hz), 1.40 (4 H, m), 2.20 (2 H, m), 12.10 (1 H); IR (cm^{-1}) 3500-3000 (COOH), 1700 (C=O); high-resolution mass calcd for $C_7H_{10}O_2F_2$ 164.153, found 164.375. Anal. Found: C, 51.48; H, 6.54. Calcd for $C_7H_{10}O_2F_2$: C, 51.22; H, 6.14.

(b) Hydrogenation of Fluorinated Acrylic Acid. A flask containing the above fluorinated acrylic acid (1.64 g, 10 mmol), 10% Pd-C (0.2 g), and methanol (10 mL) under an atmosphere of hydrogen was irradiated in the water bath of an ultrasonic laboratory cleaner (32 KHz, 35 W) for 30 h. The solution was poured into a 1 N HCl solution, and the oily material was extracted with diethyl ether. After the ethereal solution was dried over magnesium sulfate, the solvent was removed. Distillation gave 2-(difluoromethyl)hexanoic acid in 68% yield: ^{19}F NMR ($CDCl_3$) δ 38.3, 45.8 (CF_AF_B, ddd, $J_{F,F}$ = 249, $J_{F,H_{gem}}$ = 50, $J_{F,H_{vic}}$ = 11.8 Hz); ^1H NMR ($CDCl_3$) δ 0.97-1.76 (9 H, m), 2.85 (1 H, m), 6.02 (1 H, ddd, $J_{H,H_{vic}}$ = 6.5 Hz), 10.8 (1 H); IR (cm^{-1}) 1710 (C=O); high-resolution mass calcd for $C_7H_{12}O_2F_2$ 166.169; found 166.463. Anal. Found: C, 50.26; H, 7.43. Calcd for $C_7H_{12}O_2F_2$: C, 50.60; H, 7.28.

Preparation of 2-(Difluoromethyl)heptanoic Acid via Fluorinated Acrylic Acid. (a) Reaction of 2-(Trifluoromethyl)propenoic Acid with *n*-Butylmagnesium Bromide. Into the above reaction, 2-(trifluoromethyl)propenoic acid (2.33 g, 16.7 mmol), *n*-butylmagnesium bromide (50 mmol), and trimethylsilyl chloride (1.0 g) in tetrahydrofuran (70 mL) were used. Distillation gave the corresponding fluorinated acrylic acid in 48% yield: bp 92-94 °C (19 mmHg); ^{19}F NMR ($CDCl_3$) δ -7.9, -3.3 (=CF_2); ^1H NMR ($CDCl_3$) δ 1.03-2.45 (11 H, m), 12.07 (1 H); IR (cm^{-1}) 3500-3000 (COOH), 1700 (C=O); high-resolution mass calcd for $C_8H_{12}O_2F_2$ 178.178, found 178.006. Anal. Found: C, 52.81; H, 6.86. Calcd for $C_8H_{12}O_2F_2$: C, 53.93; H, 6.79.

(b) Hydrogenation of Fluorinated Acrylic Acid. A flask containing the above fluorinated acrylic acid (1.98 g, 10 mmol), 10% Pd-C (0.2 g), and methanol (10 mL) under an atmosphere of hydrogen was irradiated in the water bath of an ultrasonic laboratory cleaner (32 KHz, 35 W) for 30 h and then worked up similarly. Distillation gave 2-(difluoromethyl)heptanoic acid in 73% yield: high-resolution mass calcd for $C_8H_{14}O_2F_2$ 180.194, found 180.318.

Preparation of 2-(Difluoromethyl)nonanoic Acid via Fluorinated Acrylic Acid. (a) Reaction of 2-(Trifluoromethyl)propenoic Acid with *n*-Hexylmagnesium Bromide. In the above reaction, 2-(trifluoromethyl)propenoic acid (2.80 g, 20 mmol), *n*-hexylmagnesium bromide (50 mmol), and trimethylsilyl chloride (1.0 g) in tetrahydrofuran (100 mL) were used. Final purification was the distillation, giving the fluorinated acrylic acid in 45% yield: bp 128-130 °C (26 mmHg); ^{19}F NMR ($CDCl_3$) δ -6.8, -1.2 (=CF_2); ^1H NMR ($CDCl_3$) δ 1.07-2.30 (15 H, m), 12.14 (1 H); IR (cm^{-1}) 3500-3000 (COOH), 1710 (C=O); high-resolution mass calcd for $C_{10}H_{16}O_2F_2$ 206.232, found 206.391. Anal. Found: C, 57.94; H, 7.53. Calcd for $C_{10}H_{16}O_2F_2$: C, 58.24; H, 7.82.

(b) Hydrogenation of Fluorinated Acrylic Acid. A flask containing the above fluorinated acrylic acid (2.06 g, 10 mmol), 10% Pd-C (0.2 g), and methanol (10 mL) under an atmosphere of hydrogen was irradiated in the water bath of an ultrasonic laboratory cleaner (32 KHz, 35 W) for 30 h and then worked up similarly. Final purification was the distillation, giving 2-(difluoromethyl)nonanoic acid in 64% yield: high-resolution mass calcd for $C_{10}H_{18}O_2F_2$ 208.242, found 208.457.

Preparation of 3-Phenyl-2-(difluoromethyl)propanoic Acid via Fluorinated Acrylic Acid. (a) Reaction of 2-(Trifluoromethyl)propenoic Acid with Phenylmagnesium Bromide. Into the above reaction, 2-(trifluoromethyl)propenoic acid (2.33 g, 16.7 mmol), phenylmagnesium bromide (50 mmol), and trimethylsilyl chloride (1.0 g) in tetrahydrofuran (70 mL) were used. Final purification was the distillation, giving the fluorinated acrylic acid in 55% yield: bp 107-110 °C (32 mmHg); ^{19}F NMR ($CDCl_3$) δ -11.3, -8.6 (=CF_2); ^1H NMR ($CDCl_3$) δ 3.47 (2 H, m), 7.20 (Ar H), 12.17 (1 H); IR (cm^{-1}) 3500-3000 (COOH), 1710 (C=O); high-resolution mass calcd for $C_{10}H_8O_2F_2$ 198.168, found 198.402. Anal. Found: C, 60.46; H, 4.24. Calcd for $C_{10}H_8O_2F_2$: C, 60.61; H, 4.07.

(b) Hydrogenation of Fluorinated Acrylic Acid. A flask containing the above fluorinated acrylic acid (2.00 g, 10 mmol), 10% Pd-C (0.2 g), and methanol (10 mL) under an atmosphere of hydrogen was irradiated in the water bath of an ultrasonic laboratory cleaner (32 KHz, 35 W) for 30 h and then worked up similarly. Final purification was the distillation, gaving 2-(difluoromethyl)nonanoic acid in 77% yield: ^{19}F NMR ($CDCl_3$) δ 38.6, 44.9 (CF_AF_B, ddd, $J_{F,F}$ = 247, $J_{F,H_{gem}}$ = 48, $J_{F,H_{vic}}$ = 12.0 Hz); ^1H NMR ($CDCl_3$) δ 2.79 (1 H, m), 3.51 (2 H, d, $J_{H,H}$ = 3.0 Hz), 5.88 (1 H, ddd, $J_{H,H_{vic}}$ = 6.5 Hz), 11.4 (1 H); IR (cm^{-1}) 1710 (C=O); high-resolution mass calcd for $C_{10}H_{10}O_2F_2$ 200.184, found 200.337. Anal. Found: C, 60.28; H, 5.57. Calcd for $C_{10}H_{10}O_2F_2$: C, 60.00; H, 5.34.

Registry No. $PhCH_2OC(O)C(=CH_2)CF_3$, 111339-17-4; Bu_2LiCu, 24406-16-4; $CH_3(CH_2)_4C(=CF_2)CO_2CH_2Ph$, 123186-66-3; $CH_3(CH_2)_4CH(CHF_2)CO_2H$, 123186-67-4; $CH_3(CH_2)_5MgBr$, 3761-92-0; $CH_3(CH_2)_6C(=CF_2)CO_2CH_2Ph$, 123186-68-5; $CH_3(CH_2)_6CH(CHF_2)CO_2H$, 123186-69-6; $CH_3(CH_2)_7MgBr$, 17049-49-9; $CH_3(CH_2)C(=CF_2)CO_2CH_2Ph$, 123186-70-9; $CH_3(CH_2)_8CH(CHF_2)CO_2H$, 123186-71-0; $CF_3C(=CH_2)CO_2H$, 381-98-6; $CH_3(CH_2)_2MgBr$, 927-77-5; $CH_3(CH_2)_3C(=CF_2)CO_2H$, 123186-72-1; $CH_3(CH_2)_3CH(CHF_2)CO_2H$, 123186-73-2; $CH_3(CH_2)_3MgBr$, 693-03-8; $CH_3(CH_2)_4C(=CF_2)CO_2H$, 123186-74-3; $CH_3(CH_2)_6C(=CF_2)CO_2H$, 123186-75-4; PhMgBr, 100-58-3; $PhCH_2C(=CF_2)CO_2H$, 99764-29-1; $PhCH_2CH(CHF_2)CO_2H$, 70219-17-9.

Novel Synthesis of Piperidinecarboxamides via Aryl Isocyanate Acylation of α-Amino Carbanions

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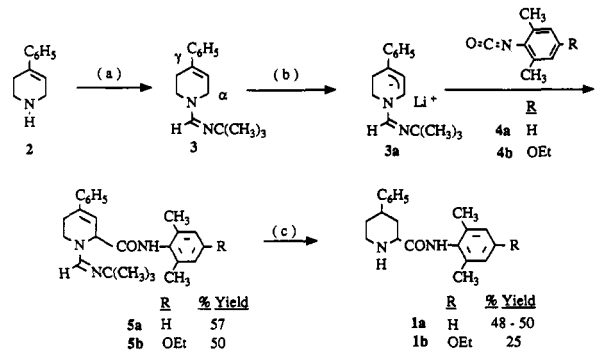
In support of one of our drug discovery programs we required access to piperidinecarboxamides of general structure **1**. We decided our approach would focus on their synthesis from **2**. The key transformation in this sequence would be the metalation of activated phenylpiperidine **3**[1] followed by its reaction with a suitable electrophile to yield an adduct such as **5**. By the choice of an appropriate electrophile in this sequence, **5** could then be easily converted into **1**. Based on related examples,[1c-e,3] it was not

(1) We chose to utilize the formamidine activating group of Meyers. (a) For leading references, see: Gonzalez, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1989**, *30*, 43. (b) For a review, see: Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. (c) Meyers, A. I.; Edwards, P. D.; Riecker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (d) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E., Jr. *J. Org. Chem.* **1985**, *50*, 1019. (e) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

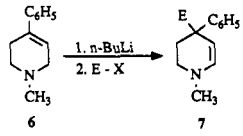
0022-3263/89/1954-5632$01.50/0

Scheme I[a]



[a] (a) $(CH_3)_2NCH{=}NC(CH_3)_3$, $C_6H_5CH_3$, $(NH_4)_2SO_4$, ↑↓, 64%; (b) *n*-BuLi, THF, −78 °C; (c) H_2, 10% Pd/C, 100% EtOH (unoptimized).

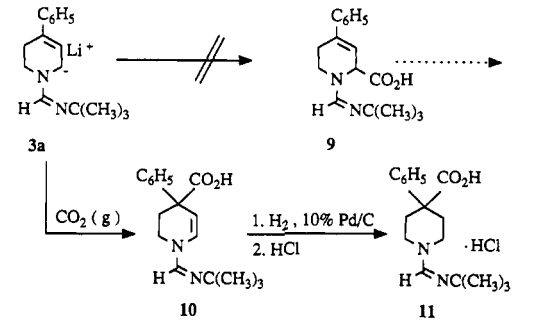
obvious to us whether the ambident anion **3a** would react at the α- or γ-carbon, relative to nitrogen. For example, the anion of the related compound **6**[2,3] is known to react at the carbon adjacent to the phenyl group, affording the products **7**. Similarly, the ambident anion from **12** is reported to afford predominantly the γ-adducts **13**.[1c-e]



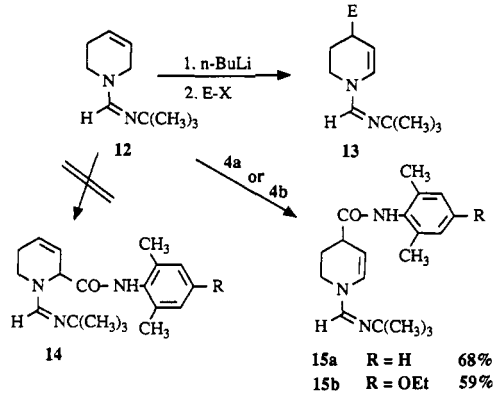
In practice the synthesis was achieved as in Scheme I. Treatment of **3a** at −78 °C[4] with the aryl isocyanates **4a** and **4b** afforded the desired α-adducts **5a** and **5b** after simple workup and recrystallization.[5,6] The ^1H NMR spectrum of the crude reaction product in each case showed only minor resonances not associated with **5** or **3**. Assignment of structure to the α-adduct **5** was clear from the resonance in the ^{13}C NMR spectrum of **5a** or **5b** at 55.6 ppm, which was shown to be a methine carbon by a DEPT[7] experiment. This resonance is consistent for C-2 of **5a**, **5b**.[8]

We initially had assumed that the conversion of **5** into **1** would require two separate operations, the hydrogenation of the tetrahydropyridine and the removal of the formamidine activating group. Hydrogenation of **5a** or **5b** over 10% Pd on charcoal in absolute EtOH, however, afforded **1a**[9] and **1b**[9] directly in 50% and 25% yield, respectively.[10]

Scheme II



Scheme III



For a more general route to targets related to **1**, we considered modifications to the sequence which would not require the use of isocyanates. Ambident anion **3a** was thus reacted with gaseous carbon dioxide. We presumed, based on our previous results, that the α-adduct **9** would predominate. The major product of this reaction, however, is the γ-adduct **10**, which was characterized as the saturated hydrochloride salt, **11** (45% overall yield) (Scheme II).

Since the metalation of **12** and subsequent reaction with a variety of electrophiles, not including isocyanate examples, furnished as the major product the γ-isomer **13** (Scheme III),[1c-e] we were curious whether the ambident anion of **12** would react with the two isocyanates of Scheme I to afford α-adduct **14** or γ-adduct **15**. In accord with the literature reports, our reaction afforded **15a** and **15b** in 68% and 59% yield. The assignment of structure was again clear from the ^{13}C NMR spectrum. The resonance at δ_c 97 ppm is consistent for C-3 of **15a**, **15b**.

In summary, α- or γ-regioselectivity in the reaction of the ambident anion **3a** appears to be sensitive to the electrophile used. In reactions of the related compound **12** with **4a** or **4b** (Scheme III), the γ-adduct **15** predominates. It is unlikely that a shifting of the reactivity of **3a** with these same isocyanates to α-adducts (Scheme I) is due to the stabilization of an extended styrene conjugation in the products, since the similar reaction of **3a** with carbon

(2) Users of this compound should be aware of its potent neurotoxicity. For a leading reference, see: Lewin, R. *Science* **1984**, *224*, 1083.

(3) (a) Levine, R.; Bell, V. U.S. Patent 3824242, July 16, 1974; *Chem. Abstr.* **1974**, *81*, 91369p. (b) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. Also note: (c) Shenvi, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942. (d) Zimmerman, D. M.; Cantrell, B. E.; Swartzendruber, J. K.; Jones, N. D.; Mendelsohn, L. G.; Leander, J. D.; Nickander, R. C. *J. Med. Chem.* **1988**, *31*, 555.

(4) Conducting the reaction at low temperatures was demonstrated as necessary. A pilot experiment at −20 °C afforded multiple products. This was not further pursued.

(5) The compound **6**, when treated under similar conditions, failed to react. Warmer temperatures were not attempted.

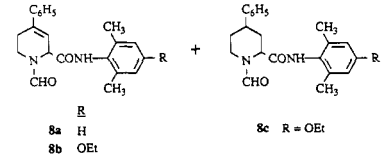
(6) Curiously, when **3a** was treated with phenyl isocyanate, several products were formed, which proved difficult to separate. The only crystalline material obtained was diphenylurea.

(7) (a) Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Johns, S. R.; Willing, R. I. *J. Chem. Soc., Chem. Commun.* **1982**, 1138. (b) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.

(8) (a) Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; Wiley-Interscience: New York, 1972. (b) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*, 3rd ed.; VCH: New York, 1987.

(9) This compound is a single isomer, tentatively assigned cis stereochemistry.

(10) The conversion of **5** into **1** has not been optimized. Varying amounts of saturated/unsaturated N-formyl derivatives, **8a–c**, were also isolated. For example, in the conversion of **5b** into **1b**, both **8b** (14%) and **8c** (9%) were isolated and characterized.



dioxide affords the unconjugated γ-orientation of **10** (Scheme II). We speculate two possible reasons for the α-regiochemistry described in Scheme I. The products observed with the aryl isocyanates most likely are the result of an unfavorable steric interaction between the 4-phenyl substituent of **3a** and the large, aromatic isocyanates. Thus the α-adducts predominate. Alternatively, an endo-type transition state in the reactions of **4** with **3a**, in which maximum overlap of π systems is maintained, might promote orientation of the reactants favoring the α-adducts. Although it is not certain what factors are responsible for the regioselectivity we have observed, these reactions provide a novel route to the targets **1**.

Experimental Section

Proton (^{1}H) NMR spectra were measured at 60 MHz on a Varian T60 instrument or at 270 MHz on a JEOL FX instrument using $CDCl_3$ or DMSO-d_6 as solvent. Carbon (^{13}C) NMR spectra were measured at 67.8 MHz using the JEOL FX instrument. Assignment of carbon resonances was made using heteronuclear off-resonance decoupling or DEPT[7] experiments. Infrared spectra were measured on a Nicolet 20 SX FT IR or on a Perkin-Elmer Model 467 instrument. Ultraviolet spectra were measured on a Gilford Response UV–vis spectrophotometer. Mass spectra were measured on a JEOL JMS-01SC. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN. Melting points are uncorrected.

Reactions requiring anhydrous or oxygen-free conditions were conducted in oven-dried (120 °C) glassware under an atmosphere of dry N_2. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl under N_2 or, alternatively, dried over 4A molecular sieves[11] and purged with N_2.

Analytical thin-layer chromatography was performed on E. Merck 5 × 20 cm Kieselgel 60 F-254 plates. Preparative high-pressure liquid chromatography, HPLC, was performed on a Waters Prep 500 instrument using two SiO_2 cartridges. Flash chromatography[12] was performed using 230–400 mesh Kieselgel 60 (E. Merck).

***N*-[(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)methylene]-1,1-dimethylethanamine (3).** A solution of 267.8 g (1.69 mol) of 4-phenyl-1,2,5,6-tetrahydropyridine, 381 mL (2.38 mol) of *N*,*N*-dimethyl-*N'*-*tert*-butylformamidine and 85 g (0.64 mol) of ammonium sulfate in 3500 mL of toluene was refluxed for 24 h. The cooled mixture was filtered and concentrated in vacuo. The crude product was then distilled to afford 260 g of **3** (64% yield, bp 135 °C at 1 mmHg), which crystallized on standing. An analytical sample was obtained as the methanesulfonic acid salt, recrystallized from 2-propanol–ether, mp 108–110 °C: NMR (^{1}H, 270 MHz, $CDCl_3$) δ 7.45 (s, 1 H, HC=N), 7.40–7.25 (multiplet of 5 H), 6.09 (br s, $W_{1/2}$ = 7.7 Hz, 1 H, C=CH), 3.97 (m, $W_{1/2}$ = 6.9 Hz, 2 H, C.2-H's), 3.48 (t, J = 5.6 Hz, 2 H, C.6-H's), 2.57 (br m, $W_{1/2}$ = 13.9 Hz, 2 H, C.5-H's), 1.19 (s, 9 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$) δ_c 150.0 (N=CH), 140.7 (C), 135.1 (C), 128.2 (CH × 2), 126.9 (CH), 124.8 (CH × 2), 121.0 (CH), 53.0 (N-C), 44.5 and 43.8 (NCH_2 and NCH_2), 31.1 (CH_3), 27.6 (CH_2); IR (KBr) 2963, 2927, 2907, 2840, 1637, 1456 cm^{-1}; mass spectrum, m/e 242 (M^+), 227 (M − CH_3), 213, 185 (M − $C(CH_3)_3$), 158, 156. Anal. Calcd for $C_{16}H_{22}N_2$–CH_3SO_3H: C, 60.33; H, 7.74; N, 8.28; S, 9.47. Found: C, 60.54; H, 7.75; N, 8.16; S, 9.60.

1-[[(1,1-Dimethylethyl)imino]methyl]-*N*-(2,6-dimethylphenyl)-1,2,5,6-tetrahydro-4-phenyl-2-pyridinecarboxamide (5a). To a −78 °C solution of 16.25 g (67 mmol) of **3** in 500 mL of dry tetrahydrofuran under N_2 was added dropwise 30 mL (75 mmol) of a 2.5 M *n*-BuLi solution in hexane over 15 min. The resulting dark red solution was stirred for 1 h at −78 °C, after which 10.7 mL (75 mmol) of 2,6-dimethylphenyl isocyanate was dripped in over 5 min. After the mixture was stirred for an additional 30 min at −78 °C, the vessel was removed from the dry ice/acetone bath and warmed to ambient temperature. After 3 h, the mixture was then diluted with 200 mL of saturated aqueous sodium bicarbonate and extracted with 300 mL of ethyl acetate. The organics were dried over magnesium sulfate, filtered, and concentrated to afford a white solid. The crude product was dissolved in hot ethyl acetate, filtered, and crystallized to afford 14.08 g of white crystals. A second crop of 0.8 g was also obtained; combined yield 57%. Although the mother liquors contained more of **5a** (270-MHz ^{1}H NMR analysis), it was not possible to purify any additional compound by crystallization. An analytical sample was prepared by a second recrystallization from ethyl acetate, mp 168–169 °C dec: NMR (^{1}H, 270 MHz, $CDCl_3$) δ 7.56 (s, 1 H, HC=N), 7.44–7.23 (multiplet of 5 H), 7.04 (s, 3 H), 6.33 (br m, $W_{1/2}$ = 9.2 Hz, 1 H, C=CH), 5.40 (br m, $W_{1/2}$ = 9.2 Hz, 1 H, C.2-H), 3.70–3.54 (multiplet of 2 H, C.6-H's), 2.66 (m, 1 H, C.5-H), 2.48 (br d, J = 17.8 Hz, 1 H, C.5-H), 2.22 (s, 6 H), 1.18 (s, 9 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$) δ_c 169.5 (C=O), 149.4 (HC=N), 140.3 (C), 136.3 (C), 135.1 (C), 133.9 (C), 128.2 (CH × 2), 127.8 (CH × 2), 127.3 (CH), 126.6 (CH), 125.1 (CH × 2), 120.4 (CH), 55.6 (NCHC=O), 53.2 (N-C), 43.6 (NCH_2), 31.1 (CH_3), 27.6 (CH_2), 18.4 (CH_3); IR (KBr) 3285, 3060, 3025, 2965, 2925, 2900, 2870, 1650 (C=O), 1630, 1500 cm^{-1}; mass spectrum, m/e 389 (M^+), 374 (M − CH_3), 316, 315, 306, 299, 244, 243. Anal. Calcd for $C_{25}H_{31}N_3O$: C, 77.08; H, 8.02; N, 10.79. Found: C, 77.22; H, 8.17; N, 10.69.

***N*-(2,6-Dimethylphenyl)-4-phenyl-2-piperidinecarboxamide (1a).** A solution of 5.0 g (12.9 mmol) of **5a** and 1.5 g of 10% Pd/C in 300 mL of absolute ethanol was hydrogenated on a Parr shaker at 45 psi of H_2 pressure. After 4 h, TLC analysis (3:3:94 ($iPrNH_2$, CH_3OH, CH_2Cl_2)) indicated that all of **5a** had been consumed. The suspension was then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Two additional hydrogenations of **5a**, for a total of 14.3 g (36.8 mmol), were conducted in the above fashion. The combined crude product from these three reactions was then purified by preparative HPLC, eluting with ethyl acetate. In this manner, 5.4 g (48%) of **1a** was obtained. As the free base failed to crystallize, an analytical sample was obtained as the methanesulfonic acid salt, recrystallized from methanol and ether, mp 272–274 °C dec: NMR (^{1}H, 270 MHz, DMSO-d_6) δ 7.41–7.27 (m, 5 H), 7.10 (s, 3 H), 4.27 (dd, J = 2.6 and 12.5 Hz, 1 H, NHC=O), 3.43 (d, J = 11.9 Hz, 1 H, NCH), 3.33 (s, 3 H, deuterium exchangeable), 3.25 (br m, $W_{1/2}$ = 32.3 Hz, 1 H, NCH), 3.05 (br m, $W_{1/2}$ = 28.5 Hz, 1 H, CHC_6H_5), 2.53 (m, 1 H, C.3-H), 2.34 (s, 3 H, CH_3SO_3), 2.14 (s, 6 H), 1.95–1.85 (m, 3 H); NMR (^{13}C, 67.8 MHz, DMSO-d_6) δ_c 166.7 (C=O), 143.9, 135.3, 133.6, 128.9, 128.0, 127.2, 127.0, 126.7, 57.4 (NCHC=O), 43.3 (NCH_2), 39.7, 39.3, 34.3 (CH_2), 28.5 (CH_2), 18.0 (CH_3); IR (KBr) 3680–2400 (br), 3550, 3485, 3210, 3030, 2850, 2820, 2730, 2520, 1655 (C=O), 1600, 1545, 1470, 1450, 1200, 1165, 1040 cm^{-1}; UV (EtOH) λ_{max} (ϵ_{max}) 215.5 (16 407), 256.5 (977); mass spectrum, m/e 308 (M^+), 278, 176, 160. Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93; S, 7.93. Found: C, 62.19; H, 7.03; N, 6.98; S, 7.95.

Less polar fractions from the HPLC purification of **1a** were isolated to afford 3.6 g of a crystalline solid, **8a**. This was further purified by chromatography on 600 g of SiO_2, eluting with hexane–ethyl acetate mixtures to afford 1 g (8%) of tetrahydropyridine **8a**: mass spectrum, m/e 334 (M^+), 306, 278, 214, 187, 186, 174.

1-[[(1,1-Dimethylethyl)imino]methyl]-*N*-(2,6-dimethyl-4-ethoxyphenyl)-1,2,5,6-tetrahydro-4-phenyl-2-pyridinecarboxamide (5b). In a procedure analogous to that used for **5a**, 10 g (41.3 mmol) of **3** was reacted sequentially with 19 mL (45.6 mmol) of a 2.4 M solution of *n*-BuLi in hexane and 8.5 mL (49.8 mmol) of 4-ethoxy-2,6-dimethylphenyl isocyanate, **4b**,[13] to obtain 9.0 g (50% yield) of **5b**, after recrystallization from ethyl acetate, mp 152–154 °C. Although the mother liquors were composed predominately of **5b** (270-MHz ^{1}H NMR analysis), no further material could be obtained by crystallization. NMR (^{1}H,

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(13) Isocyanate **4b** was prepared by refluxing an ethyl acetate solution of 4-ethoxy-2,6-dimethylaniline[14] either with excess phosgene in toluene or with 0.55 equiv of commercially available trichloromethyl chloroformate.
(14) (a) Runti, C.; Colautti, A. *Ann. Chim.* **1965**, *55*, 840. (b) Klemm, K.; Riedel, R. Ger. Offen. DE 2304286, Aug 8, 1974; *Chem. Abstr.* **1974**, *81*, 135768z.

270 MHz, $CDCl_3$) δ 9.05 (br s, $W_{1/2}$ = 15.4 Hz, 1 H, NH), 7.56 (s, 1 H, HC=N), 7.50–7.26 (m, 5 H), 6.59 (s, 2 H), 6.35 (br m, $W_{1/2}$ = 9.2 Hz, 1 H, C=CH), 5.38 (br m, $W_{1/2}$ = 9.2 Hz, 1 H, NCHC=O), 3.98 (q, J = 6.6 Hz, 2 H, OCH_2), 3.75–3.50 (m, 2 H), 2.68 (br m, $W_{1/2}$ = 27.7 Hz, 1 H), 2.50 (br d, J = 16.2 Hz, 1 H), 2.18 (s, 6 H), 1.38 (t, J = 6.6 Hz, 3 H, CH_3), 1.18 (s, 9 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$) δ_c 169.8 (C=O), 157.1 (CO), 149.3 (HC=N), 140.3 (C), 136.4 (C), 136.3 (C), 128.2, 127.3, 126.7, 125.1, 120.4 (CH), 113.6 (CH × 2), 63.1 (OCH_2), 55.6 (NCHC=O), 53.2 (NC), 43.5 (NCH_2), 31.1 (CH_3), 27.5 (CH_2), 18.6 (CH_3), 14.7 (CH_3); IR (KBr) 3240, 3050, 3030, 2965, 2920, 2875, 1640, 1600, 1500 cm^{-1}; mass spectrum, m/e 418 ($M^+ - CH_3$), 360, 359, 343, 242, 191. Anal. Calcd for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.75; H, 8.10; N, 9.59.

N-(4-Ethoxy-2,6-dimethylphenyl)-4-phenyl-2-piperidinecarboxamide (1b). In a procedure analogous to the synthesis of **1a** above, two separate 5-g batches (23.1 mmol total) of **5b**, each containing 1.5 g of 10% Pd/C catalyst in 300 mL of absolute ethanol, were hydrogenated. After workup, the combined batches were purified by chromatography on 600 g of SiO_2 to afford 2 g (25% yield) of **1b**, obtained as an amorphous solid. Analytically pure **1b** was characterized as the methanesulfonic acid salt, crystallized from methanol–ether, mp 221–223 °C: NMR (^1H, 270 MHz, DMSO-d_6) δ 7.41–7.24 (multiplet of 5 H), 6.65 (s, 2 H), 4.27 (br d, J = 10.6 Hz, 1 H, NCHC=O), 3.98 (q, J = 6.6 Hz, 2 H, OCH_2), 3.43 (br d, J = 11.9 Hz, 1 H, NCH), 3.36 (s, 3 H, deuterium exchangeable), 3.22 (br m, $W_{1/2}$ = 32.4 Hz, 1 H, NCH), 3.05 (br m, $W_{1/2}$ = 27.8 Hz, 1 H, CHC_6H_5), 2.53 (m, 1 H, C.3-H), 2.38 (s, 3 H, CH_3SO_3), 2.10 (s, 6 H), 1.92 (m, 3 H), 1.30 (t, J = 6.6 Hz, 3 H); NMR (^{13}C, 67.8 MHz, DMSO-d_6) δ_c 167.5 (C=O), 157.4, 144.3 (C), 136.8 (C), 129.2 (CH × 2), 127.2 (CH), 127.0 (CH × 2), 126.7 (C), 113.9 (CH × 2), 63.4 (OCH_2), 57.5 (NCHC=O), 43.4 (NCH_2), 40.12 (CH or CH_3), 39.6 (CH or CH_3), 34.6 (CH_2), 28.8 (CH_2), 18.6 (CH_3 × 2), 15.1 (CH_3); IR (KBr) 3690–2400 (br), 3445, 3240, 3040, 2980, 2740, 2520, 1655, 1610, 1550 cm^{-1}; mass spectrum, m/e 352 (M^+), 255, 219, 191. Anal. Calcd for $C_{23}H_{32}N_2O_5S$: C, 61.58; H, 7.17; N, 6.24; S, 7.15. Found: C, 61.48; H, 7.25; N, 6.21; S, 7.39.

Less polar fractions obtained from the above chromatography were combined with like fractions from a third experiment (10 g (23.1 mmol) of **5b** and 2.5 g of 10% Pd/C in 300 mL of EtOH) and were further purified by chromatography on SiO_2, eluting with ethyl acetate–hexane mixtures. So obtained were 2.5 g (14%) of **8b** and 1.5 g (9%) of **8c**.

Data for **8b**, mp 80 °C (amorphous solid): NMR (^1H, 270 MHz, $CDCl_3$, major rotamer) δ 8.64 (s, 1 H), 7.73 (br s, 1 H), 7.38–7.18 (multiplet of 5 H), 6.63 (s, 2 H), 5.88 (br d, J = 3.3 Hz, 1 H), 3.99 (q, J = 6.6 Hz, 2 H), 3.8 (br m, $W_{1/2}$ = 23 Hz, 1 H), 3.62 (br m, $W_{1/2}$ = 17.7 Hz, 2 H), 2.29 (br s, 1 H), 2.22 (s, 6 H), 1.91 (br m, $W_{1/2}$ = 9.2 Hz, 1 H), 1.39 (t, J = 6.6 Hz, 3 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$, major rotamer) δ_c 162.99 (C=O), 161.11 (CH=O), 157.84 (CO), 142.92 (C), 136.58 (C), 135.15 (C), 128.65 (CH), 127.41 (CH), 126.89 (CH), 125.30 (C), 117.21 (CH), 113.89 (CH), 63.25 (OCH_2), 39.29 (NCHC=O), 37.27 (NCH_2), 30.44 (CH_2), 18.52 (CH_3), 14.66 (CH_3); IR (KBr) 3700–2660 (br), 3280, 3040, 2985, 2925, 1685 (C=O), 1630 (C=O), 1509, 1493 cm^{-1}; mass spectrum, m/e 378 (M^+), 360, 350, 335, 322, 307, 214, 187, 186, 165. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.95; H, 7.07; N, 7.31.

Data for **8c**, mp 177.5–179.5 °C (CH_2Cl_2, Et_2O): NMR (^1H, 270 MHz, $CDCl_3$, major rotamer) δ 8.26 (s, 1 H), 7.70 (br s, 1 H), 7.42–7.20 (multiplet of 5 H), 6.59 (s, 2 H), 4.86 (br m, $W_{1/2}$ = 22 Hz, 1 H), 3.97 (q, J = 6.6 Hz, 2 H), 3.66 (br m, $W_{1/2}$ = 23 Hz, 2 H), 2.80 (br m, $W_{1/2}$ = 27 Hz, 1 H), 2.59 (q, J = 13.9 Hz, 1 H), 2.22 (br m, $W_{1/2}$ = 35 Hz, 1 H), 2.14 (s, 6 H), 1.85 (br m, $W_{1/2}$ = 35 Hz, 1 H), 1.38 (t, J = 6.6 Hz, 3 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$, major rotamer) δ_c 168.69 (C=O), 162.97 (C=O), 157.49 (CO), 144.46 (C), 136.47 (C), 128.59 (CH), 126.76 (CH), 126.60, 113.97, 63.25 (OCH_2), 54.10 (NCHC=O), 40.42 (NCH_2), 36.32 (CH), 31.52 (CH_2), 29.36 (CH_2), 18.46 (CH_3), 14.74 (CH_3); IR (KBr) 3650–2600 (br), 3246, 3020, 2971, 2907, 2865, 1667 (C=O), 1604, 1485, 1152; mass spectrum, m/e 380 (M^+), 220, 216, 188, 174, 165. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.31. Found: C, 72.79; H, 7.40; N, 7.34.

1-[[(1,1-Dimethylethyl)imino]methyl]-4-phenyl-4-piperidinecarboxylic Acid Monohydrochloride (11). The anion obtained from 5.0 g (20.7 mmol) of **3** in 50 mL of dry THF under N_2 at −78 °C and 9.1 mL (22.8 mmol) of a 2.5 M solution of n-BuLi in hexane was stirred for 1 h. Gaseous carbon dioxide was then passed over the surface of the reaction mixture, the red color clearing within 5 min. The cold bath was then removed, and the mixture was warmed to ambient temperature. The reaction mixture was then concentrated in vacuo. The concentrate was dissolved in 250 mL of glacial acetic acid, 1 g of 10% Pd/C catalyst was added, and the mixture was hydrogenated on a Parr shaker at 45 psi of hydrogen pressure for 5 h. The mixture was then filtered through Celite, and the filtrate was concentrated in vacuo. The concentrate was dissolved in ethanol, and excess ethereal HCl was added. The solution was then concentrated in vacuo. The product was crystallized from CH_3CN to afford 3 g of **11** (45% yield from **3**). An analytical sample was prepared by recrystallization from acetonitrile, mp 257.0–258.5 °C: NMR (^1H, 270 MHz, DMSO-d_6) δ 8.03 (s, 1 H, HC=N), 7.44–7.30 (multiplet of 5 H), 4.18 (br d, J = 13.8 Hz, 1 H), 3.91 (br d, J = 13.2 Hz, 1 H), 3.52–3.24 (multiplet of 4 H), 2.08–1.88 (multiplet of 2 H), 1.34 (s, 9 H); NMR (^{13}C, 67.8 MHz, DMSO-d_6) δ_c 174.6 (CO_2H), 151.6 (CH=N), 141.7 (C), 128.8 (CH × 2), 127.4 (CH), 125.8 (CH × 2), 55.0 (CN), 49.5 (NCH_2), 48.3 (C), 42.5 (NCH_2), 33.3 (CH_2), 32.1 (CH_2), 29.1 (CH_3); IR (KBr) 3680–2380 (br), 3430, 3193, 3134, 3063, 2973, 2917, 2890, 1721 (C=O), 1687, 1492 cm^{-1}; mass spectrum, m/e 288 (M^+), 287, 273 ($M - CH_3$), 243 ($M - CO_2H$), 231 (M − tBu), 205, 204, 160. Anal. Calcd for $C_{17}H_{24}N_2O_2 \cdot HCl$: C, 62.86; H, 7.76; N, 8.62; Cl, 10.91. Found: C, 62.87; H, 7.79; N, 8.62; Cl, 11.04.

1-[[(1,1-Dimethylethyl)imino]methyl]-N-(2,6-dimethylphenyl)-1,2,3,4-tetrahydro-4-pyridinecarboxamide (15a). The anion formed at −78 °C from 15 g (90.4 mmol) of **12**[1c,d] in 300 mL of dry THF under N_2 and 45 mL (108 mmol) of a 2.4 M solution of n-BuLi in hexane after 1 h was treated with 14.3 mL (100 mmol) of isocyanate **4a**. The resulting mixture was stirred for 30 min at −78 °C and 30 min at ambient temperature and then was worked up in a similar manner as **5a**. Pure **15a** was obtained by crystallization of the product from EtOAc–Et_2O to afford 19.2 g (68%) in two crops, mp 155–157 °C: NMR (^1H, 270 MHz, $CDCl_3$) δ 7.46 (s, 1 H), 7.26 (s, 1 H), 7.07 (br s, 3 H), 6.73 (br d, $W_{1/2}$ = 13.9 Hz, 1 H), 4.87 (br m, $W_{1/2}$ = 15 Hz, 1 H), 3.88 (br m, $W_{1/2}$ = 22 Hz, 1 H), 3.43 (br m, 1 H), 3.22 (br m, 1 H), 2.36 (br m, 1 H), 2.21 (s, 6 H), 2.06 (br m, 1 H), 1.20 (s, 9 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$) δ_c 172.14 (C=O), 146.54 (CH=N), 134.93 (C), 133.83 (C), 132.07 (CH), 128.05 (CH), 127.08 (CH), 96.78 (CH), 53.64 (CN), 40.48 (CHCON), 39.69 (CH_2), 30.76 (CH_3), 24.75 (CH_2), 18.43 (CH_3); IR (KBr) 2970, 2850, 1640, 1620 (C=O), 1480 cm^{-1}; UV (EtOH) λ_{max} (ϵ_{max}) 250.5 (19617); mass spectrum, m/e 313 (M^+), 298, 230, 205, 193, 166. Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41. Found: C, 72.78; H, 8.75; N, 13.22.

1-[[(1,1-Dimethylethyl)imino]methyl]-N-(4-ethoxy-2,6-dimethylphenyl)-1,2,3,4-tetrahydro-4-pyridinecarboxamide (15b). In a manner similar to the preparation of **15a**, 15.0 g (90.4 mmol) of **12**[1c,d] was reacted with 38.0 mL (98.8 mmol) of a 2.6 M solution of n-BuLi in hexane and 18.5 mL (108 mmol) of isocyanate **4b**.[13] The crude product was purified by preparative HPLC, eluting with 5% CH_3OH in CH_2Cl_2. Thus was obtained 19 g (59%) of **15b** as an amorphous solid, mp 89–98 °C: NMR (^1H, 270 MHz, $CDCl_3$) δ 7.45 (s, 1 H, HC=N), 7.14 (br s, $W_{1/2}$ = 4.7 Hz, 1 H, NCH=C), 6.71 (br d, J = 7.8 Hz, 1 H, C=CHC), 6.60 (s, 2 H), 4.85 (dd, J = 4.6 and 7.8 Hz, 1 H, CHCO), 3.98 (q, J = 7.3 Hz, 2 H, OCH_2), 3.87 (m, 1 H), 3.42 (ddd, J = 3.7, 10.7, and 13.8 Hz, 1 H), 3.23 (dd, J = 4.6 and 9.9 Hz, 1 H), 2.16–2.40 (m, 2 H), 2.16 (s, 6 H), 1.97–2.13 (m, 1 H), 1.39 (t, J = 7.3 Hz, 3 H, CH_3), 1.19 (s, 9 H); NMR (^{13}C, 67.8 MHz, $CDCl_3$) δ_c 172.7 (C=O), 157.4 (CO), 146.7 (CH=N), 136.3 (C), 131.9 (CH), 126.6 (C), 113.8 (CH × 2), 97.0 (CH), 63.2 (OCH_2), 53.6 (NC), 40.3 (CH), 39.6 (NCH_2), 30.8 (CH_3), 24.7 (CH_2), 18.6 (CH_3), 14.7 (CH_3); IR (KBr) 3270, 2965, 2930, 2855, 1640 (C=O), 1522, 1490, 1475 cm^{-1}; mass spectrum, m/e 357 (M^+), 342 ($M - CH_3$), 302, 274, 193, 191, 166, 165. A Karl Fischer titration revealed the amorphous sample to contain 0.39% H_2O. Anal. Calcd for $C_{21}H_{31}N_3O_2 \cdot 0.08H_2O$: C, 70.27; H, 8.75; N, 11.71. Found: C, 69.98; H, 8.56; N, 11.54.

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