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Polyfunctional Tetrahydropyrido[2,3-*b*]pyrazine Scaffolds from 4-Phenylsulfonyl Tetrafluoropyridine

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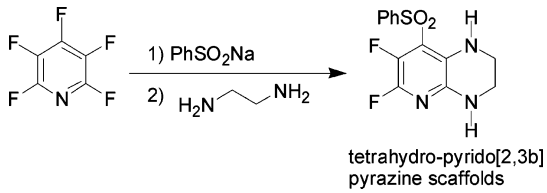

Polyfunctional tetrahydropyrido[2,3-*b*]pyrazine scaffolds can be synthesized by sequential reaction of pentafluoropyridine with sodium phenylsulfinate and an appropriate diamine. The polyfunctionality possessed by the difluorinated tetrahydropyrido[2,3-*b*]pyrazine scaffolds was demonstrated in selected model reactions with nucleophiles to give access to various polysubstituted [6,6]-ring fused systems.

Introduction

Procedures for the efficient synthesis of low molecular weight heterocyclic systems that possess several sites for further functionalization are attracting great interest from the life science industries that is due, in part, to the large and growing number of valuable pharmaceutical agents that possess heterocyclic structural subunits.[1−3] Consequently, demand for appropriate polyfunctional heterocyclic scaffolds that may be utilized for the generation of libraries of analogues for biological screening and subsequent hit-to-lead development is increasing. Heterocyclic scaffolds that possess new and unusual geometry are of particular interest due to the possibilities for increasing the molecular diversity of library and compound collections[4,5] used for the discovery of new biologically active chemical entities. However, it is very difficult to synthesize small, polyfunctional heteroaromatic systems from simple systems such as pyridine because of the inherent low reactivity and low regioselectivity of such species in functionalization processes.

In a previous paper,[6] we outlined our general approach to the synthesis of polyfunctional, heterocyclic fused ring systems and demonstrated the successful synthesis of various model tetrahydropyrido[3,4-*b*]pyrazines from pentafluoropyridine. Our approach relies upon the fact that pentafluoropyridine **1** is a highly electron deficient aromatic ring system due to the presence of the five fluorine atoms attached to the ring carbon atoms. Consequently, the fluorine atoms impart high reactivity of the system toward nucleophiles[7−9] such that a sequence of nucleophilic aromatic substitution processes[10] can be carried out to provide access to polysubstituted bicyclic nitrogen heterocycles **2** and **3** (Scheme 1).

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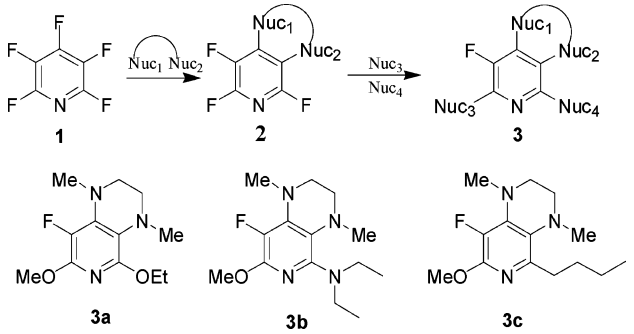
SCHEME 1. Strategy for Polysubstituted Tetrahydropyrido[3,4-*b*]pyrazine Synthesis



Initially, reaction of pentafluoropyridine **1** with a bifunctional nucleophile (Nuc_1−Nuc_2) occurs at the most activated 4-position followed by cyclization at the geometrically accessible 3-position to give **2**. Subsequent reactions with nucleophiles (Nuc_3, Nuc_4) gave systems such as **3a**−**c**.

To increase the molecular diversity[4] of the scaffolds that can be accessed by this approach, we sought to adapt the strategy outlined in Scheme 1 to obtain polyfunctional tetrahydropyrido[2,3-*b*]pyrazine scaffolds following a process that is shown in Scheme 2. Here, pentafluoropyridine **1** is first functionalized at the 4-position by reaction with a mono-functional nucleophile (Nuc_1) to give **4** before annelation to **5** and further elaboration to **6**. Initially, we focused upon the synthesis of tetrahydropyrido-[2,3-*b*]pyrazine scaffolds that we envisaged could be prepared by reaction of **4** with appropriate diamines to demonstrate the feasibility of this approach and compliment our earlier studies.

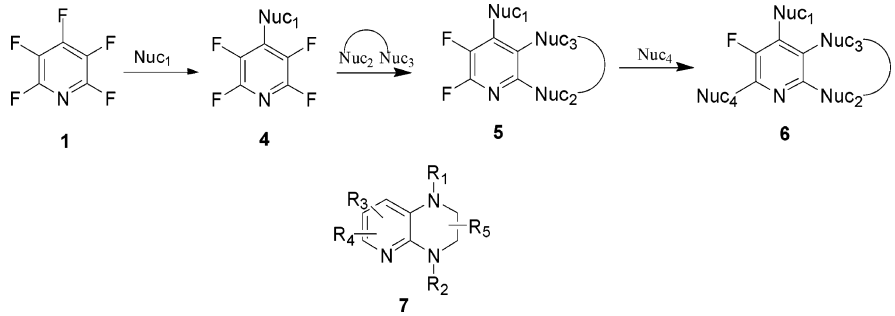
Polyfunctional tetrahydropyrido[2,3-*b*]pyrazine derivatives **7** are difficult to synthesize by conventional methodology and have previously been prepared by reactions of 2,3-diamino pyridines with dicarbonyl systems[11−13] (Hinsberg reaction), cyclizations involving appropriate chloro-aminopyridine derivatives,[14,15] or reduction[16,17] of polycyclic heteroaromatic precursors. In general, all these reported synthetic procedures require multistep sequences where the synthesis of the appropriate functionalized pyridine precursors can be very difficult indeed. Further diversification of scaffolds is hindered by the low reactivity of the largely unfunctional scaffolds that can be accessed by such processes. In this paper, we describe successful syntheses of model polysubstituted tetrahydropyrido[2,3-*b*]pyrazine scaffolds (**5**, Scheme 2) by sequential reaction of **1** with appropriate bifunctional nucleophiles.

Results and Discussion

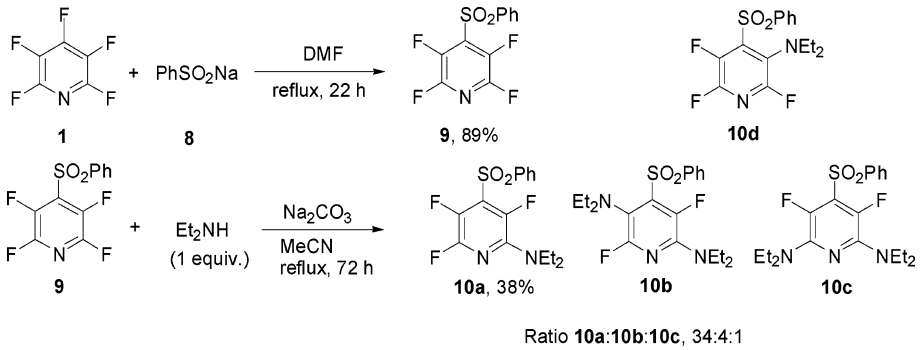
The first step of the strategy outlined in Scheme 2 requires the synthesis of 4-substituted tetrafluoropyridines, and we initially chose to prepare the 4-phenylsulfonyl derivative **9** (Nuc_1 = $PhSO_2$) by reaction of pentafluoropyridine **1** with sodium phenylsulfinate **8** in DMF, following a literature procedure[18] (Scheme 3). The phenylsulfonyl group is a strong electron withdrawing group that should help to maintain the reactivity of the pyridine ring toward further nucleophilic substitution processes, allowing annelation and further functionalization to proceed.

Before investigating annelation processes of 4-phenylsulfonyl tetrafluoropyridine **9** (Nuc_1 = SO_2Ph) with difunctional nitrogen nucleophiles, we needed to establish the effect of the 4-phenylsulfonyl substituent on the reactivity and product profile of this pyridine system toward further attack by aliphatic nitrogen nucleophiles. Reaction of diethylamine, after reflux in acetonitrile, gave a mixture of **10a**, with no other momo-aminated products observed, and two disubstituted systems **10b**,**c**. Purifica-

SCHEME 2. Strategy for Polysubstituted Tetrahydropyrido[2,3-*b*]pyrazine Synthesis



SCHEME 3. Synthesis of 4-Phenylsulfonyl Tetrafluoropyridine and Reaction with Diethylamine



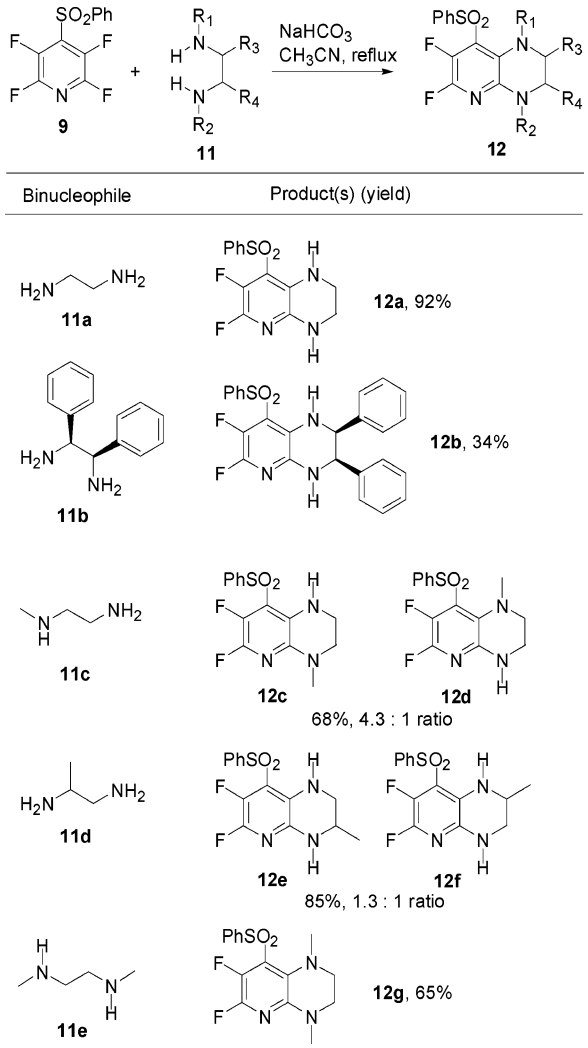
Ratio **10a**:**10b**:**10c**, 34:4:1

tion of **10a** was achieved by column chromatography, while **10b**,**c** could be identified by a combination of ^{19}F NMR and mass spectral data. The location of the dialkylamino substituent at the 2-position in **10a**, rather than the 3-position as in the other possible isomer **10d**, is confirmed by a consideration of ^{19}F NMR chemical shifts. For **10a**, we would expect to observe one resonance at a higher frequency (between −70 and −90 ppm), which can be attributed to the fluorine atom located ortho to ring nitrogen. In contrast, for isomer **10d**, two such higher frequency resonances would be expected, but this is not the case for the product obtained. Disubstituted product **10c** is readily identified by the observation of only one fluorine resonance due to the symmetry of this system, while **10b** gives two fluorine resonances.

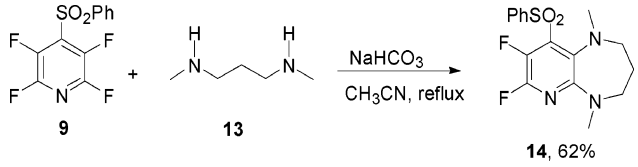
With this encouraging result in hand, we turned our attention toward annelation reactions, and we found that aliphatic diamines **11** react efficiently with **9** to give tetrahydropyrido[2,3-*b*]pyrazine systems (Table 1). Bifunctional nucleophiles **11a**,**b**, where both nucleophilic sites are primary amino groups, reacted efficiently with **9** to give high yields of ring fused systems **12a** and **12b**, respectively. Purification of **12a** was achieved by recrystallization of the crude product mixture from dichloromethane, while **12b** was purified by column chromatography on silica gel, resulting in a lower isolated yield.

The reaction of **9** with an unsymmetrical diamine **11c** bearing both primary and secondary amino sites gave a mixture of products **12c**,**d** in the ratio of 4.3:1 by ^{19}F NMR analysis of the reaction mixture, arising from initial attack of the secondary or primary amine sites at the 2-position of the pyridine ring and subsequent cyclization, respectively. Identification of **12c** followed from ^{19}F NMR analysis in which the resonance attributed to fluorine located ortho to ring nitrogen had a chemical shift of −95.4 ppm, similar to shifts observed for the dimethyl derivatives **12g**. The corresponding resonance for F-6 in **12d** occurs at −108.2 ppm, similar to the analogous system **12a** in which F-6 is adjacent to the NH group (−108.9 ppm). These structural assignments were confirmed by X-ray crystallography (see Supporting Information for ORTEP diagrams and analysis). Given the results shown in Scheme 3 (**9**−**10a**), the major product **12c** is most likely formed from initial attack of the secondary amine site, reflecting the higher nucleophilicity of secondary amines over primary systems. Products **12e** and **12f** were formed in essentially equal amounts (1.3:1) upon reaction of **9** with diamine **11d**, indicating no significant difference in the reactivity of the nucleophilic sites. After repeated recrystallization from toluene, a pure sample of **12f** was isolated and identified by X-ray crystallography (see Supporting Information).

TABLE 1. Synthesis of Tetrahydropyrido-[2,3*b*]-pyrazine Scaffolds



SCHEME 4. Synthesis of [6,7]-Fused Ring System



The secondary amine, *N*,*N*′-dimethylethylenediamine **11e**, gave **12g** upon reaction with **9** in high yield (Table 1), and by an analogous procedure, the [6,7]-fused ring system **14** was synthesized from **9** and the appropriate 1,3 diaminopropane **13** (Scheme 4).

With preparatively useful quantities of several tetrahydropyrido[2,3-*b*]pyrazine scaffolds in hand, we carried out preliminary reactions of scaffolds **12a** and **12g** with representative O, N, and S centered nucleophiles.

Both sodium methoxide and potassium phenoxide gave mixtures of products arising from substitution of the fluorine atom located adjacent to the pyridine ring nitrogen and the phenylsulfonyl group, which could not be separated satisfactorily. However, lithium diethylamide and sodium thiophenoxide led to products **15** and **16**, respectively, arising from substitution of the phenyl-

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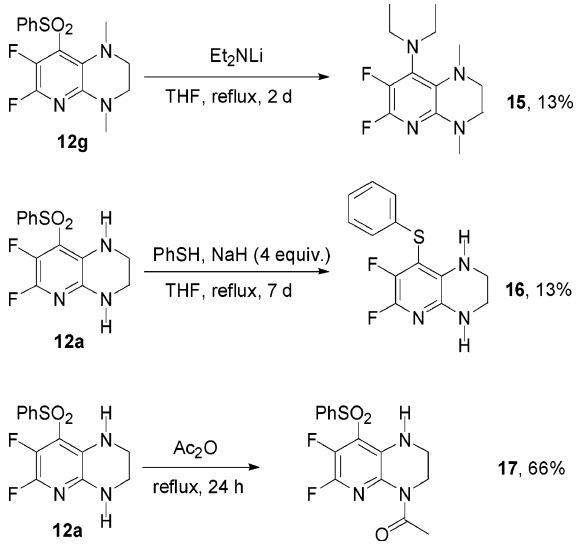
SCHEME 5. Reactions of Scaffolds 12a,g with Nucleophiles.



sulfonyl group that is, of course, a good leaving group that is attached to a site para to the ring nitrogen that is still activated toward nucleophilic attack. These results are due to the soft nitrogen and sulfur nucleophiles preferentially attacking softer C−S sites. Acetylation of the pyrazine ring in **12a** proceeds selectively at N-1 to give **17**, reflecting the greater nucleophilicity of this site as compared to N-4.

Conclusions

Tetrahydropyrido[2,3-*b*]pyrazine systems may be accessed very readily by reaction of 4-phenylsulfonyl tetrafluoropyridine with diamines, following the strategy outlined in Scheme 2 (Nuc_1 = $PhSO_2$ and Nuc_2−Nuc_3 = diamine). Further reactions of these scaffolds with representative nucleophiles proceed to give predominantly substitution of the phenylsulfonyl group, providing access to related functional [6,6]-fused ring systems.

Experimental Procedures

Synthesis of 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine 9. Pentafluoropyridine **1** (5.34 g, 31.6 mmol) was added to a solution of phenylsulfinic acid sodium salt **8** (4.99 g, 30.4 mmol) in DMF (25 mL) under argon. The reaction mixture was heated to reflux for 22 h, after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature and poured into water (250 mL), and the precipitate was isolated by filtration. Recrystallization from ethanol gave 4-benzenesulfonyl-2,3,5,6-tetrafluoropyridine[18] **9** (2.84 g, 89%) as beige crystals; mp 148.0−149.0 °C; found: C, 45.6; H, 1.8; N, 4.9; $C_{11}H_5F_4NO_2S$ requires: C, 45.4; H, 1.7; N, 4.8%; ^{19}F NMR δ: −86.19 (2F, m), −137.48 (2F, m); ^{1}H NMR δ: 8.12 (2H, m), 7.78 (1H, m), 7.65 (2H, m); ^{13}C NMR δ: 144.3 (dm, $^1J_{CF}$ 198.4), 139.4 (s), 138.9 (dm, $^1J_{CF}$ 188.5), 136.0 (s), 133.3 (t, $^2J_{CF}$ 10.7), 130.2 (s), 128.7 (s); *m/z* (EI$^+$) 291 ([M]$^+$, 80), 141 ([M − C_5F_4N]$^+$, 88), 77 ([M − $C_5F_4NSO_2$]$^+$, 100).

Reactions of 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine 9 with Diethylamine. Diethylamine (0.29 g, 4.0 mmol) and sodium carbonate (0.34 g, 4.0 mmol) were added to acetonitrile (150 mL) under argon. Compound **9** (1.16 g, 4.0 mmol) was added, and the resulting solution was heated to reflux for 3 days. The reaction mixture was cooled to room temperature, stirred with benzenesulfonic acid scavenger resin (200 mg) for 6 h, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil that consisted of three major components in a ratio of 34:4:1 (0.58 g). Purification by column chromatography on silica gel (5:1 hexane/ethyl acetate) gave *N*,*N*′-diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine **10a** (0.51 g, 38%) as a yellow oil; ([M + H]$^+$ 345.0885, $C_{15}H_{15}F_3N_2O_2S$ requires [M + H]$^+$ 345.0879); ^{19}F NMR δ: −88.55 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 27.1), −134.06 (1F, dd, $^3J_{FF}$ 33.8, $^4J_{FF}$ 11.3), −156.72 (1F, dd, $^4J_{FF}$ 27.1, $^5J_{FF}$ 11.3); ^{1}H NMR δ: 8.06 (2H, d, $^3J_{HH}$ 7.2), 7.69 (1H, tm, $^3J_{HH}$ 7), 7.57 (2H, tm, $^3J_{HH}$ 7), 3.41 (4H, q, $^3J_{HH}$ 7), 1.14 (6H, t, $^3J_{HH}$ 7); ^{13}C NMR δ: 145.36 (ddd, $^1J_{CF}$ 234.1, $^2J_{CF}$ 16.3, $^4J_{CF}$ 2.4), 142.79 (m), 140.78 (s), 139.34 (dm, $^1J_{CF}$ 265.3), 134.94 (s), 130.00 (m), 129.5 (dd, $^1J_{CF}$ 259.38, $^2J_{CF}$ 33.9), 129.70 (s), 128.39 (s), 44.7 (d, $^4J_{CF}$ 4.6), 13.7 (s); *m/z* (EI$^+$) 344 ([M]$^+$, 53), 329 ([M − CH_3]$^+$, 100), 301 ([M − CH_3CH_2N]$^+$, 76) and traces of 3,6-difluoro-*N*,*N*,*N*′,*N*′-tetraethyl-4-(phenylsulfonyl)-pyridine-2,5-diamine **10b**; ^{19}F NMR δ: −73.33 (1F, d, $^5J_{FF}$ 33.8), −134.99 (1F, d, $^5J_{FF}$ 31.3); *m/z* (EI$^+$) 397 ([M]$^+$, 70), 382 ([M − CH_3]$^+$, 100), 368 ([M − CH_3CH_2]$^+$, 33), 77 ([M−$C_9H_{20}N_3F_2SO_2$]$^+$, 30) and 3,5-difluoro-*N*,*N*,*N*′,*N*′-tetraethyl-4-(phenylsulfonyl)-pyridine-2,6-diamine **10c**; ^{19}F NMR δ: −152.61 (s); *m/z* (EI$^+$) 397 ([M]$^+$, 28), 382 ([M − CH_3]$^+$, 40), 368 ([M − CH_3CH_2]$^+$, 64), 77 ([M − $C_9H_{20}N_3F_2SO_2$]$^+$, 54).

Annelation Processes—General Procedure. Diamine **11** and sodium hydrogen carbonate were mixed in acetonitrile under argon. Compound **9** was added, and the solution was heated to reflux. The reaction mixture was cooled to room temperature and evaporated, and the residue was taken into dichloromethane. The solution was poured into 1 M hydrochloric acid (50 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$). Evaporation gave the crude material that was dissolved in dichloromethane and filtered through silica gel to remove the brown coloration. Evaporation left the crude product, which was purified by recrystallization or column chromatography on silica gel.

6,7-Difluoro-8-phenylsulfonyl-1,2,3,4-tetrahydropyrido-[2,3-*b*]pyrazine 12a. Ethylenediamine **11a** (1.2 g, 20 mmol), **9** (2.91 g, 10 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol), and acetonitrile (400 mL) gave an orange−yellow solid that was recrystallized from dichloromethane to give 6,7-difluoro-8-phenylsulfonyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **12a** (2.87 g, 92%) as yellow crystals; mp 177.5−178.5°C; found: C, 50.5; H, 3.5; N, 13.4. $C_{13}H_{11}F_2N_3O_2S$ requires: C, 50.2; H, 3. 6; N, 13.6%; ^{19}F NMR δ: −108.93 (1F, d,$^3J_{FF}$ 24.8), −157.01 (1F, d, $^3J_{FF}$ 24.8); ^{1}H NMR δ: 8.00 (2H, m), 7.66 (1H, m), 7.55 (2H, m), 3.49 (4H, s); ^{13}C NMR δ: 141.48 (s), 140.98 (dd, $^1J_{CF}$ 225.8, $^2J_{CF}$ 16.8), 140.63 (dd, $^3J_{CF}$ 14.9, $^4J_{CF}$ 3.8), 134.36 (s), 132.27 (dd, $^1J_{CF}$ 249.3, $^2J_{CF}$ 29.7), 129.36 (s), 127.75 (dm, $^3J_{CF}$ 2.5), 127.40 (s), 116.65 (d, $^2J_{CF}$ 13.4), 39.17 (s), 39.01 (s); *m/z* (EI$^+$) 311 ([M]$^+$, 100), 168 ([M − H_2SO_2Ph]$^+$, 84), 77 ([M − $C_7H_6N_3SO_2F_2$]$^+$), 62).

Phenyl 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-sulfinate 12g. *N*,*N*′-Dimethylethylenediamine **11e** (0.58 g, 6.70 mmol), **9** (1.0 g, 3.44 mmol), sodium hydrogen carbonate (1.15 g, 13.75 mmol), and acetonitrile (200 mL) gave an orange solid (1.7 g). Purification by recrystallization from *n*-hexane gave phenyl 6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-sulfinate **12g** (0.75 g, 65%) as yellow−orange light sensitive crystals; mp ∼160°C (dec.); ([M + H]$^+$ 340.0928, $C_{15}H_{16}F_2N_3SO_2$ requires [M + H]$^+$ 340.0926); ^{19}F NMR δ: −95.57 (1F, d, $^3J_{FF}$ 27), −157.04 (1F, d, $^3J_{FF}$ 27); ^{1}H NMR δ: 7.95 (2H, m), 7.60 (1H, m), 7.49 (2H, m), 3.35 (2H, m), 3.06 (3H, s), 2.92 (3H, s), 2.77 (2H, m); ^{13}C NMR δ: 146.3 (dd, $^1J_{CF}$ 231.0, $^2J_{CF}$ 16.7), 146.2 (d, $^3J_{CF}$ 13.7), 142.2 (s), 133.8 (s), 132.1 (dd, $^1J_{CF}$ 253.1, $^2J_{CF}$ 31.7), 131.1 (d, $^3J_{CF}$ 10.5), 128.7 (s), 127.9 (s), 126.9 (m), 47.1 (s), 47.0 (s), 43.4 (s), 37.0 (s); *m/z* (EI$^+$) 339 ([M]$^+$, 100), 198 ([M − SO_2Ph]$^+$, 16).

9-Benzenesulfonyl-7,8-difluoro-1,5-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[3,4-*b*][1,4]diazepine 14. *N*,*N*′-Dimethylpropane-1,3-diamine **13** (2.04 g, 20 mmol), **9** (2.91 g,

10 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol), and acetonitrile (400 mL) gave a brown−yellow oil. Purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) gave 9-benzenesulfonyl-7,8-difluoro-1,5-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[3,4-*b*][1,4]diazepine **14** (2.19 g, 62%) as yellow crystals; mp 133.0−135.0°C; found: C, 54.1; H, 4.9; N, 11.6. $C_{13}H_{11}F_2N_3O_2S$ requires: C, 54.4; H, 4.8; N, 11.9%; ^{19}F NMR δ: −89.87 (1F, d,$^3J_{FF}$ 24.3), −152.62 (1F, d, $^3J_{FF}$ 24.3); ^{1}H NMR δ: 7.89 (2H, m), 7.58 (1H, m), 7.51 (2H, m), 3.05 (2H, m), 2.90 (3H, s), 2.55 (3H, s), 2.22 (2H, m), 1.72 (2H, m); ^{13}C NMR δ: 154.80 (dm, $^3J_{CF}$ 10.8), 146.92 (dd, $^1J_{CF}$ 236.5, $^2J_{CF}$ 16.8), 142.81 (s), 138.45 (dd, $^2J_{CF}$ 4.2,$^3J_{CF}$ 3.0), 133.92 (dd, $^1J_{CF}$ 264.5, $^2J_{CF}$ 33.0), 133.28 (s), 131.05 (dd, $^3J_{CF}$ 5.8,$^4J_{CF}$ 3.5), 128.711 (s), 127.43 (s), 57.37 (s), 50.00 (s), 41.70 (s), 41.12 (s), 24.80 (s); *m/z* (EI$^+$) 353 ([M]$^+$, 100), 324 ([M − NCH_3]$^+$, 89), 182 ([M − HSO_2Ph]$^+$, 91).

Reactions of Scaffolds with Nucleophiles. *N*,*N*-Diethyl-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-8-amine 15. Butyllithium (0.47 mL, 1.18 mmol, 2.5 M in THF) was added to a solution of diethylamine (0.086 g, 1.18 mmol) in cold (−78 °C) THF (25 mL). The solution was stirred at −78 °C for 1 h before warming to room temperature and the addition of **12g** (0.20 g, 0.59 mmol). The reaction mixture was heated to reflux for 2 days after which time ^{19}F NMR indicated 100% conversion of the starting material. The reaction mixture was cooled to room temperature, the solvent was evaporated, and the residue was redissolved in dichloromethane, poured onto water (50 mL), extracted with dichloromethane (100 mL), and dried ($MgSO_4$). The solvent was evaporated to give crude product as a brown−yellow oil (0.87 g). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *N*,*N*-diethyl-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-8-amine **15** (0.02 g, 13%) as a yellow oil; ([M + H]$^+$ 271.1728, $C_{13}H_{20}N_4F_2$ requires [M + H]$^+$ 271.1729); ^{19}F NMR δ: −99.24 (1F, d, $^3J_{FF}$ 27.4), −168.29 (1F, d, $^3J_{FF}$ 27.3); ^{1}H NMR δ: 3.26 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5), 3.17 (2H, m), 2.97 (3H, s), 2.96 (2H, m), 2.56 (3H, s), 0.98 (6H, t, $^3J_{HH}$ 7.5); ^{13}C NMR δ: 145.7 (dd, $^1J_{CF}$ 224.6, $^2J_{CF}$ 15.3), 143.7 (d, $^3J_{CF}$ 16.8), 139.6 (m), 132.6 (dd, $^1J_{CF}$ 240.0, $^2J_{CF}$ 29.1), 120.4 (d, $^3J_{CF}$ 4.8), 47.5 (s), 43.6 (d, $^4J_{CF}$ 4.8), 42.0 (s), 40.5 (s), 35.9 (s), 12.3 (s); *m/z* (EI)$^+$ 270 ([M]$^+$, 100), 255 ([M − CH_3]$^+$, 16), 241 ([M − CH_2CH_3]$^+$, 26), 226 ([M − $(CH_3)_2$-CH_2]$^+$, 52), 211 ([M − $(CH_3)_3CH_2$]$^+$, 70).

6,7-Difluoro-8-phenylsulfanyl-1,2,3,4-tetrahydro-pyrido-[2,3-*b*]pyrazine 16. Sodium hydride (0.48 g, 20 mmol) was added to a solution of benzenethiol (2.20 g, 20 mmol) in tetrahydrofuran (40 mL) under argon. After hydrogen gas evolution had subsided, **12a** (1.56 g, 5 mmol) was added, and the solution heated to reflux until ^{19}F NMR indicated 100% conversion. The reaction mixture was cooled to room temperature, poured into water (20 mL), extracted with dichloromethane (3 × 20 mL), and dried ($MgSO_4$). The solvent was evaporated to give crude material as a yellow−green oil. Column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave 6,7-difluoro-8-phenylsulfanyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **16** (0.19 g, 13%) as yellow−orange crystals. mp 148−149°C; found: C, 55.8; H, 4.1; N, 14.7. $C_{13}H_{11}F_2N_3S$ requires: C, 55.9; H, 4.0; N, 15.0%; ^{19}F NMR δ: −106.13 (1F, d,$^3J_{FF}$ 24.8), −153.57 (1F, d, $^3J_{FF}$ 24.8); ^{1}H NMR δ: 7.34−7.15 (5H, m), 4.99 (1H, br s), 4.68 (1H, br s), 3.51 (1H, m), 3.50 (1H, d, $^3J_{HH}$ 3.4), 3.38 (1H, m); ^{13}C NMR δ: 142.22 (dd, $^1J_{CF}$ 227, $^2J_{CF}$ 17.2), 139.18 (dd, $^3J_{CF}$ 13.8, $^4J_{CF}$ 3.0), 137.08 (dd, $^1J_{CF}$ 242, $^2J_{CF}$ 27.4), 133.43 (s), 129.44 (s), 128.95 (dd, $^3J_{CF}$ 4.48, $^4J_{CF}$ 1.86), 127.82 (s), 126.78 (s), 112.77 (d, $^2J_{CF}$ 17.7), 40.25 (s), 39.68 (s); *m/z* (EI$^+$) 279 ([M]$^+$, 100), 200 ([M − $C_6H_5H_2$]$^+$, 28) and a mixture of two other products that could not be identified.

4-Acetyl-6,7-difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 17. Acetic anhydride (0.06 g, 0.60 mmol) was added to a solution of **12a** (0.09 g, 0.30 mmol) in acetic acid (50 mL), and the reaction mixture was stirred at room temperature for 5 h before heating to reflux for 24 h. The reaction mixture was cooled to room temperature, poured into water (30 mL), extracted with dichloromethane (100 mL), dried ($MgSO_4$), and evaporated to give crude product as a brown oil (0.12 g). Purification by mass directed automated preparative HPLC (30−85% acetonitrile in formic acid) gave 4-acetyl-6,7-difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **17** (0.07 g, 66%) as a yellow oil; ([M − H]$^+$ 352.0567, $C_{13}H_{20}N_4F_2$ requires [M − H]$^+$ 352.0566); ^{19}F NMR δ: −104.66 (1F, d, $^3J_{FF}$ 26.3), −140.85 (1F, dd, $^3J_{FF}$ 26.3); ^{1}H NMR δ: 8.04 (2H, dm, $^3J_{HH}$ 8.4), 7.72 (1H, tt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.2), 7.60 (2H, tm, $^3J_{HH}$ 8.4), 7.42 (1H, br s), 3.95 (2H, t, $^3J_{HH}$ 4.8), 3.52 (2H, m), 2.42 (3H, s); ^{13}C NMR δ: 169.7 (s), 140.7 (s), 139.0 (dd, $^1J_{CF}$ 230.7, $^2J_{CF}$ 17.5), 138.9 (dd, $^1J_{CF}$ 263.0, $^2J_{CF}$ 30.4), 134.8 (s), 131.2 (dd, $^3J_{CF}$ 4.2, $^4J_{CF}$ 1.2), 130.7 (dd, $^3J_{CF}$ 12.0, $^4J_{CF}$ 5.0), 129.5 (s), 127.5 (s), 119.3 (d, $^2J_{CF}$ 12.0), 41.0 (s), 36.7 (s), 24.5 (s,); *m/z* (EI$^+$) 352 ([M − H]$^+$, 100), 309 ([M −$HCOCH_3$]$^+$, 92).

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Supporting Information Available: Representative NMR spectra of all compounds and X-ray CIF files for those given in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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