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Tetrahydropyrido[3,4-*b*]pyrazine Scaffolds from Pentafluoropyridine

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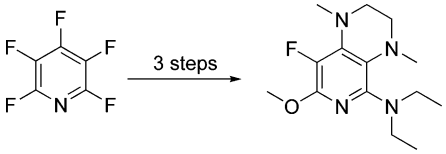

Representative polyfunctional tetrahydropyrido[3,4-*b*]pyrazine scaffolds have been synthesized very readily by a one-pot annelation reaction of pentafluoropyridine with appropriate diamines. The trifluorinated pyridopyrazine products react sequentially with various nucleophiles to give polysubstituted tetrahydropyridopyrazines, demonstrating the potential of the polyfluorinated ring fused pyridine system as a scaffold for the synthesis of previously inaccessible polysubstituted pyridopyrazine derivatives. This general approach has special relevance to the development of new chemical entities for the life science industries and particularly in the drug discovery arena, in which low molecular weight, polyfunctional heterocyclic derivatives are playing an increasingly important role.

Introduction

Effective methodology for the synthesis of low molecular weight, functional heterocycles bearing appropriate pharmacophoric features is being continually developed for the drug discovery arena since it is estimated that around 70% of all pharmaceutical products are based upon heterocyclic structures as a result of a favorable combination of druglike properties.[1−4] Lipinski suggested[5] that molecules are most likely to possess druglike physiochemical properties if they fall within the empirical "rules of 5", which are that the molecular weight is below 500, the calculated log of the octanol/water partition coefficient is less than 5, there are less than 5 hydrogen bonding donor atoms and the sum of N and O atoms is less than 10. Of course, many small heterocyclic compounds fall within these parameters.

Advances in parallel,[6] combinatorial,[7] rapid analogue,[8,9] privileged structure,[10−12] and diversity-oriented[13−15] synthesis techniques for lead generation and optimization require synthetic methodology that can be applied to maximize structural diversity from readily available core scaffolds that possess pluripotent functionality. Furthermore, effective methodology that is efficient, regio- and stereoselective, versatile, short, and high yielding, allowing the rapid synthesis of many analogues for bioassay, is essential. Unfortunately, however, analogue

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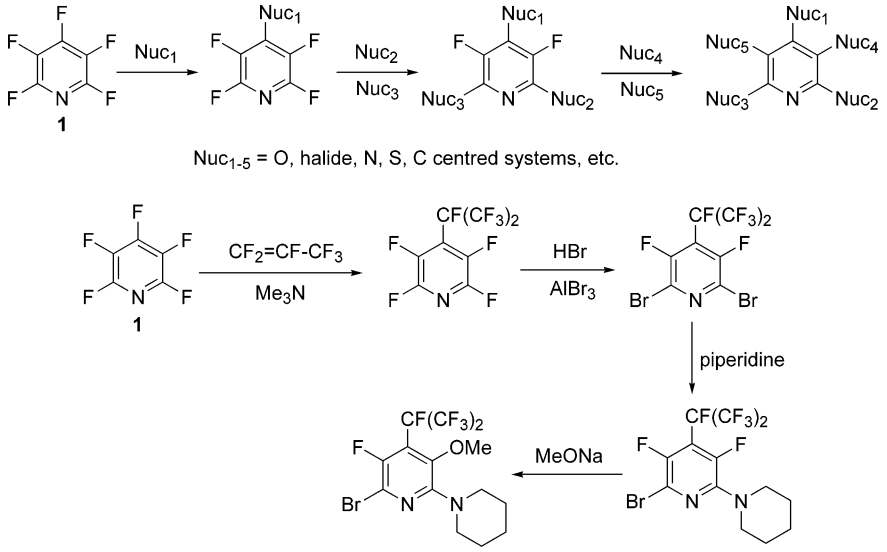
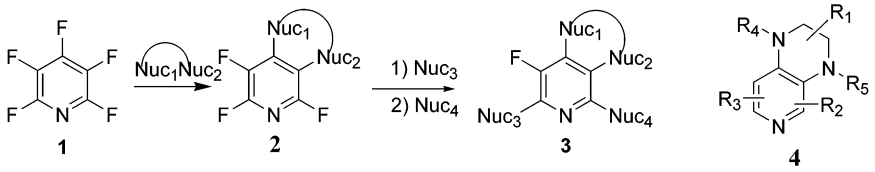
SCHEME 1. General Approach to the Synthesis of Pentasubstituted Pyridine Systems



SCHEME 2. Possible Synthetic Routes to Polyfunctional, Ring Fused Pyridine Analogues



synthesis of many polyfunctionalized heterocyclic derivatives is hampered by the inherent low reactivity and low regioselectivity of heteroaromatic systems.[16,17] For instance, preparation of highly substituted pyridine derivatives from pyridine itself is very difficult and only limited progress has been made using such an approach.[3]

In contrast, perfluorinated heteroaromatic systems[18,19] are potentially excellent scaffolds because they are highly reactive toward nucleophilic attack as a result of their electron-deficient nature, and in principle, all fluorine atoms may be displaced by nucleophiles. It is well-established[18,19] that the order of nucleophilic attack on, for example, pentafluoropyridine **1** is 4 > 2 > 3, for monosubstitution reactions involving a range of nucleophiles. Consequently, we can postulate that the order of nucleophilic substitution for a succession of reactions using pentafluoropyridine as the core scaffold could, in principle, occur as outlined in Scheme 1, although this may depend on the effect of each substituent once attached to the heterocyclic ring and the nature of the attacking nucleophile. This developing, general approach to the synthesis of polyfunctional heterocyclic systems has recently allowed us to complete the synthesis of several pentasubstituted pyridine systems[20] from pentafluoropyridine **1** by routes that fulfill many of the criteria for analogue synthesis that are discussed above (Scheme 1).

The order of nucleophilic substitution could, in principle, be altered by reaction of pentafluoropyridine with bifunctional nucleophiles, although this potentially very useful synthetic procedure has not been exploited to any real extent.[21] Substitution of the 4-position would be followed by attack at the adjacent 3-position as a result of the geometric constraints of the system as outlined in Scheme 2. Fused ring systems **2**, however, still possess further sites that are activated toward nucleophilic attack and could, therefore, provide ready access to many analogues of a wide variety of fused ring systems, of general structure **3**, if the orientation of sequential nucleophilic substitution could be controlled as outlined in Scheme 2. Of course, the large number of polyfunctional substrates bearing two nucleophilic sites that could be involved in such an annelation procedure and the wide variety of functional nucleophiles that are readily available could, potentially, provide access to many families of ring-fused pyridine systems.

Despite the relative simplicity of their structures, many bicyclic nitrogen-containing heterocycles remain, surprisingly, relatively inaccessible,[16] and the chemistry of even the least complex heterocycles of this class remains largely unexploited. Inevitably, this provides great opportunities for the discovery of small molecule, new chemical entities if suitable polyfunctional, bicyclic, nitrogenated heterocyclic scaffolds can be reliably accessed.

General methodology for the synthesis of functionalized derivatives of the [6,6]-fused ring system, tetrahydropyrido[3,4-*b*]pyrazine **4**, remains undeveloped, and we targeted the synthesis of such structures using the strategy outlined in Scheme 2 by using appropriate difunctional nitrogen nucleophiles as reagents. In fact,

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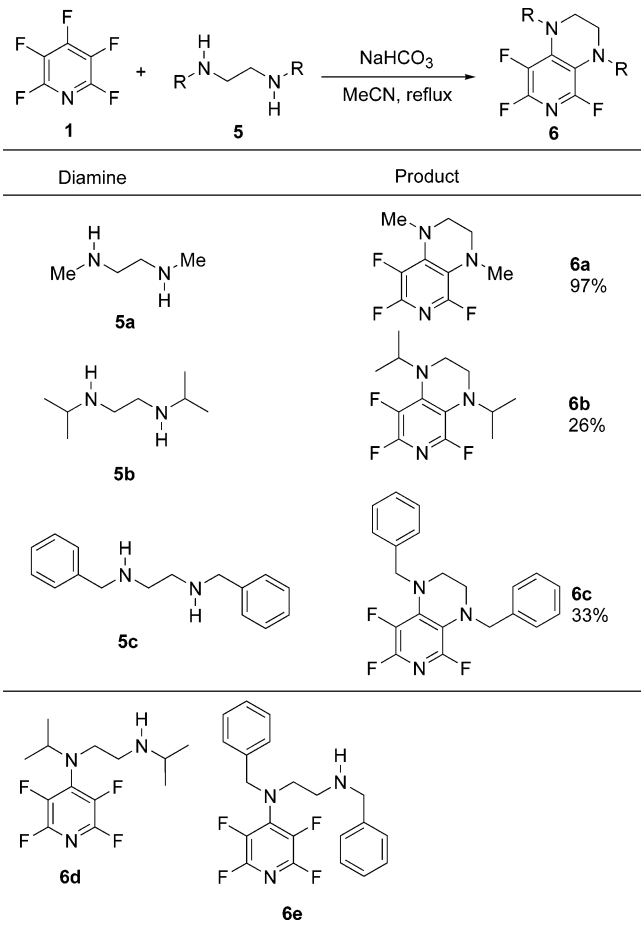
only a relatively limited number of tetrahydropyrido[3,4-*b*]pyrazines have been synthesized, albeit in low yields by multistep procedures, either from diaminopyridine[22] or chloro-aminopyridine[23] precursors or by reduction of pyrido[3,4-*b*]pyrazine derivatives by metal hydrides,[24−29] but elaboration of such scaffolds to multifunctional derivatives has proven to be very difficult and has not been developed to any degree.

In this paper, we describe successful syntheses of various polyfunctional tetrahydropyrido[3,4-*b*]pyrazine scaffolds, via intramolecular cyclization reactions between pentafluoropyridine and various model 1,2-difunctional nitrogen nucleophiles, following the general principles outlined above (Scheme 2), and further illustrative reactions of the ring fused scaffolds.

Results and Discussion

Annelation processes involving reactions between pentafluoropyridine **1** and difunctional secondary diamines **5** were studied initially because of the relatively high nucleophilicity of such diamine species (Table 1). Pentafluoropyridine **1** and *N*,*N*′-dimethylethylenediamine **5a**, in the presence of sodium bicarbonate and in dilute acetonitrile solution to minimize intermolecular reaction, gave the desired pyridopyrazine **6a** (Table 1) in excellent yield after simple recrystallization of the crude product from *n*-hexane. Cyclization processes could also be affected by microwave heating, and in a much shorter reaction time, a similar yield of **6a** was obtained from **1** and diamine **5a**. The related di*iso*propyl- and dibenzyldiamines **5b** and **5c** gave the analogous products **6b** and **6c**, respectively, by similar procedures (Table 1). Of course, there is far more steric hindrance around the nucleophilic nitrogen atoms for the ring closure step in **5b** and **5c**, and consequently cyclization to **6b** and **6c** is far slower than the corresponding synthesis of **6a**. ^{19}F NMR analysis of the crude products showed the presence of uncyclized systems **6d** and **6e** as the major products, even after prolonged heating indicating the steric retardation of this annelation process. After 5 d at reflux temperature, we decided to terminate these reactions despite the low conversions to cyclized products. Isolation of **6b** and **6c** was readily effected by column chromatography, although **6d** and **6e** were not isolated. Consequently, the lower yields of **6b** and **6c** reported are an indication of the low conversion of the second cyclization step rather than the formation of a complex mixture. The progress of all these cyclization reactions was monitored by ^{19}F NMR, and the disappearance of resonances attributed to fluorine atoms located at the 4- and 3-positions of pentafluoropyridine allowed simple identification of cyclized products **6**. Structures of **6a** and **6c** were confirmed by X-ray crystallography (Figures 1 and 2), and surprisingly, the CCDC does not contain any structures of derivatives of tetrahydropyrido[3,4-*b*]pyrazines where this bicyclic system is not a part of a larger polycyclic fragment, giving an indication of the very few systems of this type that have been synthesized previously. [Selected crystal data for **6a**: $C_9H_{10}F_3N_3$, monoclinic, space group $P2_1/c$, a = 17.7013(7), b = 6.9932(3), c = 16.8375(6) Å, β = 128.15(1)°, U = 1837.7(1) Å^3, Z = 8, $wR_2(F^2)$ = 0.1203, $R_1(F)$ = 0.0430, GOF = 0.942. For

TABLE 1. Synthesis of Trifluoro-pyrido[3,4-*b*]pyrazine Systems 6



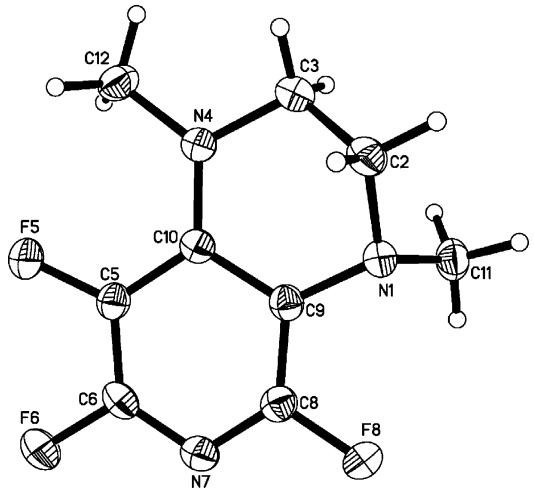


FIGURE 1. Structure of **6a**.

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(23) Couture, A.; Grandclaudon, P. *Synthesis* **1991**, *11*, 982.
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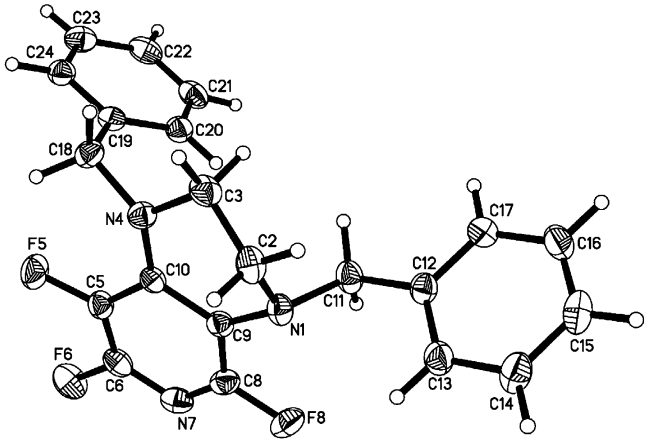
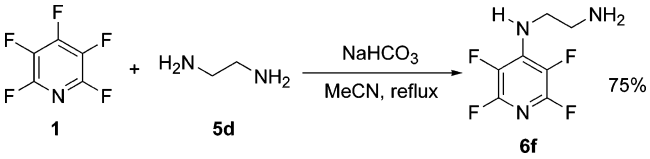


FIGURE 2. Structure of **6c**.

SCHEME 3. Reaction of Ethylene Diamine 5d with 1



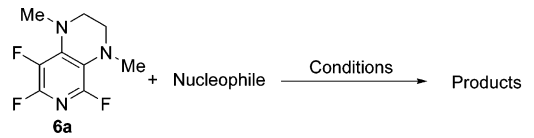
6c: $C_{21}H_{18}F_3N_3$, orthorhombic, space group $P2_12_12_1$, a = 7.4427(1), b = 14.1667(2), c = 16.6939(3) Å, U = 1760.18(5) Å^3, Z = 4, $wR_2(F^2)$ = 0.0945, $R_1(F)$ = 0.0338, GOF = 1.040.]

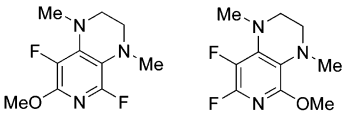
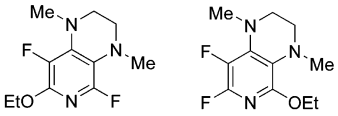
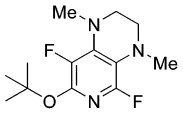
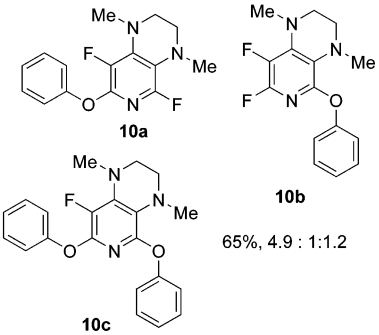
In contrast, reactions of primary diamine nucleophile **5d** gave noncyclized product **6f** only, arising only from substitution of the 4-position, despite prolonged heating and reactions involving the use of much stronger organic bases such as LDA and butyllithium (Scheme 3), reflecting the lower nucleophilicity of primary amine sites compared to secondary amines.

With model fluorinated pyridopyrazine **6a** in hand, we then assessed the reactivity of this core scaffold system with a series of nucleophiles, as shown in Tables 2 and 3. The major product **7a** of reaction of **6a** with sodium methoxide, either using refluxing acetonitrile or microwave heating, arises from substitution of fluorine at the 7-position with a minor isomer **7b**, arising from substitution of fluorine at the 5-position, formed in the ratio 10:1, respectively, as assessed by ^{19}F NMR and HPLC analysis. ^{19}F NMR indicated clean conversion of **6a** to **7a/b**, and isolation of **7a** was achieved by column chromatography, which resulted in some handling losses. Similarly, sodium ethoxide gave a mixture of isomers **8a** and **8b** in a similar ratio (8:1) after microwave heating (Table 2), although reaction of **6a** with potassium *tert*-butoxide gave essentially only **9**, with only traces of other products observed in the crude mixture by ^{19}F NMR. Products **10a**−**c**, formed by reaction of **6a** with potassium phenoxide, could not be separated, but enriched samples obtained by column chromatography allowed identification by NMR and mass spectrometry.

The structures of **7a** and **8a** and, therefore, the orientation of nucleophilic substitution were confirmed unambiguously by X-ray crystallography (Figures 3 and 4) and all other related products were characterized by comparison to the ^{19}F and ^{13}C NMR spectral data of **7a**.

TABLE 2. Model Nucleophilic Substitution Reactions of 6a



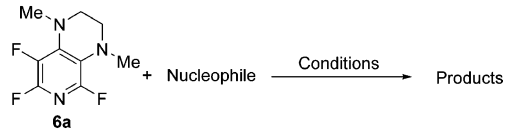
Nucleophile	Conditions	Product(s)[a]
MeONa	MeONa, MeOH reflux, 2 d	 **7a** 76%, 10 :1 **7b**
EtONa	EtONa, EtOH reflux, 2 d	 **8a** 80%, 8:1 **8b**
t-BuOK	THF, 90°C	 **9**, 66%
	Microwaves THF, 150°C, 1 h	 **10a** **10b** **10c** 65%, 4.9 : 1:1.2

[a] Minor products **7b** and **8b** were identified by ^{19}F NMR and GC−MS analysis but could not be isolated. Products **10a**−**c** were not separated but were identified by spectroscopic analysis of enriched samples.

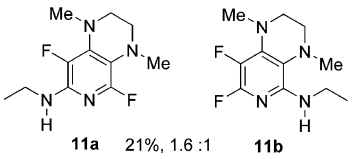
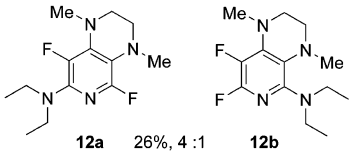
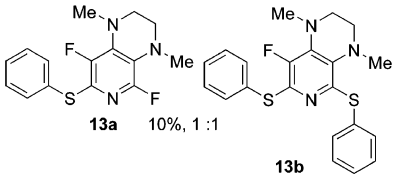
Structures of isomeric products which were isolated in only trace quantities followed from NMR data. [Selected crystal data for **7a**: $C_{10}H_{13}F_2N_3O$, monoclinic, space group $P2_1/c$, a = 5.3233(2), b = 13.1981(5), c = 14.7664(6) Å, β = 96.62(2)°, U = 1030.53(7) Å^3, Z = 4, $wR_2(F^2)$ = 0.1077, $R_1(F)$ = 0.0403, GOF = 1.014. For **8a**: $C_{11}H_{15}F_2N_3O$, monoclinic, space group $P2_1/c$, a = 8.7228(3), b = 18.3386(7), c = 7.2367(3) Å, β = 99.59(2)°, U = 1141.44(8) Å^3, Z = 4, $wR_2(F^2)$ = 0.1206, $R_1(F)$ = 0.0411, GOF = 0.955.]

The regioselectivity of nucleophilic substitution of **6a** may be explained by a consideration of the activating influences of ring nitrogen and the fluorine substituents attached to the pyridine ring, following similar well-established arguments[18,19] that have been used to interpret the regioselectivity of nucleophilic substitution processes of perfluorinated heteroaromatic systems. Pyridine nitrogen significantly activates sites *ortho* and *para* to itself, which in this case are the 5- and 7-positions. The 7-position is attacked preferentially because, here, activation by *ortho* and *meta* fluorine

TABLE 3. Nucleophilic Substitution Reactions of 6a with Model N, S, and C Nucleophiles



6a

Nucleophile	Conditions	Product(s)[a]
EtNHLi	THF, 90°C	 **11a** 21%, 1.6 :1 **11b**
Et_2NLi	THF, 90°C	 **12a** 26%, 4 :1 **12b**
	Microwaves THF, 150°C, 1 h	 **13a** 10%, 1 :1 **13b**

[a] Minor products **11b**, **12b** and **13b** were identified by ^{19}F NMR and GC−MS analysis but could not be isolated.

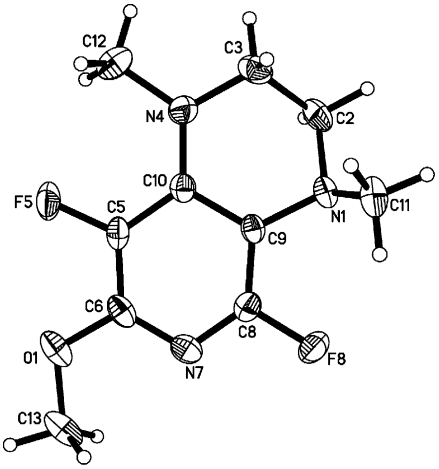


FIGURE 3. Structure of **7a**.

atoms is very activating, whereas the 5-site is activated by only one *meta* fluorine and significantly deactivated by a *para* fluorine atom (Figure 5). Of course, nucleophilic attack at the 5-position is hindered to some extent by the neighboring N-CH_3 group, and this may contribute to the regioselectivity observed.

Molecules **6a**, **6c**, **7a**, and **8a** have some common geometrical features; in all compounds the N4 atom is planar, the N1 atom has a pyramidal configuration of the bonds, and the N4−C10 bonds in all compounds (mean 1.367 Å) are significantly shorter than the N1−C9 bonds (mean 1.414 Å). In molecules **6a** and **6c**, the N7−C6 bond is shorter than N7−C8, whereas in molecules **7a** and **8a** this bond distribution is reversed, indicating that in **7a** and **8a** the oxygen atoms are also involved in the delocalization of the charge. The polar

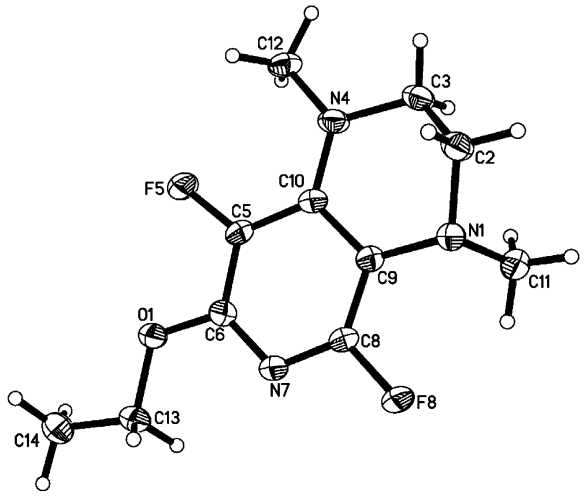


FIGURE 4. Structure of **8a**.

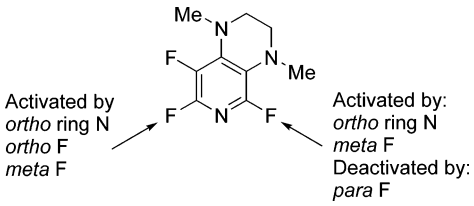


FIGURE 5. Activating influences on **6a** for nucleophilic aromatic substitution processes.

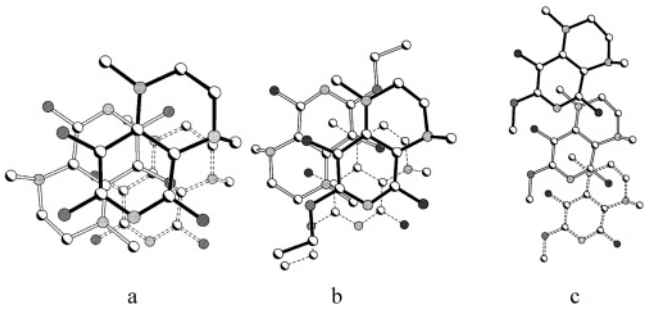
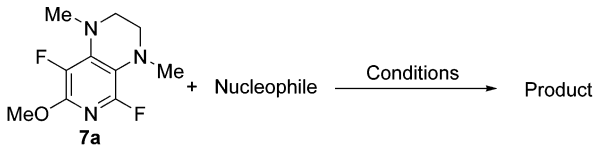


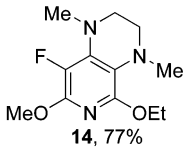
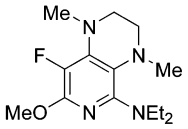
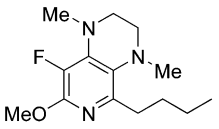
FIGURE 6. Stacking of the molecules in structures (a) **6a**, (b) **8a**, and (c) **7a**.

characteristics of **6a**, **7a**, and **8a** determine their packing in their respective crystals (Figure 6): **6a** and **8a** form stacks with an antiparallel orientation of adjacent molecules, molecules of **7a** are also arranged in stacks with partial parallel overlapping of their aromatic substructures, and the packing of molecules **6c** does not show any $\pi\cdots\pi$ stacking, probably because of the presence of bulky benzyl groups. In this case, the molecules are linked together by a number of weak C−H···C(Ph) interactions (the shortest H···C contact is 2.836 Å).

Given the successful outcome of reactions between **6a** and various oxygen nucleophiles, we began to explore reactions of this pyridopyrazine scaffold with representative nitrogen and sulfur nucleophiles; these are collated in Table 3. Again, we observed that nucleophilic substitution occurs preferentially at C-7, with substitution at C-5 a competing process. Low isolated yields of **11a** and **12a** were obtained due to difficulties in purification because of the large quantities of nucleophiles used to achieve satisfactory conversion. Reaction of lithium

TABLE 4. Nucleophilic Substitution Reaction of 7a



Nucleophile	Conditions	Product(s)
EtONa	EtOH, 90°C	 **14**, 77%
Et_2NLi	THF, 90°C	 **15**, 64%
BuLi	THF, 90°C	 **16**, 31%

thiophenoxide proceeds smoothly, but isolation of the products **13** is severely hampered by formation of phenyl disulfide as a byproduct.

The results of reactions between **6a** and a range of nucleophiles (Tables 2 and 3) demonstrate that the pyridopyrazine scaffold can indeed be further functionalized, following the general strategy outlined in Scheme 2. Subsequently, further representative nucleophilic substitution reactions of **7a**, the most readily accessible system derived from **6a**, with a short range of nucleophiles were studied (Table 4) and gave several polysubstituted pyridopyrazine derivatives, again following the strategy indicated above (Scheme 2). Reaction of **7a** with sodium ethoxide, lithium diethylamide, and *n*-butyllithium gave single products **14**, **15**, and **16**, respectively, all arising from substitution of the most activated fluorine atom located *ortho* to the pyridine ring nitrogen atom. Products could be identified by ^{19}F NMR, which showed only one peak at −160 ppm indicating the presence of fluorine located *meta* to nitrogen. Furthermore, a NOE experiment, where the resonance attributed to the methylene group attached directly to the pyridine ring in **16** was irradiated leading to an enhancement of the 4-N-CH_3 signal, confirmed the regiochemistry.

Conclusions

We have demonstrated that pentafluoropyridine **1** can be used as a substrate for the synthesis of polysubstituted pyridopyrazine derivatives upon reaction with various diamines. The fluorinated fused heterocyclic products can act as functional core scaffolds and react further with nucleophiles to give products arising from substitution at sites that are *ortho* to pyridine ring nitrogen with a high degree of control, the regioselectivity for which may be explained by a consideration of the activating influences of ring fluorine and nitrogen. Therefore, the approach of using perfluorinated heterocycles for the synthesis of otherwise relatively inaccessible polysubstituted [6,6] fused ring heterocycles is possible, although difficult separation of the major products from small quantities of minor products can sometimes be problematic. Clearly many polysubstituted pyridopyrazine derivatives could be synthesized from the vast number of nucleophilic species available following the general principles outlined here and further applications of this annelation/functionalization strategy for the synthesis of many heterocyclic scaffolds will be reported in subsequent publications.

Experimental Section

All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz (^1H NMR), 376 MHz (^{19}F NMR), and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by either ^{19}F NMR or gas chromatography using an SE30 column. Column chromatography was carried out on silica gel (particle size 0.040−0.063 mm), and TLC analysis was performed on silica gel TLC plates.

All crystallographic data were collected at $T = 120(1)$ K on a SMART-CCD 6000 diffractometer (λ Mo Kα, ω-scan, 0.3°/frame). The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, and H-atoms were located on the difference map and refined isotropically. Crystallographic data for the structures **6a**, **6c**, **7a**, and **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 268150-268153.

Synthesis of Pyrido[3,4-*b*]pyrazine Scaffolds 6. 5,7,8-Trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]-pyrazine 6a. *N*,*N*′-Dimethylethylene-1,2-diamine **5a** (1.76 g, 20 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol), pentafluoropyridine **1** (1.69 g, 10 mmol), and acetonitrile (400 mL) were heated to reflux for 5 d to give the crude material (single product by GC and NMR) as a brown solid. Recrystallization from *n*-hexane gave **6a** (2.1 g, 97%) as needlelike white crystals: mp 54.3−54.9 °C. Found: C, 49.7; H, 4.7; N, 19.3. $C_9H_{10}F_3N_3$ requires: C, 49.8; H, 4.6; N, 19.4. δ_F −85.00 (1 F, dd, F-5), −99.30 (1F, dd, F-7), −162.64 (1F, m, F-8); δ_H 3.28 (3H, d, $^5J_{HF}$ 4.8, 1-NCH_3), 3.23 (2H, m, CH_2), 3.04 (2H, m, CH_2), 2.73 (3H, s, 4-NCH_3); δ_C 148.4 (dd, $^1J_{CF}$ 233.3, $^3J_{CF}$ 16.3, C-5), 145.1 (ddd, $^1J_{CF}$ 230.4, $^2J_{CF}$ 17.6, $^3J_{CF}$ 17.6, C-7), 140.0 (dt, $^2J_{CF}$ 6.1, $^3J_{CF}$ 3.8, C-4*b*), 131.8 (ddd, $^1J_{CF}$ 244.6, $^2J_{CF}$ 30.5, $^4J_{CF}$ 4.8, C-8), 116.6 (dd, $^2J_{CF}$ 29.1, $^3J_{CF}$ 4.3, C-3*b*), 48.5 (s, CH_2), 46.0 (s, CH_2), 43.6 (d, $^4J_{CF}$ 5.3, 4-NCH_3), 41.6 (d, $^4J_{CF}$ 12.9, 1-NCH_3); *m*/*z* (EI$^+$) 218 ([M + H]$^+$, 6), 217 ([M]$^+$, 100), 202 ([M − CH_3]$^+$, 42) 187 ([M − $2CH_3$]$^+$, 36) 146 ([M − C_4H_9N]$^+$ 28). Single crystals for X-ray studies were grown from dichloromethane/hexane.

5,7,8-Trifluoro-1,4-diisopropyl-1,2,3,4-tetrahydropyrido-[3,4-*b*]pyrazine 6b. *N*,*N*′-Diisopropylethylene-1,2-diamine **5b** (2.88 g, 20 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol), pentafluoropyridine **1** (1.69 g, 10 mmol), and acetonitrile (400 mL) were refluxed at 90 °C for 5 d to yield the crude product as a brown solid (3.47 g). Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave **6b** (0.71 g, 26%) as an orange solid: mp 50.7−53.5 °C; [M + H]$^+$ 274.1525, $C_{13}H_{18}F_3N_3$ requires [M + H]$^+$ 274.1526; δ_F −82.67 (1F, m, F-5), −100.13 (1F, m, F-7), −161.45 (1F, m,

F-8); δ_H 4.50 (1H, sept d, $^3J_{HH}$ 6.5, $^5J_{HF}$ 3.0, 1-NC*H*$(CH_3)_2$), 3.56 (1H, septet, $^3J_{HH}$ 7.0, 4-NC*H*$(CH_3)_2$), 3.16 (2H, m, NCH_2), 3.04 (2H, m, NCH_2), 1.21 (6H, dd, $^3J_{HH}$ 7.0, $^4J_{HF}$ 1.5, NCH$(CH_3)_2$), 1.11 (6H, dd, $^3J_{HH}$ 6.5, $^4J_{HF}$ 0.5, NCH$(CH_3)_2$); δ_C 148.4 (dd, $^1J_{CF}$ 232.3, $^3J_{CF}$ 15.6, C-5), 144.8 (ddd, $^1J_{CF}$ 229.9, $^2J_{CF}$ 19.1, $^3J_{CF}$ 19.1, C-7), 139.3 (dt, $^2J_{CF}$ 6.5, $^3J_{CF}$ 3.4, C-4*b*), 132.1 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 29.6, $^4J_{CF}$ 4.8, C-8), 116.0 (dd, $^2J_{CF}$ 27.8, $^3J_{CF}$ 4.4, C-3*b*), 53.2 (d, $^4J_{CF}$ 6.1, 4-NC*H*$(CH_3)_2$), 51.2 (d, $^4J_{CF}$ 15.8, 1-NC*H*$(CH_3)_2$), 40.9 (s, NCH_2), 39.1 (s, NCH_2), 20.8 (s, NCH$(CH_3)_2$), 20.3 (s, NCH$(CH_3)_2$); *m/z* (EI)$^+$ 273 ([M]$^+$, 84), 258 ([M − CH_3]$^+$, 100), 230 ([M − $CH(CH_3)_2$]$^+$, 27), 216 ([M − $CH_2CH(CH_3)_2$]$^+$, 92), 202 ([M − $(CH_2)_2CH(CH_3)_2$]$^+$, 16).

1,4-Dibenzyl-5,7,8-trifluoro-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 6c. *N*,*N*′-Dibenzylethane-1,2-diamine **5c** (2.4 g, 10 mmol), sodium hydrogen carbonate (1.68 g, 20 mmol), pentafluoropyridine **1** (0.85 g, 5 mmol), and acetonitrile (175 mL) were heated to reflux for 5 d to yield the crude material as a brown oil (2.68 g). Purification by column chromatography on silica gel (1:2 ethyl acetate/*n*-hexane) gave **6c** (0.61 g, 33%) as beige crystals: mp 97.5−98.5 °C; [M + H]$^+$ 370.1526, $C_{21}H_{18}F_3N_3$ requires [M + H]$^+$ 370.1529; δ_F −83.54 (1F, m, F-5), −98.78 (1F, m, F-7), −161.23 (1F, m, F-8); δ_H 7.00−7.80 (10H, m, Ar H), 4.67 (2H, s, CH_2Ph), 3.95 (2H, s, CH_2Ph), 3.08 (2H, m, NC*H*$_2$CH$_2$), 2.80 (2H, m, NCH$_2$C*H*$_2$); δ_C 148.9 (dd, $^1J_{CF}$ 233.7, $^3J_{CF}$ 16, C-5), 145.1 (ddd, $^1J_{CF}$ 230.3, $^2J_{CF}$ 19.1, $^3J_{CF}$ 19.1, C-7), 139.4 (dt, $^2J_{CF}$ 7.7, $^3J_{CF}$ 4.5, C-4*b*), 138.0 (s, Ar C), 137.5 (s, Ar C), 132.1 (ddd, $^1J_{CF}$ 244.8, $^2J_{CF}$ 30.1, $^4J_{CF}$ 4.6, C-8), 129.1 (s, Ar CH), 129.0 (s, Ar CH), 128.9 (s, Ar CH), 128.0 (s, Ar CH), 127.9 (s, Ar CH), 127.3 (s, Ar CH), 116.6 (dd, $^2J_{CF}$ 28.2, $^3J_{CF}$ 4.2, C-3*b*), (s, Ar CH), 59.5 (d, $^5J_{CF}$ 3.8, CH_2), 57.3 (d, $^4J_{CF}$ 12.6, CH_2), 43.9 (s, CH_2), 43.4 (s, CH_2); *m/z* (EI$^+$) 369 ([M]$^+$, 54), 278 ([M − CH_2Ph]$^+$, 49), 91 ([CH_2Ph]$^+$, 100). Crystals for X-ray studies were grown from dichloromethane/*n*-hexane.

***N*-(2,3,5,6-Tetrafluoropyridin-4-yl)ethane-1,2-diamine 6f.** Ethylenediamine **5d** (1.20 g, 20 mmol), sodium hydrogen carbonate (4.24 g, 40 mmol), pentafluoropyridine **1** (1.69 g, 10 mmol), and acetonitrile (400 mL) were heated to reflux for 2 d to give the crude product as a white solid (3.13 g). Purification by recrystallization from methanol gave **6f** (1.56 g, 75%) as a white solid: mp 114.0−116.5 °C. Found: C, 40.3; H, 3.4; N, 20.1. $C_7H_7F_4N_3$ requires: C, 40.2; H, 3.4; N, 20.1. δ_F (d_6-acetone) −98.42 (2F, m, F-2,6), −166.28 (2F, m, F-3,5); δ_H (d_6-acetone) 6.50 (1H, br s, NH), 3.75 (2H, m, NHC*H*$_2$CH$_2$NH$_2$), 3.46 (2H, m, NHCH$_2$C*H*$_2$NH$_2$), 3.00 (2H, br 2, NH_2); δ_C (d_6-acetone) 144.1 (dm, $^1J_{CF}$ 230.0, C-2), 138.4 (m, C-4), 131.1 (ddm, $^1J_{CF}$ 245.4, $^2J_{CF}$ 35.9, C-3), 50.8 (s, CH_2NH_2), 44.8 (t, $^4J_{CF}$ 3.8, $NHCH_2$); *m/z* (EI$^+$) 210 ([M + H]$^+$, 95), 193 ([M − NH_2]$^+$, 100).

Nucleophilic Substitution Reactions of 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 6a. 7-Methoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 7a. Sodium (0.7 g, 30.23 mmol) was added to anhydrous methanol (30 mL) under argon followed by the addition of **6a** (0.82 g, 3.78 mmol). The resulting solution was heated at 66 °C for 42 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured into water (30 mL), extracted with dichloromethane (3 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated to yield the crude product as a yellow oil. Purification by column chromatography on silica gel (2:1 ethyl acetate/*n*-hexane) gave **7a** (0.66 g, 76%) as white crystals: mp 46.0−46.5 °C. Found: C, 52.4; H, 5.7; N, 18.3. $C_{10}H_{13}F_2N_3O$ requires: C, 52.4; H, 5.7; N, 18.3. δ_F −86.81 (1F, d, $^5J_{FF}$ 22.6, F-5), −161.91 (1F, m, F-8); δ_H 3.88 (3H, s, OCH_3), 3.20 (3H, d, $^5J_{HF}$ 3.6, 1-NCH_3), 3.18 (2H, m, CH_2), 3.02 (2H, m, CH_2), 2.68 (3H, s, 4-NCH_3); δ_C 149.74 (dd, $^1J_{CF}$ 228.7, $^4J_{CF}$ 1.1, C-5), 146.33 (dd, $^2J_{CF}$ 17.8, $^3J_{CF}$ 13.4, C-7), 139.00 (dd, $^2J_{CF}$ 8.0, $^3J_{CF}$ 4.9, C-4*b*), 133.57 (dd, $^1J_{CF}$ 236, $^4J_{CF}$ 5.0, C-8), 113.17 (d, $^2J_{CF}$ 30.5, C-3*b*), 54.03 (s, OCH_3), 48.70 (s, CH_2), 45.60 (s, CH_2), 43.55 (d, $^4J_{CF}$ 4.2, 4-NCH_3), 41.52 (d, $^4J_{CF}$ 13.3, 1-NCH_3); *m/z* (EI$^+$) 229 ([M]$^+$, 100), 214 ([M − CH_3]$^+$ 66), 199 ([M − C_2H_6]$^+$, 14). The reaction also gave a trace amount of 7,8-difluoro-5-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **7b** as a colorless oil: δ_F −100.31 (1F, d, $^3J_{FF}$ 24.8, F-7), −166.63 (1F, dd, $^3J_{FF}$ 24.8, $^5J_{HF}$ 4.5, F-8); δ_H 3.94 (3H, s, OCH_3), 3.16 (3H, d, $^5J_{HF}$ 3.9, 1-NCH_3), 3.15 (2H, m, NCH_2), 3.02 (2H, m, NCH_2), 2.64 (3H, s, 4-NCH_3); *m/z* (EI$^+$) 229 ([M]$^+$, 100, 214 ([M − CH_3]$^+$, 81), 199 ([M − C_2H_6]$^+$, 16). Crystals of **7a** for X-ray studies were grown from dichloromethane/*n*-hexane.

7-Ethoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 8a. Sodium (0.11 g, 4.6 mmol) was added to anhydrous ethanol (30 mL) under argon followed by the addition of **6a** (1.0 g, 4.6 mmol). The resulting solution was refluxed at 100 °C for 48 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was then cooled to room temperature, poured onto water (30 mL), extracted with dichloromethane (3 × 30 mL) and dried ($MgSO_4$). The solvent was evaporated to yield the crude product as a yellow solid. Purification by recrystallization from *n*-hexane gave **8a** (0.90 g, 80%) as off-white crystals: mp 71.3−72.2 °C. Found: C, 54.2; H, 6.2; N, 17.1. $C_{11}H_{15}F_2N_3O$ requires: C, 54.3; H, 6.2; N, 17.3. δ_F −86.67 (1F, d, $^5J_{FF}$ 22.6, F-5), −161.44 (1F, dm, $^5J_{FF}$ 24.5, F-8); δ_H 4.31 (2H, q, $^3J_{HH}$ 7.2, OC*H*$_2$CH$_3$), 3.21 (3H, d, $^5J_{HF}$ 4.5, 1-NCH_3), 3.18 (2H, m, NCH_2), 3.04 (2H, m, NCH_2), 2.70 (3H, s, 4-NCH_3), 1.38 (3H, t, $^3J_{HH}$ 7.2, OCH$_2$C*H*$_3$); δ_C 149.71 (d, $^1J_{CF}$ 228.4, C-5), 146.08 (dd, $^2J_{CF}$ 14.0, $^3J_{CF}$ 11.0, C-7), 139.04 (dd, $^2J_{CF}$ 6.4, $^3J_{CF}$ 4.1, C-4*b*), 133.62 (dd, $^1J_{CF}$ 241, $^4J_{CF}$ 5, C-8), 112.84 (d, $^2J_{CF}$ 30.1, C-3*b*), 62.55 (s, O*C*H$_2$CH$_3$), 48.75 (s, CH_2), 45.61 (s, CH_2), 43.60 (d, $^4J_{CF}$ 4.6, 4-NCH_3), 41.53 (d, $^4J_{CF}$ 13.3, 1-NCH_3), 14.92 (s, OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 243 ([M]$^+$, 100), 213 ([M − $(CH_3)_2$]$^+$, 88). The reaction also gave trace quantities of 5-ethoxy-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **8b**: δ_F −100.18 (1F, dm, $^3J_{FF}$ 29.0, F-7), −166.83 (1F, dm, $^3J_{FF}$ 24.6, F-8); δ_H 3.71 (2H, q, $^3J_{HH}$ 7.0, OC*H*$_2$CH$_3$), 3.20 (3H, d, $^5J_{HF}$ 4.2, 1-NCH_3), 3.17 (2H, t, $^3J_{HH}$ 5.2, NCH_2), 3.04 (2H, t, $^3J_{HH}$ 5.2, NCH_2), 2.67 (3H, s, 4-NCH_3), 1.23 (3H, t, $^3J_{HH}$ 7.0, OCH$_2$C*H*$_3$); *m/z* (EI$^+$) 243 ([M]$^+$, 100), 213 ([M − $(CH_3)_2$]$^+$, 80).

7-*tert*-Butoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 9. Potassium *tert*-butoxide (0.22 g, 2 mmol) and **6a** (0.22 g, 1 mmol) were added to dry tetrahydrofuran (15 mL) under argon and refluxed at 90 °C for 90 h after which time an additional 2 equiv of potassium *tert*-butoxide (0.22 g, 2 mmol) was added. Refluxing was continued for 18 h and HPLC indicated 97% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent was evaporated, and the residue rwas edissolved in dichloromethane. The mixture was poured onto 0.5 M hydrochloric acid (30 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$), and the solvent was evaporated to dryness to yield the crude product as a yellow oil (0.19 g). Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane, 0%-100%) gave **9** (0.18 g, 66%) as a colorless oil. Found: C, 57.6; H, 7.1; N, 15.5. $C_{13}H_{19}F_2N_3O$ requires: C, 57.6; H, 7.0; N, 15.5. δ_F −84.22 (1F, d, $^5J_{CF}$ 26.3, F-5), −155.20 (1F, m, F-8); δ_H 3.14 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 3.12 (2H, m, CH_2), 2.99 (2H, t, $^3J_{HH}$ 4.4, CH_2), 2.68 (3H, s, 4-NCH_3), 1.48 (9H, s, C−CH_3); δ_C148.7 (dd, $^1J_{CF}$ 229.1, $^4J_{CF}$ 1.5, C-5), 145.l (dd, $^2J_{CF}$ 18.9, $^3J_{CF}$ 13.4, C-7), 138.7 (dd, $^2J_{CF}$ 8.3, $^3J_{CF}$ 6.6, C-4*b*), 136.4 (dd, $^1J_{CF}$ 243.3, $^4J_{CF}$ 5.3, C-8), 114.0 (d, $^2J_{CF}$ 31.5, C-3*b*), 81.2 (s, O*C*$(CH_3)_3$), 48.4 (s, NCH_2), 45.7 (s, NCH_2), 43.4 (d, $^4J_{CF}$ 5.1, 4-NCH_3), 41.5 (d, $^4J_{CF}$ 13.4, 1-NCH_3), 28.9 (s, C*C*H_3)$_3$); *m/z* (EI)$^+$ 272 ([M + H]$^+$, 38), 257 ([MH − CH_3]$^+$, 65).

5,8-Difluoro-1,4-dimethyl-7-phenoxy-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 10a. Phenol (0.19 g, 2 mmol) and potassium metal (0.17 g, 3 mmol) were added to tetrahydrofuran (15 mL) under argon. The reaction mixture was stirred until all of the potassium had dissolved. The resulting solution was transferred to a sealed microwave vial under argon containing **6a** (0.11 g, 0.5 mmol) and the vial was irradiated with microwaves at 150 °C for 1 h, after which time HPLC indicated 89% conversion of starting material. The solvent was

evaporated, and the residue was redissolved in dichloromethane and then poured onto 1 M hydrochloric acid (30 mL). The aqueous phase was extracted with dichloromethane (100 mL) and dried ($MgSO_4$), and the solvent was evaporated to dryness to yield the crude product as a yellow oil (0.23 g). Attempted purification by column chromatography on silica gel (ethyl acetate in *n*-hexane, 0−70%) gave a mixture consisting of **10a**, δ_F −82.52 (1F, d, $^5J_{FF}$ 22.6, F-5), −156.02 (1F, m, F-8); δ_H 7.33 (2H, t, $^3J_{HH}$ 8.4, Ar H), 7.12 (1H, d, $^3J_{HH}$ 7.2, Ar H), 7.07 (2H, d, $^3J_{HH}$ 8.8, Ar H), 3.25 (3H, d, $^5J_{HF}$ 4.8, 1-NCH_3), 3.21 (2H, m, CH_2), 3.04 (2H, m, CH_2), 2.73 (3H, s, 4-NCH_3); *m/z* (EI)$^+$ 292 ([M + H]$^+$, 100), 277 ([MH − CH_3]$^+$, 52), and 7.8-difluoro-1,4-dimethyl-5-phenoxy-1,2,3,4-tetrahydropyrido-[3,4-*b*]pyrazine **10b** in the ratio 7.9:1, respectively, (0.095 g, 65%) as a white solid: δ_F −96.71 (d, $^3J_{FF}$ 22.6, F-7), −163.39 (m, F-8); *m/z* (EI)$^+$ 292 ([M + H]$^+$, 100), 277 ([MH − CH_3]$^+$, 48). 8-Fluoro-1,4-dimethyl-5,7-diphenoxy-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **10c** was also isolated in a trace amount: δ_F −156.49 (1F, m, F-8); δ_H 7.21 (4H, m, Ar CH), 7.00 (6H, m, Ar CH), 3.25 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 3.24 (2H, m, CH_2), 3.08 (2H, m, CH_2), 2.79 (3H, s, 4-NCH_3); *m/z* (EI)$^+$ 366 ([M + H]$^+$, 100), 351 ([MH − CH_3]$^+$, 46).

***N*-Ethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-7-amine 11a.** Butyllithium in tetrahydrofuran (1 mL, 2 mmol, 2 M) was added to a solution of ethylamine (0.09 g, 2 mmol) in tetrahydrofuran (30 mL) at −78 °C. The resulting solution was stirred at −78 °C for 1 h before warming to room temperature and addition of **6a** (0.22 g, 1 mmol). The reaction mixture was heated to reflux for 5 d, and over the course of the reaction, an additional 14 equiv (28 mmol) of the lithium ethylamide salt was added, following the procedure outlined above. HPLC indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent was evaporated, and the residue was redissolved in dichloromethane, poured into water (50 mL), extracted with dichloromethane (100 mL), and dried ($MgSO_4$). The solvent was evaporated to dryness to yield the crude product as a brown oil (0.27 g). Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane 0−100%) gave **11a** (0.05 g, 21%) as an off white solid: mp 79.0−80.0 °C. Found: C, 54.5; H, 6.7; N, 22.8. $C_{11}H_{16}F_2N_4$ requires: C, 54.6; H, 6.6; N, 23.1. δ_F −86.00 (1F, d, $^5J_{FF}$ 22.6, F-5), −162.08 (1F, q, $^5J_{FF}$ 22.6, F-8); δ_H 4.13 (1H, br s, NH), 3.38 (2H, q, $^3J_{HH}$ 6.8, CH_2CH$_3$), 3.17 (5H, m, 1-NCH_3, NCH_2), 3.03 (2H, m, NCH_2), 2.66 (3H, s, 4-NCH_3), 1.21 (3H, t, $^3J_{HH}$ 7.2, NHCH$_2$CH_3); *m/z* (EI)$^+$ 242 ([M]$^+$, 100), 227 ([M − CH_3]$^+$, 90), 213 ([M − CH_2CH_3]$^+$, 14). The reaction also gave trace quantities of *N*-ethyl-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-5-amine **11b**: δ_F −98.16 (1F, d, $^3J_{FF}$ 26.3, F-7), −172.07 (1F, q, $^3J_{FF}$ 22.6, F-8); δ_H 4.69 (1H, br s, NH), 3.36 (2H, q, $^3J_{HH}$ 7.2, NHCH_2CH$_3$), 3.23 (2H, t, $^3J_{HH}$ 4.8, NCH_2CH$_2$), 3.19 (3H, d, $^5J_{HF}$ 4.0, 1-NCH_3), 2.97 (2H, t, $^3J_{HH}$ 5.2, NCH$_2$CH_2), 2.50 (3H, s, 4-NCH_3), 1.21 (3H, t, $^3J_{HH}$ 7.2, NHCH$_2$CH_3); *m/z* (EI)$^+$ 243 ([M]$^+$, 100).

***N*,*N*-Diethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-7-amine 12a.** To diethylamine (0.073 g, 1 mmol) in tetrahydrofuran (5 mL) at −78 °C was added butyllithium (0.59 mL, 1 mmol, 1.7 M in pentane), and the solution stirred for 1 h before warming to room temperature. The mixture was added to **6a** (0.22 g, 1 mmol) in tetrahydrofuran (25 mL) and heated to reflux at 75 °C for 24 h. After this time, ^{19}F NMR indicated no conversion of starting material so over the period of 120 h, excess lithium diethylamide salt (3.54 mL, 6 mmol) was added to the reaction mixture following the procedure outlined above. After refluxing for 144 h ^{19}F NMR indicated 100% conversion of starting material so the reaction was cooled to room temperature, poured into water (30 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$), and the solvent was evaporated to dryness to yield the crude product as a brown oil (0.57 g). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave **12a** (0.38 g, 26%) as a colorless oil: [M + H]$^+$ 270.1668, $C_{13}H_{20}N_4F_2$ requires [M + H]$^+$ 270.1656; δ_F −83.92 (1F, d, $^5J_{FF}$ 24, F-5), −150.42 (1F, d, $^5J_{FF}$ 25, F-8); δ_H 3.29 (4H, q, $^3J_{HH}$ 6.8, CH_2CH$_3$), 3.12 (2H, m, NCH_2), 3.10 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 2.98 (2H, m, NCH_2), 2.66 (3H, s, 4-NCH_3), 1.10 (6H, t, $^3J_{HH}$ 6.8, CH_2CH_3); δ_C 150.4 (d, $^1J_{CF}$ 225.3, C-5), 141.9 (dd, $^2J_{CF}$ 18.0, $^3J_{CF}$ 11.0, C-7), 139.3 (dd, $^2J_{CF}$ 8.0, $^3J_{CF}$ 8.0, C-4*b*), 136.6 (dd, $^1J_{CF}$ 240.1, $^4J_{CF}$ 4.6, C-8), 111.7 (d, $^2J_{CF}$ 32.4, C-3*b*), 48.7 (s, NCH_2), 46.0 (s, NCH_2), 44.6 (d, $^4J_{CF}$ 5.0, CH_2CH$_3$), 43.6 (d, $^4J_{CF}$ 4.6, 4-NCH_3), 42.1 (d, $^4J_{CF}$ 13.3, 1-NCH_3), 13.8 (s, CH_2CH_3); *m/z* (EI$^+$) 270 ([M]$^+$, 96), 255 ([M − CH_3]$^+$, 100), 241 ([M − CH_3CH_2]$^+$, 70), 226 ([M − $(CH_3)_2CH_2$]$^+$, 79), 211 ([M − $(CH_3)_3CH_2$]$^+$, 35). The reaction also gave a trace amount of *N*,*N*-diethyl-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-5-amine **12b** as a colorless oil: δ_F −98.02 (1F, d, $^3J_{FF}$ 28.4, F-7), −166.21 (1F, d, $^3J_{FF}$ 29.3, F-8); *m/z* (EI$^+$) 270 ([M]$^+$, 100), 255 ([M − CH_3]$^+$, 69), 241 ([M − CH_3CH_2]$^+$, 89), 225 ([M − $(CH_3)_3$]$^+$, 88), 211 ([M − $(CH_3)_3CH_2$]$^+$, 96).

5,8-Difluoro-1,4-dimethyl-7-(phenylsulfanyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 13a. Lithium thiophenoxide (16 mL, 16 mmol, 1 M in tetrahydrofuran) was added to a sealed microwave vial under argon containing **6a** (0.22 g, 1 mmol) and tetrahydrofuran (1 mL). The vial was irradiated with microwaves at 150 °C for 1 h after which time HPLC indicated 98% conversion of starting material. The above procedure was repeated three more times and the reaction mixtures were cooled to room temperature and combined. The solvent was evaporated and the residue redissolved in dichloromethane, poured onto 1 M hydrochloric acid (50 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated, and the excess lithium thiophenoxide was removed by passing through an SCX column to yield the crude product as a yellow oil (0.66 g). Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane 0%-40%) followed by mass directed automated preparative HPLC (50−99% acetonitrile in formic acid) gave **13a** (0.37 g, 10%) as an amber oil. Found: C, 58.7; H, 4.9; N, 13.5. $C_{15}H_{15}F_2N_3S$ requires: C, 58.6; H, 4.9; N, 13.7. δ_F −78.41 (1F, d, $^5J_{FF}$ 23.2, F-5), −131.43 (1F, dq, $^5J_{FF}$ 23.2, $^5J_{HF}$ 4.1, F-8); δ_H 7.42 (2H, d, $^3J_{HH}$ 7.2, Ar H), 7.29 (2H, t, $^3J_{HH}$ 6.8, Ar H), 7.23 (1H, d, $^3J_{HH}$ 6.8, Ar H), 3.16 (5H, overlapping d & t, 1-NCH_3 & CH_2), 3.03 (2H, t, $^3J_{HH}$ 4.0, CH_2), 2,79 (3H, s, 4-NCH_3); δ_C 151.0 (d, $^1J_{CF}$ 232.0, C-5), 146.0 (dd, $^1J_{CF}$ 246.2, $^5J_{CF}$ 3.3, C-8), 137.2 (dd, $^2J_{CF}$ 9.8, $^3J_{CF}$ 8.2, C-7), 132.9 (s, Ar C), 131.7 (s, Ar CH), 130.5 (dd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 18.2, C-4*b*), 128.9 (s, Ar CH), 127.4 (s, Ar CH), 119.6 (dd, $^2J_{CF}$ 30.7, $^3J_{CF}$ 2.6, C-3*b*), 48.2, (s, NCH_2), 46.6 (s, NCH_2), 43.2 (d, $^5J_{CF}$ 7.2, 4-NCH_3), 41.9 (d, $^5J_{CF}$ 12.9, 1-NCH_3); *m/z* (EI)$^+$ 308 ([M + H]$^+$, 85), 277 ([MH − $(CH_3)_2$]$^+$, 100), 233 ([MH − $(CH_3)_2NCH_2CH_2$]$^+$, 88). The reaction also produced trace quantities of 8-fluoro-1,4-dimethyl-5,7-bis(phenylsulfanyl)-1,2,3,4-tetrahydropyrido-[3,4-*b*]pyrazine **13b**: δ_F −135.91 (1F, q, $^5J_{HF}$ 3.8, F-8); δ_H(CCl_3; Me_4Si) 7.0−7.3 (10H, m, Ar H), 3.26 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.21 (3H, d, $^5J_{HF}$ 1.6, 1-NCH_3), 3.05 (2H, t, $^3J_{HH}$ 5.2, CH_2), 2.76 (3H, s, 4-NCH_3); *m/z* (EI)$^+$ 398 ([M + H]$^+$, 100).

5-Ethoxy-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 14. Sodium (18.5 mg, 0.8 mmol) was added to anhydrous ethanol (30 mL) under argon followed by the addition of **7a** (0.2 g, 0.8 mmol). The resulting solution was heated at reflux for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 mL), extracted with dichloromethane (3 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated to yield the crude product as a brown oil. Purification by column chromatography on silica gel (3:1 ethyl acetate/*n*-hexane) gave **14** (0.17 g, 77%) as a colorless oil. Found: C, 56.8; H, 7.2; N, 16.2. $C_{12}H_{18}FN_3O_2$ requires: C, 56.5; H, 7.1; N, 16.5. δ_F(CCl_3; CFCl_3) −166.18 (s); δ_H(CCl_3; Me_4Si) 4.38 (2H, q, $^3J_{HH}$ 7.2, OCH_2CH$_3$), 3.90 (3H, s, OCH_3), 3.14 (3H, d, $^5J_{HF}$ 3.6, 1-NCH_3), 3.12 (2H, m, NCH_2), 3.02 (2H, m, NCH_2), 2.65 (3H, s, 4-NCH_3), 1.40 (3H, t, $^3J_{HH}$ 6.8, OCH$_2$CH_3); δ_C(CCl_3) 150.0 (d, $^4J_{CF}$ 1.5, C-5), 146.2

(d, $^2J_{CF}$ 12.6, C-7), 138.3 (d, $^2J_{CF}$ 4.9, C-4*b*), 132.3 (d, $^1J_{CF}$ 238.6, C-8), 113.6 (s, C-3*b*), 61.7 (s, OCH_2), 53.4 (s, OCH_3), 48.9 (s, NCH_2), 45.1 (s, NCH_2), 42.6 (s, 4-NCH_3), 41.7 (d, $^4J_{CF}$ 13.4, 1-NCH_3), 15.2 (s, OCH_2CH_3); *m/z* (EI^+) 255 ($[M]^+$, 100), 240 ($[M - CH_3]^+$, 15), 226 ($[M - CH_2CH_3]^+$ 92), 210 ($[M - OCH_2CH_3]^+$, 43).

***N*,*N*-Diethyl-8-fluoro-7-methoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-amine 15.** To diethylamine (0.29 g, 4 mmol) in tetrahydrofuran (20 mL) at −78 °C was added butyllithium (2 mL, 4 mmol, 2 M in tetrahydrofuran), and the solution was stirred for 1 h before warming to room temperature. **7a** (0.23 g, 1 mmol) was added, and the reaction mixture was heated to reflux for 4 d. Over the course of the reaction, excess lithium diethylamide salt (24 mmol) prepared following the procedure outlined above was added to the reaction mixture. The reaction was cooled to room temperature, the solvent was evaporated, and the residue redissolved in dichloromethane. The solution was poured into 1 M hydrochloric acid (30 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$), and the solvent was evaporated to dryness to yield the crude product as a brown oil (0.27 g). Purification by mass directed automated preparative HPLC (15−55% acetonitrile in formic acid) gave **15** (0.18 g, 64%) as an orange oil: $[M + H]^+$ 283.1927, $C_{14}H_{23}FN_4O$ requires $[M + H]^+$ 283.1934; δ_F −158.19 (1F, d, $^5J_{HF}$ 3.8, F-8); δ_H 3.92 (3H, s, OCH_3), 3.61 (4H, $^3J_{HH}$ 7.2, CH_2CH_3), 3.39 (2H, m, NCH_2CH_2), 3.30 (3H, d, $^5J_{HF}$ 4.8, 1-NCH_3), 3.05 (2H, m, NCH_2CH_2), 2.68 (3H, s, 4-NCH_3), 1.17 (6H, t, $^3J_{HH}$ 6.8, CH_2CH_3); δ_C 150.5 (d, $^2J_{CF}$ 12.8, C-7), 137.9 (d, $^4J_{CF}$ 2.6, C-5), 136.2 (s, C-3*b*), 134.1 (d, $^1J_{CF}$ 249.8, C-8), 124.0 (s, C-4*b*), 53.7 (s, OCH_3), 51.7 (s, $N(CH_2CH_3)_2$), 48.0 (s, NCH_2), 44.4 (s, NCH_2), 43.7 (s, $N(CH_2CH_3)_2$), 40.8 (s, 4-NCH_3), 40.6 (d, $^4J_{CF}$ 12.5, 1-NCH_3), 10.7 (s, CH_2CH_3); *m/z* $(EI)^+$ 283 ($[M + H]^+$, 100), 268 ($[MH - CH_3]^+$, 10), 254 ($[MH - CH_2CH_3]^+$, 80), 239 ($[MH - CH_2CH_3CH_3]^+$, 9).

5-Butyl-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 16. Butyllithium (1.4 mL, 2.71 mmol, 2 M in tetrahydrofuran) was added to a solution of **7a** (0.31 g, 1.35 mmol) in tetrahydrofuran (20 mL). The reaction mixture was heated to reflux for 6 d, and over the course of the reaction more butyllithium (5.6 mL, 10.84 mmol, 2 M in tetrahydrofuran) was added. The reaction mixture was cooled to room temperature, and the solvent was evaporated to dryness. The residue was redissolved in dichloromethane, poured onto water (50 mL), extracted with dichloromethane (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated to dryness to yield the crude product as a brown oil (0.39 g). Purification by column chromatography on silica gel (ethyl acetate in hexane, 0−50%) gave **16** (0.11 g, 31%) as a colorless oil. Found: C, 62.8; H, 8.3; N, 15.4. $C_{14}H_{22}N_3FO$ requires: C, 62.9; H, 8.2; N, 15.7. δ_F −160.54 (1F, d, $^5J_{HF}$ 4.1, F-8); δ_H 3.85 (3H, s, OCH_3), 3.13 (2H, m, NCH_2), 3.09 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 2.92 (2H, m, NCH_2), 2.57 (2H, t, $^3J_{HH}$ 8.0, Ar CH_2), 2.48 (3H, s, 4-NCH_3), 1.63 (2H, quintet, $^3J_{HH}$ 7.6, $CH_2CH_2CH_3$), 1.30 (2H, sextet, $^3J_{HH}$ 7.6, CH_2CH_3), 0.86 (3H, t, $^3J_{HH}$ 7.6, CH_3); δ_C 148.4 (d, $^2J_{CF}$ 10.6, C-7), 145.8 (d, $^4J_{CF}$ 4.6, C-5), 135.4 (d, $^2J_{CF}$ 2.0, C-4*b*), 133.0 (d, $^1J_{CF}$ 247.3, C-8), 126.1 (d, $^3J_{CF}$ 1.0, C-3*b*), 52.0 (s, OCH_3), 47.6 (s, NCH_2), 43.4 (s, NCH_2), 42.4 (s, 4-NCH_3), 40.0 (d, $^4J_{CF}$ 13.0, 1-NCH_3), 30.4 (s, Ar CH_2), 29.6 (s, $CH_2CH_2CH_3$), 21.8 (s, CH_2CH_3), 13.1 (s, CH_2CH_3); *m/z* $(EI)^+$ 268 ($[M + H]^+$, 80), 253 ($[MH - CH_3]^+$, 17), 225 ($[MH - CH_3(CH_2)_2]^+$, 5), 211 ($[MH - CH_3(CH_2)_3]^+$, 7).

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Supporting Information Available: Representative NMR spectra of compounds **8a**, **13a**, **14**, **15** and **16** and X-ray data in CIF format for **6a**, **6c**, **7a**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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