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'Through-Space' Hydrogen–Fluorine, Carbon–Fluorine and Fluorine–Fluorine Spin–Spin Coupling in 2-Phenyl-3-alkyl-4,5,6,7-tetrahydroindazoles

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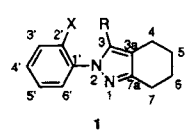
^{1}H, ^{13}C and ^{19}F NMR experiments for a series of 3-alkyl-2-phenyl-4,5,6,7-tetrahydroindazoles revealed a six-bond through-space coupling between the *ortho*-fluorine and the hydrogen or fluorine atom of the position 3-alkyl group. This was further supported by NOE experiments. Molecular mechanics calculations on a representative structure indicated that several low energy conformers met the fluorine–carbon distance constraint suggested by the NMR data, and dynamic annealing experiments produced a conformer which was in complete agreement with the NMR data. This through-space interaction is speculated to be a result of repulsion between N-1 of the tetrahydroindazole and the *ortho*-fluorine lone pair electrons.

KEY WORDS Through-space coupling Tetrahydroindazoles Protoporphyrinogen oxidase Molecular mechanics

INTRODUCTION

Our interest in 'through-space' spin–spin coupling[1,2] in 2-phenyl-3-alkyl-4,5,6,7-tetrahydroindazoles (**1**) originated from a molecular modeling study toward the design of novel inhibitors of protoporphyrinogen oxidase (PPO) [EC 1.3.3.4].[3] PPO catalyzes the oxidation of protoporphyrinogen IX (**2**) to protoporphyrin IX (**3**)[4] and is the site of action of membrane disrupting herbicides.[5–13] It has been recognized that the herbicidal activity of PPO inhibitors, of structural type **4**, is generally enhanced by substitution at the *ortho*-phenyl position with fluorine.[7,8] Conformational searching on structure **1** (R = CH_3, X = F) using SYBYL molecular modeling software indicated that the most stable conformers of the molecule were those in which the distance from the fluorine to the methyl carbon was *ca.* 3 Å. This corresponded to a C-2′—C-1′—N-2—C-3 torsion angle of *ca.* 70° or 300°. These conformations were more stable by 0.4–1.1 kcal than those in which the phenyl ring was flipped to position the fluorine away from the methyl group (C-2′—C-1′—N-2—C-3 torsion *ca.* 120° or 250°). Although numerous other conformers were observed within 2–3 kcal of these energy minima, these results indicated the possibility of an attractive interaction between the *ortho*-fluorine and the methyl group, or of a repulsive interaction between the fluorine and N-1. If such an interaction exists, it could restrict the aryl–heterocycle bond rotation to a conformation which binds more favorably with the enzyme active site. Intrigued by this hypothesis, we embarked on the synthesis and NMR study of compounds of structural class **1** and the results are reported in this paper.



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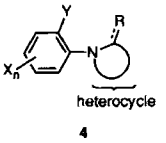

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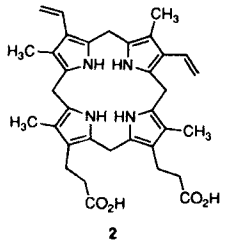

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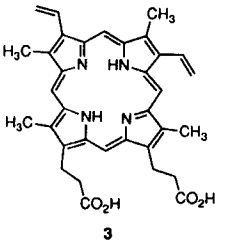

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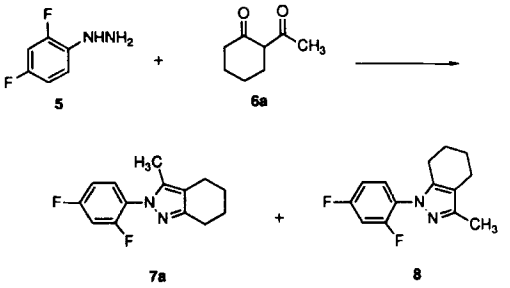
RESULTS

When 2,4-difluorophenylhydrazine (**5**) was allowed to react with 2-acetylcyclohexanone (**6a**) in toluene (Scheme 1), compound **7a** was obtained as the result of



5 **6a** **7a** **8**

Scheme 1

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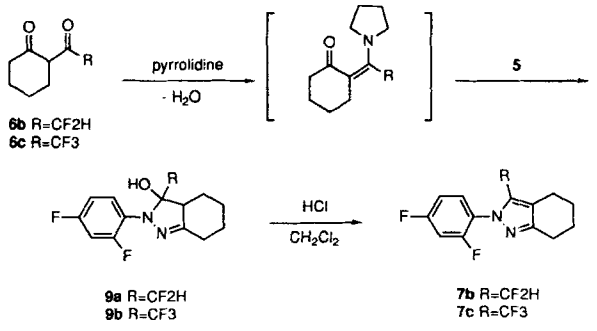
Table 1. ^{13}C NMR data (75 MHz, proton decoupled) for 7

Compound	1′	2′	3′	4′	5′	6′	3	3a	4–7	7a	R
7a	124.5[a] dd[b] $^2J(13)$[c]	156.9 dd $^1J(252)$	104.5 d $^2J(25)$	161.9 dd $^1J(252)$	111.6 dd $^2J(22)$	129.8 d	136.2 s	114.5 s	23.3, 23.2, 20.3	150.6 s	9.4 d
7b	123.6 dd $^2J(12)$	157.0 dd $^1J(254)$	104.8 d $^2J(24)$	162.6 dd $^1J(254)$	111.7 dd $^2J(23)$	130.1 d	132.4 t $^2J(28)$	118.3 s	23.1, 22.7, 22.6, 20.1	150.9 s	109.1 dt $^1J(235)$
7c	123.8 dd $^2J(13)$	158.1 dd $^1J(254)$	104.7 d $^2J(24)$	163.1 dd $^1J(254)$	111.3 dd $^2J(23)$	130.4 d	129.2 q $^2J(38)$	119.3 s	23.1, 22.5, 22.4, 20.4	150.9 s	120.3 q $^1J(270)$

[a] Chemical shifts (ppm) are given relative to $CDCl_3$.
[b] Peak splitting indicated by s = singlet, d = doublet, q = quartet, dd = doublet of doublets, dt = doublet of triplets.
[c] One- and two-bond coupling constants (Hz).

nucleophilic attack by the terminal hydrazine nitrogen at the cyclohexanone carbonyl. The 1-aryl regioisomer **8** was not formed under these conditions. Examination of the NMR spectra for **7a** revealed doublets in both the proton (2.1 ppm, $J = 1.8$ Hz) and carbon (9.4 ppm, $J = 3.8$ Hz) spectrum (Table 1). Both doublets were attributed to long-range coupling of the methyl group to the *ortho*-fluorine on the aryl ring. Since C-3 of the heterocyclic ring was not split by fluorine in the carbon spectrum, a 'through-space' coupling mechanism was inferred. This was supported by heteronuclear NOE experiments and proton coupled ^{19}F NMR spectra. Irradiation of the methyl protons in **7a** induced a 4.7% NOE enhancement of the fluorine signal at -117 ppm. This signal was found to be split into a multiplet of quartets in the proton coupled ^{19}F NMR spectra, with the same six-bond coupling constant [$^6J(H,F) = 1.8$ Hz] as found in the proton spectra. Both experiments suggest a close spatial proximity of the fluorine atom to the methyl group, and the existence of 'through-space' (H–F) and 'indirect through-space' (C–F) coupling mechanisms.

With these results at hand we wanted to determine if 'through-space' F–F coupling could also be observed. Toward this end the difluoromethyl (**7b**) and trifluoromethyl (**7c**) analogs were prepared (Scheme 2) following the literature procedure for the synthesis of



Scheme 2

substituted pyrazoles.[14] The ^{19}F NMR spectra indicated the existence of a six-bond F–F coupling with coupling constants of 3.3 and 4.6 Hz for **7b** and **7c**, respectively (Table 2). Identical six-bond coupling constants were measured by examining either the arylfluorine or alkylfluorine NMR signal (see Experimental).

Table 2. Structure 7: ^{19}F coupling constants (Hz)

Coupling constant	7a	7b	7c
$^6J(H,F)$	1.8	0.5	—
$^6J(F,F)$	—	3.3	4.6
$^5J(C,F)$	3.8	3.3	0

Compound **7b** also exhibited a six-bond H–F coupling of 0.5 Hz and a five-bond C–F coupling of 3.3 Hz. Interestingly, the expected five-bond 'indirect through-space' C–F coupling in **7c** was not observed.

The existence of spin–spin coupling between nuclei separated by five or six bonds has been well documented as an indicator of close spatial proximity.[15–18] Myhre *et al.*[19] and Abushanab[20] reported correlations of observed H–F coupling constants by protons on proximate methyl carbons with C—F internuclear distance. This strong dependence of $J(H,F)$ on distance has also been validated through mathematical relationships.[21] Fluorine atoms which are intramolecularly buttressed are also known to exhibit 'through-space' F–F coupling.[22] Mallory[23] suggested that this coupling is a result of direct overlap of the two lone-pair orbitals to form one bonding and one antibonding molecular orbital delocalized over both fluorines. This same dependence of coupling constants on internuclear distance has also been reported[2,15,16,18] for 'indirect through-space' C–F coupling. It is also worth mentioning that the lack of observed C–F coupling in **7c** is not totally unexpected. Contreras *et al.*[2] predicted that long-range couplings would be reduced by replacing a methyl group in a coupled system with a trifluoromethyl group.

Using the plot of Myhre *et al.*[19] showing the H–F coupling constant as a function of the separation of the nuclei, the distance between the methyl carbon and the *ortho*-fluorine in **7a** was estimated at *ca.* 2.8 Å. This corresponds to a phenyl–heterocycle torsion angle (C-2′—C-1′—N-2—C-3) of *ca.* 60° or 310° (Fig. 1).

A global conformational search on structure **1** indicated that the minimum energy structure is that in which the phenyl–heterocycle torsion angle was 69° and the fluorine–methyl carbon distance was 3.05 Å. However, within 3 kcal of this minimum energy structure were numerous other conformers in which the

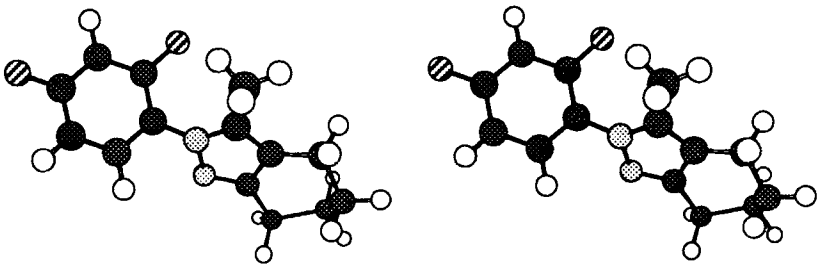
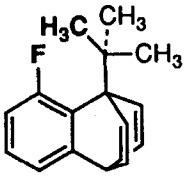
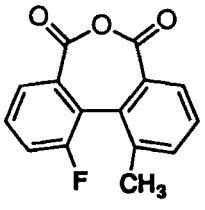
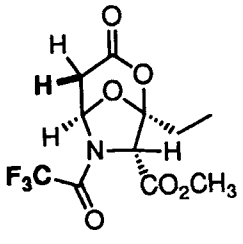
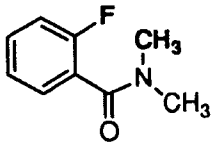
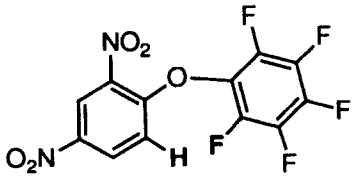


Figure 1. Stereoview of **7a** showing a 2.8 Å separation between the *ortho*-fluorine and methyl carbon.

torsion angle ranged from 60° to 140° and 240° to 316°, while the fluorine–methyl carbon distance ranged from 2.6 to 4.6 Å.

Molecular dynamics calculations were carried out to explain better the behavior of structure **1**. In a dynamic annealing experiment (see Experimental), **1** was taken through three annealing cycles of stepwise heating to 600 K followed by stepwise cooling to 100 K. After the third cycle, the system was cooled to 0 K to freeze out a single, low-energy conformer having a fluorine–methyl carbon distance of 2.85 Å and a phenyl–heterocycle torsion angle of 51°. To simulate better the conditions of the NMR study, a single annealing cycle to 500 K was run on **1** solvated in a $CHCl_3$ shell. The conformer frozen out in this calculation had a fluorine–methyl carbon distance of 2.80 Å and a phenyl–heterocycle torsion angle of 48°, in excellent agreement with that predicted from Myhre *et al.*'s plot.

Table 3. Literature examples of six-bond H–F coupling

Structure[a]	^6J(H,F) (Hz)	C—F distance (Å) Predicted[b]	Measured[c]	Ref.
	2.9	2.7	3.0	17
	3.7	2.6	3.1	24
	0.8	3.1	3.1	15
	1.2	2.9	2.9	25
	1.2	3.0	3.3	26

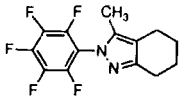
[a] Atoms involved in coupling are indicated in bold.
[b] See Ref. 19.
[c] Model building, structure minimizations and distance measurements were performed using SYBYL molecular modeling software.

A partial literature review of compounds which possess six-bond H–F coupling in the range of **7a** and **7b** is shown in Table 3. All were claimed to demonstrate 'through-space' coupling. The C—F distances were measured from the minimized structures using SYBYL or from information taken from the literature references. The C—F distances were found to compare favorably with those predicted using the plot of Myhre *et al.*,[19] lending support to their correlation and application in six-bond systems.

DISCUSSION

The results presented here lend strong support to a time averaged structure for **7** in which the *ortho*-fluorine on the phenyl ring is in close proximity to the 3-alkyl group. There are at least two possible explanations for this phenomenon: an intramolecular attraction between the fluorine and alkyl group or an intramolecular repulsion between the fluorine and N-1. Although examples of through-space hydrogen bonding between hydrogen and fluorine have been reported,[27,28] we do not believe this is occurring here. Examination of the coupling constants from Table 2 shows a reduction in the average ^6J(H,F) value going from **7a** to **7b** and a reduction of ^6J(F,F) from **7c** to **7b**. This implies free rotation about the alkyl group–heterocycle C—C bond and absence of any significant intramolecular H—F or F—F bonding.

An alternative explanation for the through-space coupling in **7** is the existance of a repulsion between the N-1 lone pair electrons of the heterocycle and those of the *ortho*-fluorine on the phenyl ring. The observed proximity of the *ortho*-fluorine to the 3-substituent of the heterocycle is the result of relieving this lone pair–lone pair repulsion. If this is true, a compound having a 2,6-difluorophenyl substitution pattern would not be expected to show coupling between the 3-substituent and the *ortho*-fluorine atoms. In this case, the repulsion would be equal in both conformers resulting in a time-averaged perpendicular orientation of the two rings. We tested this hypothesis by preparing compound **10** from perfluorophenylhydrazine using the methodology for the synthesis of **7a**. The high-resolution ^{1}H NMR spectrum for **10** showed no six-bond H–F coupling, and therefore supports the latter interpretation.



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EXPERIMENTAL

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-T spectrometer at Rutgers University, New Brunswick, NJ. Elemental analyses were determined at FMC, Analytical Services Department.

^{1}H and ^{13}C data were recorded on a General Electric QE-300 spectrometer using a dual H/C probe. Samples were prepared by dissolving the appropriate amount of material in 0.5 ml of $CDCl_3$. ^{1}H data were taken at 300.14 MHz using a sweep width of 6024 Hz, an acquisition time of 1.36 s, a pulse angle of 30°, a recycle time of 500 ms, a 16K data size and using no apodization. ^{13}C data were taken at 75.478 MHz with MLEV ^{1}H decoupling using a sweep width of 18 182 Hz, an acquisition time of 0.9 s, a pulse angle of 30°, a recycle time of 500 ms, a 32K data size and with exponential line broadening of 1 Hz. Chemical shifts were referenced to internal TMS for ^{1}H data and $CDCl_3$ for ^{13}C data [$\delta_C(^{13}CDCl_3) = 77.0$]. ^{19}F data were recorded on a Nicolet NT-300 spectrometer using a ^{19}F{^{1}H} probe. Routine ^{19}F data were recorded at 282.312 MHz using a sweep width of 76 923 Hz, an acquisition time of 0.426 s, a pulse angle of 30°, a recycle time of 575 ms, a 64K data size, MLEV ^{1}H decoupling and with exponential line broadening of 1 Hz.

^{19}F{^{1}H} NOED spectra were generated using a presaturation experiment, {[D3,P2,AT,D5]$_n$ D6}@ frequency list, where D3 = presaturation time of 2 s, P2 = pulse width of 4 ms (30°), AT = acquisition time of 1.64 s, D5 = 50 ms and D6 = 10 s separation between decoupler frequencies. The frequency list consisted of the target methyl protons plus an off-resonance frequency for a control. This experiment used a sweep width of 10 000 Hz with a frequency selective CW ^{1}H irradiation power (sufficient for 50% saturation of the methyl resonance) and interleaved collection of data. The data were also exponential line broadened by 2 Hz.

Molecular modeling studies were conducted using SYBYL molecular modeling software, purchased from TRIPOS, Inc., St Louis, MO. The TRIPOS force field was employed throughout.[29] A model of structure **1** (R = CH_3, X = F) was constructed, and atomic point charges were added using the Gasteiger–Hückel method. The structure was minimized using the MAXIMIN2 algorithm. A global conformational search on **1** was conducted by independently rotating the N-2—C-1′ and C-3—R(CH_3) bonds in 1° increments and calculating the energy associated with each conformer. A dynamic annealing simulation was conducted on **1** by calculating 1 ps of molecular dynamics at 100 K, 1 ps at 200 K, 1 ps at 400 K, 4 ps at 600 K, 1 ps at 400 K and 1 ps at 200 K. This temperature profile was repeated for a total of three cycles before cooling the system for 1 ps at 100 K, 2 ps at 50 K and 2 ps at 0 K. A solvated dynamic annealing calculation was done by surrounding **1** with a solvent shell of 207 $CHCl_3$ molecules and calculating 2 ps of molecular dynamics at 100 K, 2 ps at 200 K, 2 ps at 300 K, 2 ps at 400 K, 6 ps at 500 K, 2 ps at 400 K, 2 ps at 300 K, 2 ps at 200 K, 2 ps at 100 K and 2 ps at 0 K. Time steps of 1 fs were used in the dynamics calculations, along with a temperature coupling factor of 10 fs, a non-bonded reset frequency of 25 fs and a momentum removal frequency of 25 fs. In both the dynamics and the conformational search calculations, the distance between the fluorine and methyl carbon and the torsion angle C-2—C-1′—N-2—C-3 were monitored. Mean values for each

were calculated at each temperature interval in the dynamic simulations.

Syntheses

2-Difluoroacetylcyclohexanone (6b). To a stirred suspension of 4.4 g (0.08 mol) of sodium methoxide in 100 ml of diethyl ether at 10 °C was added 10 g (0.08 mol) of ethyl difluoroacetate followed by the dropwise addition of 7.8 g (0.08 mol) of cyclohexanone in 10 ml of diethyl ether. After warming to room temperature the mixture was stirred for 18 h, then quenched by the slow addition of 6 ml of acetic acid. The mixture was filtered through a 5 cm bed of silica gel, eluted with 200 ml of diethyl ether, rotary evaporated, then distilled at reduced pressure to yield 7.1 g (50%) of a clear liquid, b.p. 60–62 °C (7 Torr); ^{1}H NMR, δ 1.68 (m, 4H, H-4,5), 2.41 (m, 4H, H-3,6), 6.04 [t, 1H, CF_2H, J(H,F) = 53 Hz], 15.2 (s, 1H, OH). Analysis: calculated for $C_8H_{10}F_2O_2 \cdot 0.25\ H_2O$, C 53.18, H 5.86; found, C 53.23, H 6.09%.

2-Trifluoroacetylcyclohexanone (6c). Prepared as above using 14.2 g (0.1 mol) of ethyl trifluoroacetate to yield 9.8 g (51%) of a clear liquid, b.p. 49–51 °C (7 Torr); ^{1}H NMR, δ 1.70 (m, 4H, H-4,5), 2.46 (m, 4H, H-3,6), 15.1 (s, 1H, OH). Analysis: Calculated for $C_8H_9F_3O_2$, C 49.49, H 4.67; found, C 49.56, H 4.90%.

2-(2′,4′-Difluorophenyl)-3-difluoromethyl-3-hydroxy-3,3a,4,5,6,7-hexahydroindazole (9a). To a solution of 1.7 g (0.01 mol) of 2-difluoroacetylcyclohexanone (**6b**) in 10 ml of THF at 0 °C was added 0.8 ml (0.01 mol) of pyrrolidine followed by 1 g of 3 Å molecular sieve. After stirring at 0 °C for 30 min, a solution of 1.4 g (0.01 mol) of 2,4-difluorophenylhydrazine (**5**) in 5 ml of THF was added and the mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was concentrated to 5 ml then flash chromatographed using 4:1 heptane–ethyl acetate to afford 1.4 g (47%) of **9a** as an oil: ^{1}H NMR, δ 1.43 (m, 2H, H-6), 1.71, 2.20 (m, 2H, H-4), 1.97 (m, 2H, H-5), 2.73 (m, 2H, H-7), 3.10 (m, 1H, H-3a), 5.96 (t, 1H, CF_2H), 6.86, 7.33 (m, 3H, Ph). Analysis: calculated for $C_{14}H_{14}F_4N_2O$, C 55.63, H 4.67, N 9.27; found, C 55.39, H 4.50, N 9.15%.

2-(2′,4′-Difluorophenyl)-3-trifluoromethyl-3-hydroxy-3,3a,4,5,6,7-hexahydroindazole (9b). Prepared as above with 13.6 g (0.07 mol) of **6c**, 5.0 g (0.07 mol) of pyrrolidine and 9.8 g (0.07 mol) of **5** to yield 15.4 g (69%) of a white solid after chromatography (4:1 heptane–ethyl acetate), m.p. 155–156 °C; ^{1}H NMR, δ 1.43 (m, 2H, H-6), 1.72, 2.19 (m, 2H, H-4), 1.98 (m, 2H, H-5), 2.72 (m, 2H, H-7), 3.17 (q, 1H, H-3a), 6.87, 7.33 (m, 3H, Ph); MS, m/z (%) 320 (M^+)(29), 302 ($M^+ - H_2O$)(12), 251 ($M^+ - CF_3$)(100), 233 ($M^+ - CHF_3O$)(11), 127 ($M^+ - C_8H_{10}NF_3O$)(34), 113 (M^+ – heterocycle)(21); HRMS, calculated for $C_{14}H_{13}F_5N_2O$, 320.0948; found, 320.0948.

2-(2′,4′-Difluorophenyl)-3-methyl-4,5,6,7-tetrahydroindazole (7a). A mixture of 5.0 g (27.7 mmol) of the HCl salt of **5** and 3.8 g (27.7 mmol) of **6a** in 100 ml of toluene was treated dropwise with 9.7 ml (55.4 mmol) of triethylamine then heated at reflux with azeotropic removal of water. After 3 h, the mixture was cooled, filtered to remove solids, then concentrated at reduced pressure to afford 6.9 g of a crude oil. The residue was flash chromatographed (4:1 heptane–ethyl acetate) to afford 5.7 g (83%) of an oil, b.p. 135–140 °C (0.75 Torr), which solidified on standing. Recrystallization from light petroleum afforded an analytical sample, m.p. 60–61 °C; ^{1}H NMR, δ 1.81 (m, 4, H-5,6), 2.07 [d, 3, CH_3, ^6J(H,F) = 1.8 Hz], 2.48 (t, 2, H-4), 2.71 (t, 2, H-7), 7.04, 7.45 (m, 3, Ph); ^{19}F NMR, δ −109.44 [d, F-4′, ^4J(F,F) = 7.3 Hz], −117.24 [d, F-2′, ^4J(F,F) = 7.3 Hz]. Analysis: calculated for $C_{14}H_{14}F_4N_2$, C 67.73, H 5.68, N 11.28; found, C 67.52, H 5.39, N 11.35.

2-(2′,4′-Difluorophenyl)-3-difluoromethyl-4,5,6,7-tetrahydroindazole (7b). A solution of 1.4 g (4.6 mmol) of **9a** in 50 ml of CH_2Cl_2 was treated with 3 drops of concentrated HCl and then stirred at room temperature. After 1 h, the solution was dried over $MgSO_4$, filtered, and then concentrated at reduced pressure to afford an oil. Trituration with light petroleum afforded a white solid (1.2 g, 92%), m.p. 63–64 °C; ^{1}H NMR, δ 1.82 (m, 4, CH_2), 2.72 (m, 4, CH_2), 6.51 [t, 1, CF_2H, J(H,F) = 54 Hz], 6.97, 7.42 (m, 3, Ar); ^{19}F NMR, δ −107.33 [d, F-4′, ^4J(F,F) = 8 Hz], −113.50 (bs, CF_2H), −117.96 [dt, F-2′, ^4J(F,F) = 8 Hz, ^6J(F,F) = 3.3 Hz]. Analysis calculated for $C_{14}H_{12}F_4N_2$, C 59.16, H 4.26, N 9.86; found, C 59.58, H 4.42, N 9.42.

2-(2′,4′-Difluorophenyl)-3-trifluoromethyl-4,5,6,7-tetrahydroindazole (7c). Prepared as above with 14.8 g (0.048 mol) of **9b** to afford 13.2 g (92%) of an oil: ^{1}H NMR, δ 1.82 (m, 4, CH_2), 2.71 (m, 4, CH_2), 6.95, 7.38 (m, 3, Ar); ^{19}F NMR, δ −58.57 [d, CF_3, ^6J(F,F) = 4.4 Hz], −106.64 [d, F-4′, ^4J(F,F) = 8.5 Hz], −117.03 [dq, F-2′, ^4J(F,F) = 8.6 Hz, ^6J(F,F) = 4.3 Hz]. Analysis: calculated for $C_{14}H_{11}F_5N_2$, C 55.63, H 3.67, N 9.27; found, C 55.74, H 3.67, N 9.00%.

2-(2′,3′,4′,5′,6′-Pentafluorophenyl)-3-methyl-4,5,6,7-tetrahydroindazole (10). A solution of 3.1 g (15.6 mmol) of perfluorophenylhydrazine in 50 ml of toluene was treated dropwise with 2 ml (15.6 mmol) of 2-acetylcyclohexanone then heated at reflux with azeotropic removal of water. After 3 h, the mixture was cooled then concentrated at reduced pressure to afford 4.5 g of a crude oil. The residue was flash chromatographed (9:1 heptane–ethyl acetate) to afford 2.1 g (44%) of a solid. Recrystallization from light petroleum afforded an analytical sample, m.p. 120–121 °C; ^{1}H NMR, δ 1.79 (m, 4, H-5,6), 2.04 (s, 3, CH_3), 2.47 (t, 2, H-4), 2.69 (t, 2, H-7). Analysis: calculated for $C_{14}H_{11}F_5N_2$, C 55.64, H 3.67, N 9.27; found, C 55.65, H 3.80, N 9.22%.

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