Regioselective Friedel−Crafts Alkylation of Anilines and Amino-Substituted Heteroarenes with Hexafluoroacetone Sesquihydrate

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A variety of arenes, including anilines, pyrroles, indoles, aminooxazoles, aminothiazoles, aminoquinolines, and aminopyridines, underwent regioselective Friedel–Crafts alkylation in neat hexafluoroacetone sesquihydrate in a broad range of temperatures, reaction times, and yields (2%–94%) depending strongly on the electron density of the substrate. Prior *N*,*N*-dibenzylation of aniline and 2-aminopyridine strongly promoted substrate reactivity and resulted in higher yields (> 80%). The described Friedel–Crafts alkylations in hexafluoroacetone sesquihydrate occurred regioselectively at the *para*-positions of anilines or at the positions β to the sp^2-hybridized nitrogen atom in heteroarenes.

Introduction

Hexafluoroacetone (HFA)[1] was discovered in 1941 but has been extensively explored only since the beginning of the sixties, when industrial production processes were discovered at DuPont. Since then hexafluoroacetone has found widespread application in academia and industry.

HFA is a highly reactive gas (b.p. 27 °C) in its anhydrous state, due to the electron-withdrawing power of the six fluorine atoms. Hexafluoroacetone sesquihydrate ($HFA{\cdot}1.5H_2O$) is a liquid (b.p. 100 °C) with exceptional solvent properties and is used in the processing of silk fibers at low temperature, but has a tendency to dissociate upon heating. At DuPont the less corrosive and more volatile 1,1,1,3,3,3-hexafluoro-2-propanol (b.p. 58 °C) was developed and marketed as an ideal solvent for processing polymers.

HFA was synthetically used for trapping organolithium and magnesium species, in aldol reactions with enolates, in Diels−Alder reactions with dienes, and in Friedel−Crafts reactions with arenes.[1] More specialized applications include its use for the protection of amino acids,[2] the synthesis of tuned ligands for transition metal catalysis,[3] and the synthesis of novel weakly coordinating anions such as tetrakis(polyfluoroalkoxy-aluminates) for optimization of catalyst performance.[4]

Current pharmaceutical applications aim at providing enhanced metabolic stability in drug candidates, which frequently carry the 1,1,1,3,3,3-hexafluoropropan-2-ol motif, as demonstrated by the vitamin D_3 analogues falecalcitriol[5] and RO0652299,[6] the malonyl-CoA decarboxylase inhibitors,[7] the PDE4 inhibitor L-791,943,[8] the LXR agonist T0901317,[9] and the platelet aggregation inhibitor RO0211421.[10]

Current synthetic strategies for the introduction of the 1,1,1,3,3,3-hexafluoropropan-2-ol substructure into a target molecule basically comprise two alternative strategies:[11] quenching of an organometallic species (e.g., aryl-Li, aryl-MgX, etc.) with gaseous anhydrous HFA at low temperature, or Lewis acid-catalyzed Friedel−Crafts reactions of arenes. While the former is generally the preferred route if strong bases (e.g., BuLi, Mg, etc.) are applicable, the latter offers a complementary synthetic strategy. Electron-poor arenes such as benzene undergo Friedel−Crafts reactions with gaseous HFA at ambient temperature when activated by strong Lewis acid catalysts (e.g. $AlCl_3$, Scheme 1).[12−15] The more electron-rich anilines undergo Friedel−Crafts reactions with gaseous HFA or one of its hydrates in the presence of catalytic amounts of toluene-4-sulfonic acid, but need higher temperatures.[16] Highly electron-rich arenes such as indoles react with gaseous HFA in the absence of catalysts.[16,17] More recently, a patent from Chugai Biopharmaceuticals in San Diego reported the Friedel−Crafts alkylation of 2-aminothiazole with neat HFA−trihydrate and molecular sieves (100 °C, 8 h), which afforded the 5-substituted hexafluoro-2-propanol in 73% yield.[7]

Results and Discussion

We have investigated a wide range of substituted anilines and (hetero)arenes in thermal reactions in neat hexafluoroacetone sesquihydrate and have obtained *para*-selective Friedel−Crafts alkylations in yields of up to 94% in the absence of catalyst. Initially we carried out parallel reac-

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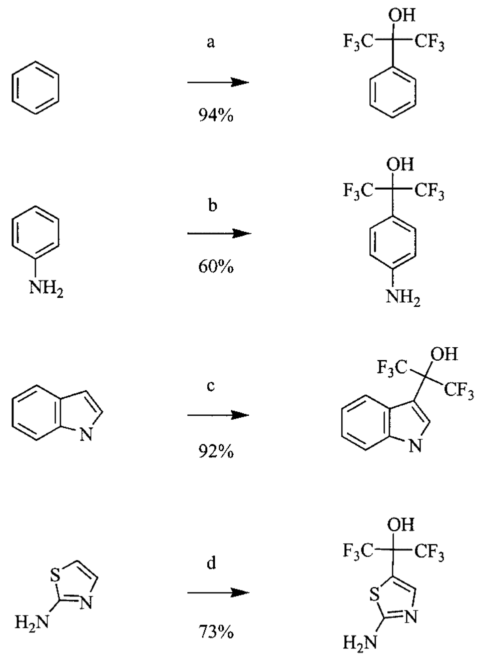
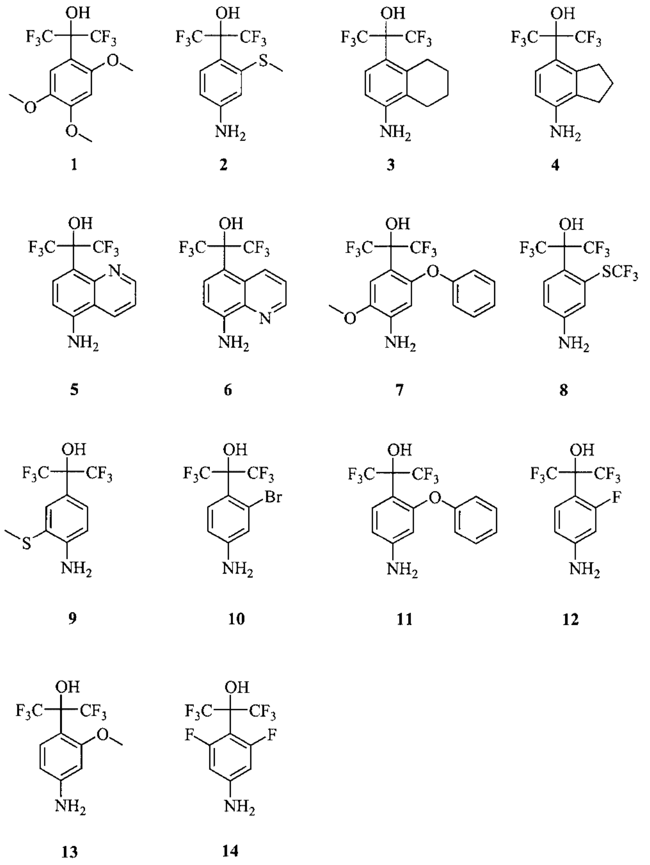


Scheme 1. Previously published reaction conditions required for the Friedel−Crafts alkylation of benzene, aniline, and indole with hexafluoroacetone: a) HFA (g), cat. $AlCl_3$, neat, 20−50 °C; b) HFA (g), cat. TsOH, neat, 130 °C, 1 h; c) HFA (g), Et_2O, 20 °C, 1 h; d) HFA $3{\cdot}H_2O$, mol. sieves, 100 °C, 8 h



Scheme 2. Chemical structures of the 1,1,1,3,3,3-hexafluoropropan-2-ols **1**−**14** obtained by Friedel−Crafts alkylation of anisoles and anilines in neat hexafluoroacetone sesquihydrate under the reaction conditions specified in Table 1

Table 1. Reaction conditions and yields for the synthesis of 1,1,1,3,3,3-hexafluoropropan-2-ols **1**−**14** (see Scheme 1) from anisole and aniline precursors

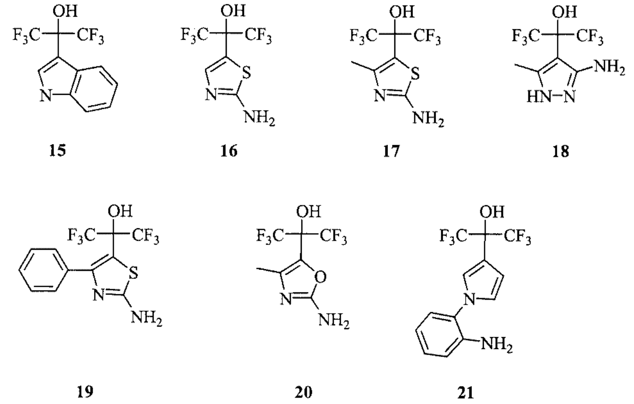
Compound	Precursor	Temp.[a] T [°C]	Time t	Yield[b] [%]
1	1,2,4-trimethoxybenzene	140	48 h	74
2	3-(methylmercapto)aniline	60	5 d	68
3	5-aminotetralin	100	0.5 h	66
4	4-aminoindane	100	1 h	53
5	5-aminoquinoline	80	2 d	63
6	8-aminoquinoline	80	2 d	52
7	2-methoxy-5-phenoxyaniline	60	4 d	50
8	3-(trifluoromethylthio)aniline	140	3 d	43
9	2-(methylmercapto)aniline	80	11 d	35
10	3-bromoaniline	140	3 d	22
11	3-phenoxyaniline	80	2 d	15
12	3-fluoroaniline	140	3 d	6
13	3-methoxyaniline	25	3 h	6
14	3,5-difluoroaniline	60	7 d	2

[a] Temperature of the heating block. [b] Yields of isolated and purified compounds.

tions in screw-cap tubes on a synthesizer, but eventually realized that neat hexafluoroacetone sesquihydrate really behaved like a solvent with a boiling point of 100 °C. Experimental conditions (reaction temperature and time) were determined empirically according to the reactivity of the substrate, but steric and electronic effects of the aromatic ring substituents were equally contributing factors.

1,2,4-Trimethoxybenzene was used to find initial reaction conditions, and afforded compound **1** in 74% yield after heating at 140 °C for two days (Scheme 2 and Table 1). Anilines substituted with electron-donating substituents (OMe, SMe, alkyl, aryl, phenoxy) were treated at lower temperatures (20−100 °C) in order to avoid *ortho*/*para*-bis(alkylation), and afforded compounds **2**−**7**, **9**, **11**, **13** in 68%, 66%, 53%, 63%, 52%, 50%, 35%, 15%, and 6% yields, respectively. Anilines substituted with bulky or electron-poor substituents (3-SCF_3, 3-Br, 3-F) reacted at higher temperatures (140 °C) after several days, affording compounds **8**, **10**, and **12** in 43%, 22%, and 6% yields, respectively. Under these conditions, alkylation occurred only at the *para*-positions of the anilines. The ^1H NMR spectrum of compound **12** measured in $CDCl_3$ revealed an intramolecular hydrogen bond of the benzylic hydroxy group to the fluorine atom in the *ortho*-position on the benzene ring with a coupling constant of 14 Hz.

Five-membered heteroarenes such as indoles,[13] 2-aminothiazoles,[7] 2-aminooxazoles, 3-aminopyrazoles, and pyrroles reacted readily in neat hexafluoroacetone sesquihydrate and afforded the Friedel−Crafts alkylation products **15**−**21** in moderate to excellent yields (Scheme 3 and Table 2). As would be expected, indole reacted most readily, already at 80 °C within 1 h, affording **15** in 78% yield, in comparison with the 92% yield reported in the reaction



Scheme 3. Chemical structures of the 1,1,1,3,3,3-hexafluoropropan-2-ols **15–21** obtained by Friedel–Crafts alkylation of indoles, pyrroles, 2-aminothiazoles, etc. in neat hexafluoroacetone sesquihydrate under the reaction conditions specified in Table 2

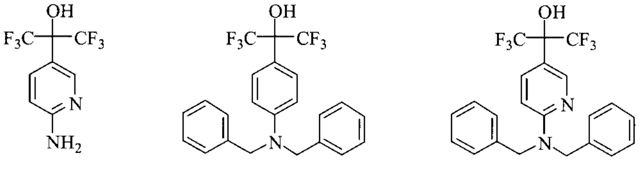
Table 2. Reaction conditions and yields for the synthesis of 1,1,1,3,3,3-hexafluoropropan-2-ols **15–21** (see Scheme 3) from anisole and aniline precursors

Compound	Precursor	Temp.[a] T [°C]	Time t	Yield[b] [%]
15	indole	80	1 h	78
16	2-aminothiazole	100	8 h	30
17	2-amino-4-methylthiazole	80	7 d	79
18	3-amino-5-methylpyrazole	80	2 h	72
19	2-amino-4-phenylthiazole	80	7 d	41
20	2-amino-4-methyl-oxazole	80	2 h	39
21	1-(2-aminophenyl)pyrrole	100	2.5 h	23

[a] Temperature of the heating block. [b] Yields of isolated and purified compounds.

with gaseous HFA.[13] 2-Aminothiazole reacted at 100 °C within 8 h, but the 30% yield was considerably lower than the 73% yield reported in the Chugai procedure.[7] For steric reasons, the 4-methyl- and 4-phenyl-2-aminothiazoles reacted much more slowly than the 4-unsubstituted parent, affording compounds **17** and **19** only after being heated for a week at 80 °C, in 79% and 41% yields, respectively. In all examples the Friedel–Crafts alkylation occurred at the position β to the sp^2-hybridized N-atom of the five-membered heteroarene, which was confirmed by 2D NMR measurements in the case of the 4-unsubstituted examples **15**, **16**, and **21,** but was obviously the only positional choice in the 4-substituted examples **17–20**.

Six-membered (hetero)arylamines such as aniline, 2-aminopyridine, and 2-aminopyrimidine without additional electron-donating substituents other than the amino group were much less reactive, but nevertheless 2-aminopyridine regioselectively afforded the C-5-substituted Friedel–Crafts alkylation product **22** in low yield after being heated at 130 °C for 15 days (Scheme 4 and Table 3), while there was no reaction with 2-aminopyrimidine. We managed to improve the Friedel–Crafts alkylation of aniline and 2-aminopyridine (but not 2-aminopyrimidine) in neat hexafluoroacetone sesquihydrate by *N,N*-dibenzylation of the precursors, which enhanced the reactivity and resulted in the *N,N*-dibenzyl-protected products **23** and **24** in excellent yields. Furthermore, these reactions were now conveniently performable on multi-gram scales in standard equipment with HFA sesquihydrate as solvent at reflux. *N,N*-Dibenzylaniline went into solution upon heating to 80 °C and reacted within minutes, while 2-(dibenzylamino)pyridine required 4 days at 100 °C. 2-(Dibenzylamino)pyrimidine was not transformed successfully under these conditions.



Scheme 4. Chemical structures of the 1,1,1,3,3,3-hexafluoropropan-2-ols **22**, **23**, and **24** obtained by Friedel–Crafts alkylation of (dibenzylamino)(hetero)arenes in neat hexafluoroacetone under the reaction conditions specified in Table 3

Table 3. Reaction conditions and yields for the synthesis of 1,1,1,3,3,3-hexafluoropropan-2-ols **22**, **23**, and **24** (see Scheme 4)

Compound	Precursor	Temp. T [°C]	Time t	Yield[a] [%]
22	2-aminopyridine	130[b]	15 d	17
23	*N,N*-dibenzylaniline	80[b]	10 min	94
24	2-(dibenzylamino)pyridine	100[c]	4 d	81

[a] Yields of isolated and purified compounds. [b] Temperature of the heating block. [c] Under reflux conditions.

Conclusion

Hexafluoroacetone sesquihydrate as a solvent and reagent can be effectively used for the introduction of the 1,1,1,3,3,3-hexafluoropropan-2-ol group into (hetero)aromatic compounds through Friedel–Crafts alkylation if the electron density of the substrate is sufficiently high. The dibenzylamino group is of particular utility in promoting these transformations. Furthermore, under optimized conditions these reactions occur regioselectively at the *para*-positions of anilines or at the positions β to the sp^2-hybridized nitrogen atom in heteroarenes.

Experimental Section

General Remarks: Parallel reactions with hexafluoroacetone sesquihydrate were carried out on gram scales in Pyrex glass tubes (40 mL) with screw-caps and double Teflon sealing on a Buechi Synchore shaker at block temperatures of 25 °C to 140 °C. Multigram reactions were carried out under nitrogen in normal round-bottomed flasks fitted with reflux condensers, the oil bath temperatures being increased to 120 °C maximum, giving a gentle reflux. All chromatographic purifications were performed on a Jones

Flashmaster II instrument with use of prepacked silica gel cartridges.

1,1,1,3,3,3-Hexafluoro-2-(2,4,5-trimethoxyphenyl)propan-2-ol (1): 1,2,4-Trimethoxybenzene (0.9 mL, 5.75 mmol) and hexafluoroacetone sesquihydrate (1.3 mL, 11.5 mmol) were shaken and heated on a Büchi Synchore shaker in a screw-cap Pyrex tube with double Teflon sealing at 140 °C for 2 days. After cooling, the mixture was partitioned between ethyl acetate (2 × 30 mL) and water (2 × 30 mL). The organic layer was dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by chromatography on silica gel by application of a heptane/ethyl acetate gradient. White crystals (1.45 g, 74%) were obtained; m.p. 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.54 (s, 1 H, 6-H), 6.94 (s, 1 H, 3-H), 7.50 (br. s, 1 H, OH) ppm. MS (EI): *m*/*z* (%) = 334 (90) [M^+], 265 (100), 195 (35), 168 (63). $C_{12}H_{12}F_6O_4$ (334.211): calcd. C 43.13, H 3.62, F 34.11, O 19.15; found C 43.26, H 3.61, F 34.23, O 19.43.

2-(4-Amino-2-methylsulfanylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (2): This compound was obtained analogously, from 3-(methylmercapto)aniline (1.0 g, 7.2 mmol) at 60 °C for 5 days; white crystals; m.p. 97 °C; yield 1.5 g (68%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3 H, SCH_3), 5.70 (br. s, 2 H, NH_2), 6.47 (d, $J_{5,6}$ = 8.4 Hz, 1 H, 5-H), 6.62 (s, 1 H, 3-CH), 7.04 (d, $J_{6,5}$ = 8.4 Hz, 1 H, 6-H), 9.10 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 306 (100) [M^+ + H]. $C_{10}H_9F_6NOS$ (305.241): calcd. C 39.35, H 2.97, F 37.34, N 4.59, O 5.24, S 10.51; found C 39.61, H 2.79, F 37.21, N 4.70, O 5.52, S 10.57.

2-(4-Amino-5,6,7,8-tetrahydronaphthalen-1-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (3): This compound was obtained analogously, from 5-aminotetralin (2.5 g, 16.5 mmol) at 100 °C for 0.5 h; light yellow crystals; m.p. 121 °C; yield 3.6 g (66%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.66 (m, 2 H, 6-H), 1.77 (m, 2 H, 7-H), 2.43 (t, *J* = 6.5 Hz, 2 H, 8-H), 2.64 (t, *J* = 6 Hz, 2 H, 5-H), 5.24 (br. s, 2 H, NH_2), 6.52 (d, *J* = 8.3 Hz, 1 H, 2-H), 7.00 (d, *J* = 8.3 Hz, 1 H, 3-H), 10.48 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 314 (100) [M^+ + H]. $C_{13}H_{13}F_6NO$ (313.240): calcd. C 49.85, H 4.18, F 36.39, N 4.47, O 5.11; found C 50.30, H 4.19, F 36.24, N 4.55, O 5.10.

2-(7-Aminoindan-4-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (4): This compound was obtained analogously, from 4-aminoindane (2.5 g, 18.8 mmol) at 100 °C for 1 h; white crystals; m.p. 154 °C; yield 3.0 g (53%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.01 (p, *J* = 7.5 Hz, 2 H, 2-H), 2.68 (t, *J* = 7.5 Hz, 2 H, 3-H), 2.82 (t, *J* = 7.5 Hz, 2 H, 1-H), 5.29 (br. s, 2 H, NH_2), 6.59 (d, *J* = 8 Hz, 1 H, 6-H), 7.01 (d, *J* = 8.2 Hz, 1 H, 5-H), 9.54 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 300 (100) [M^+ + H]. $C_{12}H_{11}F_6NO$ (299.213): calcd. C 48.17, H 3.71, F 38.10, N 4.68, O 5.35; found C 48.26, H 3.69, F 38.29, N 4.88, O 5.49.

2-(5-Aminoquinolin-8-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5): This compound was obtained analogously, from 5-aminoquinoline (1.4 g, 9.7 mmol) at 80 °C for 2 days; yellow crystals; m.p. > 220 °C; yield 1.92 g (63%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.74 (br. s, 2 H, NH_2), 6.83 (d, $J_{6,7}$ = 8.4 Hz, 1 H, 6-H), 7.58 (dd, $J_{3,4}$ = 8.3, $J_{3,2}$ = 4.4 Hz, 1 H, 3-H), 7.69 (d, $J_{7,6}$ = 8.4 Hz, 1 H, 7-H), 8.80 (dd, $J_{4,3}$ = 8.3, $J_{4,2}$ = 1.4 Hz, 1 H, 4-H), 8.84 (dd, $J_{2,3}$ = 4.4, $J_{2,4}$ = 1.4 Hz, 1 H, 2-H), 13.64 (s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 309 (100) [M^+ − H]. $C_{12}H_8F_6N_2O$ (310.196): calcd. C 46.46, H 2.60, F 36.75, N 9.03, O 5.16; found C 46.38, H 2.62, F 36.97, N 9.00, O 5.13.

2-(8-Aminoquinolin-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (6): This compound was obtained analogously, from 8-aminoquinoline (2.0 g, 13.6 mmol) at 80 °C for 2 h; yellow crystals; m.p. 136 °C; yield 2.2 g (52%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.68 (br. s, 2 H, NH_2), 7.10 (d, $J_{6,7}$ = 8.8 Hz, 1 H, 6-H), 7.32 (d, $J_{7,6}$ = 8.8 Hz, 1 H, 7-H), 7.60 (dd, $J_{3,4}$ = 8.1, $J_{3,2}$ = 4 Hz, 1 H, 3-H), 8.23 (dd, $J_{4,3}$ = 8.1, $J_{4,2}$ = 1.7 Hz, 1 H, 4-H), 8.81 (dd, $J_{2,3}$ = 4, $J_{2,4}$ = 1.7 Hz, 1 H, 2-H), 9.24 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 311 (100) [M^+ + H]. $C_{12}H_8F_6N_2O$ (310.196): calcd. C 46.46, H 2.60, F 36.75, N 9.03, O 5.16; found C 46.56, H 2.58, F 36.84, N 9.02, O 5.07.

2-(4-Amino-5-methoxy-2-phenoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (7): This compound was obtained analogously, from 5-phenoxy-*o*-anisidine (1.0 g, 4.6 mmol) at 60 °C for 4 days; light orange crystals; m.p. 79 °C; yield 887 mg (50%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.78 (s, 3 H, CH_3), 5.24 (s, 2 H, NH_2), 6.20 (s, 1 H, 3-H), 6.90 (d, *J* = 8 Hz, 2 H, Ph), 7.07 (t, *J* = 7.4 Hz, 1 H, Ph), 7.16 (s, 1 H 6-H), 7.35 (t, *J* = 8 Hz, 2 H, Ph), 8.23 (s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 380 (100) [M^+ − H]. $C_{16}H_{13}F_6NO_3$ (381.271): calcd. C 50.40, H 3.44, F 29.90, N 3.67, O 12.59; found C 50.51, H 3.40, F 29.86, N 3.69, O 12.72.

2-(4-Amino-2-trifluoromethylsulfanylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (8): This compound was obtained analogously, from 3-(trifluoromethylthio)aniline (0.37 mL, 2.5 mmol) at 140 °C for 3 days; white crystals; m.p. 102 °C; yield 395 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (br. s, 2 H, NH_2), 7.24 (d, $J_{3,5}$ = 1.6 Hz, 1 H, 3-H), 7.32 (dd, $J_{5,6}$ = 8.4, $J_{5,3}$ = 1.6 Hz, 1 H, 5-H), 7.55 (d, $J_{6,5}$ = 8.4 Hz, 1 H, 6-H), 8.20 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 358 (100) [M^+ −1]. $C_{10}H_6F_9NOS$ (359.211): calcd. C 33.44, H 1.68, F 47.60, N 3.90, O 4.45, S 8.93; found C 33.40, H 1.58, F 47.61, N 3.90, O 4.57, S 8.95.

2-(4-Amino-3-methylsulfanylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (9): This compound was obtained analogously, from 2-(methylmercapto)aniline (1.77 mL, 13.9 mmol) at 80 °C for 11 days; pink crystals; m.p. 138 °C; yield 1.5 g (35%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.3 (s, 3 H, CH_3), 5.60 (s, 2 H, NH_2), 6.76 (d, *J* = 8.6 Hz, 1 H, 6-H), 7.23 (d, *J* = 8.6 Hz, 1 H, 5-H), 7.65 (s, 1 H, 2-H), 8.34 (s, 1 H, OH) ppm. MS (EI): *m*/*z* (%) = 305 (100) [M^+], 236 (97), 166 (43), 139 (57). $C_{10}H_9F_6NOS$ (324.223): calcd. C 39.35, H 2.97, F 37.34, N 4.59, O 5.24, S 10.51; found C 39.36, H 2.73, F 37.92, N 4.81, O 5.27, S 10.29.

2-(4-Amino-2-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (10): This compound was obtained analogously, from 3-bromoaniline (0.32 mL, 2.8 mmol) at 140 °C for 3 days; white crystals; m.p. 119 °C; yield 210 mg (22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (br. s, 2 H, NH_2), 7.15 (d, $J_{3,5}$ = 2 Hz, 1 H, 3-H), 7.21 (dd, $J_{5,6}$ = 8.8, $J_{5,3}$ = 2 Hz, 1 H, 5-H), 7.37 (d, $J_{6,5}$ = 8.8 Hz, 1 H, 6-H), 8.33 (br. s, 1 H, OH) ppm. MS (EI): *m*/*z* (%) = 338 (78) [M^+], 237 (70), 268 (100), 200 (82). $C_9H_6BrF_6NO$ (338.044): calcd. C 31.98, H 1.79, Br 23.64, F 33.72, N 4.14, O, 4.73; found C 32.34, H, 1.73, Br 23.52, F, 33.54, N 4.14, O 4.95.

2-(4-Amino-2-phenoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (11): This compound was obtained analogously, from 3-phenoxyaniline (1.5 g, 8.1 mmol) at 80 °C for 2 h; light yellow crystals; m.p. 84 °C; yield 435 mg (15%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.78 (br. s, 2 H, NH_2), 6.21 (dd, $J_{5,6}$ = 8.8, $J_{5,3}$ = 2.4 Hz, 1 H, 5-H), 6.31 (d, $J_{3,5}$ = 2.4 Hz, 1 H, 3-H), 7.05 (d, *J* = 7.6 Hz, 2 H, OPh), 7.12 (d, $J_{6,5}$ = 8.8 Hz, 1 H, 6-H), 7.18 (t, *J* = 7.4 Hz, 1 H, OPh), 7.41 (t, *J* = 8 Hz, 2 H, OPh), 9.04 (br. s, 1 H, OH) ppm. MS (ESI): *m*/*z* (%) = 350 (100) [M^+ − H]. $C_{15}H_{11}F_6NO_2$ (351.245): calcd. C 51.29, H 3.16, F 32.45, N 3.99, O 9.11; found C 51.38, H 3.06, F 32.13, N 4.01, O 9.20.

2-(4-Amino-2-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (12): This compound was obtained analogously, from 3-fluoroaniline (0.43 mL, 4.4 mmol) at 140 °C for 3 days; white crystals; m.p. 132 °C; yield 68 mg (5.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (br. s, 2 H, NH_2), 4.09 (d, $J_{H,F}$ = 14 Hz, 1 H, OH) 6.41 (dd, $J_{H,F}$ = 15.2, $J_{3,5}$ = 2.4 Hz, 1 H, 3-H)**,** 6.49 (dd, $J_{5,6}$ = 8.4, $J_{5,3}$ = 2.4 Hz, 1 H, 5-H)**,** 7.41 (dd, $J_{H,F}$, = 9.2, $J_{6,5}$ = 8.4 Hz, 1 H, 6-H**)** ppm. MS (EI): *m/z* (%) = 277 (66) [M^+], 238 (11), 208 (66), 138 (100). $C_9H_6F_7NO$ (277.138): calcd. C 39.00, H 2.18, F 47.99, N 5.05, O 5.77; found C 39.17, H 2.12, F 47.73, N 5.04, O 6.01.

2-(4-Amino-2-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (13): This compound was obtained analogously, from *m*-anisidine (1 g, 8.1 mmol) at 25 °C for 3 h; white crystals; m.p. 141 °C; yield 150 mg (6.3%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 3.71 (s, 3 H, OCH_3), 5.50 (br. s, 2 H, NH_2), 6.21 (dd, $J_{5,6}$ = 8.8, $J_{5,3}$ = 2 Hz, 1 H, 5-H)**,** 6.28 (d, $J_{3,5}$ = 2 Hz, 1 H, 3-H)**,** 7.24 (d, $J_{6,5}$ = 8.8 Hz, 1 H, 6-H)**,** 7.77 (s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 288 (100) [$M^+ - H$]. $C_{10}H_9F_6NO_2$ (289.174): calcd. C 41.54, H 3.14, N 4.84; found C 41.64, H 3.07, N 4.80.

2-(4-Amino-2,6-difluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (14): This compound was obtained analogously, from 3,5-difluoroaniline (1.0 g, 7.6 mmol) at 60 °C for 7 days; white crystals; m.p. 135 °C; yield 41 mg (2%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 6.12 (br. s, 2 H, NH_2), 6.20 (d, 2 H, $J_{H,F}$ = 14.4, 3-H, 5-H), 8.26 (br. s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 294 (100) [$M^+ - H$].

1,1,1,3,3,3-Hexafluoro-2-(1*H*−indol-3-yl)propan-2-ol (15): This compound was obtained analogously, from indole (2.0 g, 17 mmol) at 80 °C for 1 h; white crystals; m.p. 75 °C; yield 3.8 g (78%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.07 (t, *J* = 7.3 Hz, 1 H, 6-H), 7.16 (t, *J* = 7.3 Hz, 1 H, 7-H), 7.46 (d, *J* = 8.0 Hz, 1 H, 4-H), 7.54 (s, 1 H, 2-H), 7.79 (d, *J* = 8.0 Hz, 1 H, 7-H), 8.30 (s, 1 H, OH), 11.54 (s, 1 H, NH) ppm. MS (ESI): *m/z* (%) = 282 (100) [$M^+ -$ H]. $C_{11}H_7F_6NO$ (283.170): calcd. C 46.66, H 2.49, F 40.25, N 4.95, O 5.65 found: calcd. C 46.72, H 2.45, F 40.16, N 4.99, O 5.77.

2-(2-Aminothiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (16): This compound was obtained analogously, from 2-aminothiazole (2.0 g, 20 mmol) at 80 °C for 3 h; white crystals; m.p. 195 °C; yield 1.62 g (30%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.12 (s, 1 H, 4-H), 7.30 (br. s, 2 H, NH_2), 8.81 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): 75.8 [m, *C*(CF_3)$_2$OH], 113.6 [s, C-3], 122.9 (q, $J_{C,F}$ = 286 Hz, CF_3), 140.4 [s, C-4, HSQC cross-peak with 4-H], 171 [s, C-1] ppm. MS (ESI): *m/z* (%) = 265 (100) [$M^+ - H$]. $C_6H_4F_6N_2OS$ (266.165): calcd. C 27.08, H 1.51, F 42.83, N 10.52, O 6.01, S 12.05; found C 27.43, H 1.46, F 42.59, N 10.42, O 5.79, S 12.08.

2-(2-Amino-4-methylthiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (17): This compound was obtained analogously, from 2-amino-4-methylthiazole (1.5 g, 13 mmol) at 80 °C for 7 days; white crystals; m.p. 161 °C; yield 2.9 g (79%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.23 (s, 3 H, CH_3), 7.13 (br. s, 2 H, NH_2), 8.58 (br. s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 279 (100) [$M^+ - H$]. $C_7H_6F_6N_2OS$ (280.191): calcd. C 30.01, H 2.16, F 40.68, N 10.00, O 5.71, S 11.44; found C 30.38, H 2.05, F 40.44, N 10.20, O 5.87, S 11.47.

2-(3-Amino-5-methyl-1*H*−pyrazol-4-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (18): This compound was obtained analogously, from 3-amino-5-methylpyrazole (2 g, 20 mmol) at 80 °C for 2 h; pink crystals; m.p. 116 °C; yield 3.9 g (72%). ^{1}H NMR (400 MHz, [D_6]DMSO): two tautomers δ = 2.12 (s, 3 H, CH_3), 4.6/4.9 (2 s, br, 2 H, NH_2), 8.5/ 9.3 (2 s, br, 1 H, OH), 11.4/11.9 (2 s, br, 1 H, NH) ppm. MS (ESI): *m/z* (%) = 262 (100) [$M^+ - H$]. $C_7H_7F_6N_3O$ (263.140): calcd. C 31.95, H 2.68, F 43.32, N 15.97, O 6.08; found C 32.18, H 2.63, F 43.44, N 16.04, O 6.13.

2-(2-Amino-4-phenylthiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (19): This compound was obtained analogously, from 2-amino-4-phenylthiazole (1.2 g, 6.7 mmol) at 80 °C for 7 days; white crystals; m.p. 179 °C; yield 951 mg (41%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.26 (s, 2 H, NH_2), 7.30 (s, 5 H, Ph), 8.40 (s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 341 (100) [$M^+ - H$]. $C_{12}H_8F_6N_2OS$ (342.262): calcd. C 42.11, H 2.36, F 33.30, N 8.18, O 4.67, S 9.37; found C 42.49, H 2.23, F 33.08, N 8.43, O 4.70, S 9.29.

2-(2-Amino-4-methyloxazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (20): This compound was obtained analogously, from 2-amino-4-methyloxazole (1.5 g, 15.3 mmol) at 80 °C for 2 h; light yellow crystals; m.p. 140 °C; yield 1.6 g (39%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.05 (s, 3 H, CH_3), 6.86 (br. s, 2 H, NH_2), 8.61 (br. s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 263 (100) [$M^+ - H$]. $C_7H_6F_6N_2O_2$ (264.124): calcd. C 31.83, H 2.29, F 43.16, N 10.61, O 12.11; found C 31.89, H 2.28, F 42.85, N 10.60, O 12.03.

2-[1-(2-Aminophenyl)-1*H*-pyrrol-3-yl]-1,1,1,3,3,3-hexafluoropropan-2-ol (21): This compound was obtained analogously, from 1-(2-aminophenyl)pyrrole (2.5 g, 15.8 mmol) at 100 °C for 2.5 h; white crystals; m.p. 120 °C; yield 1.2 g (23%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.79 (br. s, 2 H, NH_2), 6.37 (s, 1 H, 5-H), 6.66 (dt, J_1 = J_2 = 6.1, J_3 = 1.4 Hz, 1 H, 4′-H), 6.87 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1 H, 3′-H), 6.98 (t, *J* = 2.7 Hz, 1 H, 4-H), 7.06 (dd, J_1 = 7.8, J_2 = 1.4 Hz, 1 H, 6′-H), 7.09 (t, *J* = 1.9 Hz, 1 H, 2′-H), 7.12 (dt, J_1 = 7.6, J_2 = 1.4 Hz, 1 H, 5′-H), 8.05 (s, 1 H, OH) ppm. Assignments confirmed by 2D HMBC data (not shown) ppm. MS (ESI): *m/z* (%) = 323 (76) [$M^+ - H$], 383 (100). $C_{13}H_{10}F_6N_2O$ (324.223): calcd. C 48.16, H 3.11, F 35.16, N 8.64, O 4.93; found C 48.17, H 3.02, F 35.10, N 8.69, O 4.99.

2-(6-Aminopyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (22): This compound was obtained analogously, from 2-aminopyridine (5.0 g, 52 mmol) at 130 °C for 15 days; white crystals; m.p. 170 °C; yield 2.4 g (17.5%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 6.35 (br. s, 2 H, NH_2), 6.50 (d, $J_{5,6}$ = 8.8 Hz, 1 H, 5-H), 7.55 (d, $J_{6,5}$ = 8.8 Hz, 1 H, 6-H), 8.14 (s, 1 H, 2-H), 8.45 (s, 1 H, OH) ppm. MS (ESI): *m/z* (%) = 259 (100) [$M^+ - H$]. $C_8H_6F_6N_2O$ (260.136): calcd. C 36.94, H 2.32, F 43.8.2 N 10.77, O 6.15; found C 37.17, H 2.27, F 43.55, N 10.83, O 6.27.

2-[4-(Dibenzylamino)phenyl]-1,1,1,3,3,3-hexafluoropropan-2-ol (23): This compound was obtained analogously, from *N*,*N*-dibenzylaniline (3.0 g, 11 mmol) and HFA $1\cdot5\cdot H_2O$ (6 mL, 55 mmol) at 80 °C for 10 min; light yellow oil; yield 4.5 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (s, 1 H, OH), 4.67 (s, 4 H, NCH_2Ph), 6.75 (d, *J* = 6.8 Hz, 2 H, 3-H), 7.22−7.36 (m, 10 H, 2 Ph), 7.44 (d, *J* = 6.8 Hz, 2 H, 2-H), ppm. MS (ESI): *m/z* (%) = 440.5 (100) [$M^+ - H$].

2-(Dibenzylamino)pyridine: Sodium hydride in oil (55%, 2.0 g, 47 mmol) was suspended under nitrogen in dry DMF (40 mL) and cooled in ice. 2-Aminopyridine (2 g, 21 mmol) was added, and stirring in ice was continued for 15 min. Benzyl bromide (5.6 mL, 47 mmol) was added and the reaction mixture was allowed to warm slowly to 25 °C with control of the exotherm and the gas evolution. Stirring at 25 °C was continued for 1 h. DMF was evaporated and the residue was extracted with ethyl acetate and 50% saturated NaCl solution. The crude product was purified by chromatography on silica gel heptane/DCM gradient of 100:0 to 50:50). A colorless oil (5 g, 85%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79

(s, 2 H, NCH_2Ph), 6.54 (d, J = 8.4 Hz, 1 H, 3-H), 6.58 (dd, J_1 = 6.8, J_2 = 5.2 Hz, 1 H, 5-H), 7.22−7.30 (m, 11 H, 5-H + 2 Ph), 7.43 (dt, J_1 = 7.2, J_2 = 1.6 Hz, 1 H, 4-H), 8.20 (d, J_1 = 5.2 Hz, 1 H, 6-H) ppm. MS (ESI): m/z (%) = 289.3 (100) $[M^+ + H]$.

2-[6-(Dibenzylamino)pyridin-3-yl]-1,1,1,3,3,3-hexafluoropropan-2-ol (24): 2-(Dibenzylamino)pyridine (4 g, 15 mmol) and hexafluoroacetate sesquihydrate (8 mL, 75 mmol) were heated at 120 °C (oil bath temperature; reaction medium 100 °C) for 4 days. The reaction mixture was extracted with ethyl acetate (2 × 100 mL) and water (2 × 100 mL). The crude product was purified by silica gel chromatography in heptane/ethyl acetate (10:1, 2 ×). The purified product (5.2 g, 81%) was crystallized from hot heptane (150 mL), affording white crystals, m.p. 60 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 4.83 (s, 4 H, NCH_2Ph), 6.68 (d, J = 8 Hz, 1 H, 5-H), 7.23−7.35 (m, 10 H, 2 Ph), 7.63 (dd, J_1 = 8, J_2 = 2 Hz, 1 H, 4-H), 8.33 (d, J = 2 Hz, 1 H, 2-H), 8.55 (s, 1 H, OH) ppm. MS (ESI): m/z (%) = 441 (100) $[M^+ + H]$. $C_{22}H_{18}F_6N_2O$ (440.39): calcd. C 60.00, H 4.12, F 25.88.2 N 6.36, O 3.63; found C 59.78, H 4.34, F 25.89, N 6.34, O 3.56.

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