Unexpected Reactivity of cyclic Perfluorinated Iodanes with Electrophiles

Stefan Gruber, *^[a] Simon M. Ametamey, ^[a] and Roger Schibli^[a]

Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zurich Vladimir-Prelog-Weg 4, 8093 Zurich (Switzerland)

*To whom correspondence should be addressed. E-mail: stefan.gruber@pharma.ethz.ch

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1. General Experimental Information

All reactions were performed with anhydrous solvents (except the NMR-screenings which were done with CDCl₃ from a standard bottle) in standard glassware under air. Anhydrous solvents were purchased in septum-sealed bottles from *Acros* and stored over 4Å molecular sieves under an atmosphere of argon. All cyclic perfluorinated iodanes were synthesized according to known literature procedures.^[1] All NMR spectra were recorded with a Bruker Avance FT-NMR spectrometer (400 MHz) and chemical shifts (δ) are given in ppm. ¹H and ¹³C NMR spectra are referenced relative to the solvent peak using the Bruker internal referencing procedure (edlock) and ¹⁹F NMR spectra are referenced relative to CFCl₃ in CDCl₃. Coupling constants (*J*) are reported in units of hertz (Hz) and to specify the signal multiplicity, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. High resolution mass spectra data (HRMS, *m/z*) were obtained at the mass spectrometry service in the Laboratory für Organisch Chemie at ETH Zürich on VG-TRIBRIB for electron impact ionization (EI) and a Varian IonSpec Spectrometer for electrospray ionization (ESI).

2. Experimental Procedures and Characterization Data

General procedure for the reaction of perfluorinated iodanes with electrophiles:

The electrophile (1.5 or 2.0 equiv) was added to a CDCl₃ solution (0.5 mL) of the perfluorinated iodane (0.019 mmol, 1.0 equiv.) in a vial or NMR-tube and stirred for 1 hour at rt or at 70 °C. After this time 0.1 ml of a CDCl₃ solution containing the internal standard was added (PhOCF₃; 0.019 mmol/ 0.1 mL stock solution) and the mixture was transferred in an NMR tube and analyzed by ¹⁹F{¹H}NMR and product formation was further verified by GC-MS. For the different perfluorinated products one example of the ¹⁹F{¹H}NMR spectrum of the reaction mixture is given below:















Reaction between perfluorinated iodane 3 and chlorine gas in CDCI₃ (no internal standard added):



Figure S1. Section of the ¹H NMR spectrum showing the aromatic region after treating perfluorinated iodane **3** with chlorine gas (295 K, 400 MHz, CDCl3).



Figure S2. a) Reaction between **6** and PyHBr₃ without radical-trapping reagent; b) Reaction between **6** and PyHBr₃ in the presence of TEMPO; c) Reactions between **6** and PyHBr₃ in the presence of p-benzoquinone.

Monitoring the reaction between 11 and Br₂ at -45 °C:



Figure S3. Section of the ¹⁹F{¹H} NMR spectrum of the reaction mixture obtained from 11 in the presence of Br_2 (2 equiv.) in CD_2CI_2 at 228 K.

Postulated structure of *

- Structure is consistent with five nonequivalent fluorides on $-C_6F_5$ (see Figure S3).
- Structure is consistent with two nonequivalent methyl groups (see Figure S4).
- Structure is consistent with ortho-fluorides and meta-fluorides, respectively of the F₅C₆-fragment that are involved in selective exchange process (see Figure S5).



Figure S4. Section of the HSQC spectrum of the reaction mixture obtained from 11 in the presence of $Br_2(2 \text{ equiv.})$ in CD_2Cl_2 at 228 K.



Figure S5. Section of the ¹⁹F, ¹⁹F 2D EXSY spectrum showing the selective exchange cross-peaks between the ortho-fluorides and the meta-fluorides, respectively of the F_5C_6 -fragment.

Warming this mixture to room temperature for 15 min:

a) Reaction mixture at 228 K (spectrum measured at 228K)



Figure S6. Section of the ¹⁹F{¹H} NMR spectrum showing the disappearance of * and **11**, respectively and the formation of BrC_6F_5 upon warming to room temperature.

Synthesis of chloride-derived perfluorinated iodane 9:



HCl in dioxane (4 M, 144 μ L, 0.578 mmol, 20 equiv.) was added dropwise to a solution of perfluorinated iodane **3** (15.0 mg, 0.029 mmol, 1 equiv.) in anhydrous CH₂Cl₂ (0.3 mL), which afforded immediately the precipitation of a white solid. The reaction mixture was stirred at rt for 1 h after which time the solid was filtered and washed with anhydrous CH₂Cl₂ (2 x 0.3 mL) and dried at HV to afford compound **9** as a with solid (15.2 mg, 93%). An acetone solution of this solid was layered with hexane and stored at rt, to afford crystals of **9** suitable for X-ray diffraction.

¹**H-NMR** (400 MHz, MeOD): δ 8.42 (dt, *J* = 7.4, 1.3 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.02 - 7.77 (m, 2H), 7.64 (dd, *J* = 9.0, 0.7 Hz, 2H), 7.27 - 7.21 (m, 2H), (OH in exchange with OD of MeOD at δ 4.86).

¹⁹F{¹H}-NMR (376 MHz, MeOD): δ -80.9 (t, *J* = 7 Hz), -81.3 (t, *J* = 7 Hz).

¹³C{¹H}-NMR (126 MHz, DMSO-*a*₆): δ 165.1, 147.1, 139.4, 135.1, 133.1, 132.7, 131.8, 130.6, 124.1, 119.9, 118.6, (note: CF₂CF₂ carbons were not observed).

HRMS (ESI): calcd. m/z for [C₁₅H₉BrF₄IO₃]⁺ ([M-CI]⁺): 518.8710; found: 518.8718.

Synthesis of chloride-derived perfluorinated iodane 10:



HCl gas (generated *ex situ* using NaCl and H_2SO_4) was bubbled through a solution of perfluorinated iodane **6** (50.0 mg, 0.094 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (0.5 mL) for 15 min and then the reaction mixture was stirred for further 30 min at rt. After this time the reaction mixture was concentrated under vacuum and the residue was washed with anhydrous hexane (3 x 0.5 mL) and dried at HV to afford compound **10** as a with solid (49 mg, 92%). A CH_2Cl_2 solution of this solid was layered with hexane and stored at 4 °C, to afford crystals of **10** suitable for X-ray diffraction.

¹**H-NMR** (400 MHz, CDCl₃): 8.20 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.27 (m, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 4.36 (s, 1H), 1.73 (s, 6H).

¹⁹F{¹H}-NMR (376 MHz, CDCl₃): δ -84.1 (t, J = 7 Hz), -85.0 (t, J = 7 Hz).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ 147.3, 147.1, 139.7, 133.2, 130.4, 130.1, 123.5, 121.0, 113.8, 111.7, 74.3, 32.2. (note: CF₂CF₂ carbons were not observed).

HRMS (ESI): calcd. m/z for [C₁₇H₁₅BrF₄IO₂]⁺ ([M-CI]⁺): 532.9231; found: 532.9232.

Synthesis of bromide-derived perfluorinated iodane 12:



HBr in AcOH (~33 wt%, 53 μ L, 0.531 mmol, 5 equiv.) was added dropwise to a solution of perfluorinated iodane **11** (15.0 mg, 0.035 mmol, 1 equiv.) in anhydrous CH₂Cl₂ (0.5 mL) and the resulting mixture was stirred at rt for 30 min. Then the reaction mixture was concentrated under vacuum and the residue was washed with anhydrous hexane (2 x 0.5 mL) and dried at HV to afford compound **12** as a with solid (16 mg, 90%). A CH₂Cl₂ solution of this solid was layered with hexane and stored at 4 °C, to afford crystals of **12** suitable for X-ray diffraction.

¹**H-NMR** (400 MHz, CD₂Cl₂): δ 7.58 (td, *J* = 7.5, 1.0 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.30 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 1.80 (s, 1H), (OH was not observed).

¹⁹F{¹H}-NMR (376 MHz, CD₂Cl₂): δ -120.0 - -120.2 (m), -142.3 (tt, J = 20.4, 5.6 Hz), -155.3 - -155.5 (m).

¹³C{¹H}-NMR (101 MHz, CD₂Cl₂): δ 147.1, 131.9, 131.8, 129.3 (2x overlap), 113.2, 77.5, 30.6, (note: C₆F₅ carbons were not observed).

HRMS (ESI): calcd. m/z for $[C_{15}H_{11}F_5IO]^+$ ([M-BrI]⁺): 428.9769; found: 428.9770.

Isolation of 1-(2-bromo-1,1,2,2-tetrafluoroethyl)-1H-imidazole:



Pyridinium tribromide (257 mg, 0.805 mmol) 1.5 equiv) was added to a CH_2Cl_2 solution (3 mL) of 1-(1,1,2,2-tetrafluoro-2-(1*H*-imidazol-1-yl)ethyl)-1 λ 3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (200 mg, 0.483 mmol, 1.0 equiv.) in a flask and the resulting mixture was stirred at rt for 1 h. Then the reaction mixture was concentrated under vacuum (250 mbar, 25 °C bath temperature) and the residue was washed with hexane (3 x 3 mL). The combined hexane layers were washed with sat. NaHCO₃ (2 mL), brine (2 mL) dried over MgSO₄, filtered and concentrated under vacuum (250 mbar, 25 °C bath temperature) to obtain a transparent oil (87 mg, 73%). ¹H and ¹⁹F data are consistent with literature values.^[2] **HRMS (ESI):** calcd. m/z for [C₅H₄BRF₄N₂]⁺ ([M+HI]⁺): 246.9488; found: 246.9489.

Isolation & characterization of 1-bromo-4-(2-chloro-1,1,2,2-tetrafluoroethoxy)benzene:



 Cl_2 gas (generated *ex situ* using trichloroisocyanuric acid and HCl) was bubbled through a solution of perfluorinated iodane **3** (20.0 mg, 0.039 mmol) in anhydrous CD_2Cl_2 (1.0 mL) at 0 °C for 30 min and then the reaction mixture was stirred for further 30 min at 0 °C. After this time all the volatiles (CD_2Cl_2 solution containing 1-bromo-4-(2-chloro-1,1,2,2-tetrafluoroethoxy)benzene) were blown with nitrogen gas via a cannula into a second flask that was cooled with liquid nitrogen. The condensed CD_2Cl_2 solution containing 1-bromo-4-(2-chloro-1,1,2,2-tetrafluoroethoxy)benzene was used for characterization by NMR and HRMS.

¹**H-NMR** (400 MHz, CD₂Cl₂): δ 7.41 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H). ¹⁹**F**{¹**H**}-**NMR** (376 MHz, CD₂Cl₂): δ -73.3 (t, J = 3 Hz), -87.1 (t, J = 3 Hz). ¹³C{¹**H**}-**NMR** (101 MHz, CD₂Cl₂): δ 147.7, 133.0, 130.4, 123.5, (note: CF₂CF₂ carbons were not observed). **HRMS (GC-EI):** calcd. m/z for [C₈H₄BrClF₄O⁺⁺]: 305.9065; found: 305.9063.

3. Radiochemistry

No-carrier-added [¹⁸F]fluoride was produced via the ${}^{18}O(p,n){}^{18}F$ nuclear reaction by irradiation of enriched [¹⁸O]water and was immediately trapped on an anion-exchange cartridge (Waters SepPak Accell QMA cartridge carbonate). The trapped [¹⁸F]fluoride was eluted from the cartridge with 1.0 mL of an MeCN/H₂O (3/1) solution containing Cs₂CO₃ (1.3 mg) into a tightly closed Reacti-Vial[™] that was pre-charged with Kryptofix-222 (1.5 mg). The [¹⁸F]fluoride was dried by azeotropic distillation of acetonitrile at 90 °C under vacuum with a stream of nitrogen. The azeotropic drying process was repeated 3 times with 1 mL of acetonitrile each time. After this procedure, the solid was additionally dried under vacuum at 90 °C for 5 min. To the dried [¹⁸F]fluoride complex (typically ~10 GBq), a solution of XeF₂ (20.3 mg) in 1,2-dichloroethane (0.3 mL) was added and the resulting reaction mixture was stirred at rt for 30 min. After this time a solution of perfluorinated iodane **3**(2.1 mg) in 1,2-dichloroethane (0.2 mL) was added to the closed Reacti-Vial[™] and the mixture was heated at 70 °C (in a metal heating block) for 30 min. After cooling for ca. 5 min an aliquot (~ 50 MBq) was taken from the reaction mixture, added to a vial containing 0.5 mL of EtOH/H2O (9/1) and analyzed by analytical HPLC. HPLC analysis was performed with a VWR-Hitachi L-2230 system equipped with a L-2450 diode array detector and a Berthold radiodetector using a reverse phase column (Bondclone, C18, 10 µm, 300 x 3.9 mm) with the following conditions: H₂O (solvent A), MeCN (solvent B); 0.0-18.0 min, 25-95% B; 18.0-22.0 min, 95% B; 22.0-22.1 min, 95-25% B; 22.1-25.0 min, 25% B; flow rate 1 mL/min, UV = 245 nm). The radiochemical yields were determined by radio-HPLC analysis of the crude product by integration of the product peak ($[^{18}F]$ **5**) vs. free ${}^{18}F^{-}/[^{18}F]$ XeF₂. Identity of $[^{18}F]$ **5** ($t_{\rm R}$: 15.90 min) was confirmed by coinjection with non-radioactive 5 (reference compound 15.81).



Figure S7. HPLC traces of model compound [¹⁸F]5 co-injected with 5 (top: UV trace; bottom: radio trace).

4. Crystallography

Single crystalline samples were measured on the following instrument:

- Rigaku Oxford Diffraction XtaLAB Synergy-S Dualflex kappa diffractometer equipped with a Dectris Pilatus 300 HPAD detector and using microfocus sealed tube Cu-K α radiation with mirror optics (λ = 1.54178 Å, **9** and **10**) or microfocus sealed tube Mo-K α radiation using mirror optics (λ = 0.71073 Å, **12**).

All measurements were carried out at 100 K using an Oxford Cryosystems Cryostream 700 or 800 sample cryostat. Data collected were integrated using CrysAlisPro and corrected for absorption effects using a combination of empirical (ABSPACK) and numerical corrections.^[3] The structures were solved using SHELXS,^[4] SHELXT^[5] or Superflip^[6] and refined by full-matrix least-squares analysis (SHELXL)^[4,7] using the program package OLEX2.^[8] Unless otherwise indicated below, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters (in terms of a riding model). CCDC XXX (9), XXX (10) and XXX (12) contain the supplementary crystallographic data for this paper, including structure factors and refinement instructions. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or *via* https://www.ccdc.cam.ac.uk/getstructures.



Figure S8. Crystal packing of compound **9** showing the additional chlorine-iodine interaction between the molecule in the asymmetric unit and a symmetry generated partner with a distance of 3.346(1) Å.

Table S1. Crystal data and structure refinement for compound 9.				
Empirical formula	$C_{15}H_9BrClF_4IO_3$			
Formula weight	555.49			
Temperature/K	100			
Crystal system	triclinic			
Space group	P-1			
a/Å	7.9867(2)			
b/Å	8.2391(2)			
c/Å	13.6897(2)			
$\alpha/^{\circ}$	74.798(2)			
β/°	84.253(2)			
$\gamma/^{\circ}$	86.584(2)			
Volume/Å ³	864.41(3)			
Z	2			
$\rho_{calc}g/cm^3$	2.1340			
μ/mm^{-1}	19.206			
F(000)	528.8			
Crystal size/mm ³	$0.123\times 0.066\times 0.028$			
Radiation	Cu Ka ($\lambda = 1.54184$)			
2Θ range for data collection/° 6.72 to 159.72				
Index ranges	$-10 \le h \le 10, -10 \le k \le 10, -17 \le l \le 17$			
Reflections collected	33322			
Independent reflections	$3694 \ [R_{int} = 0.0495, R_{sigma} = 0.0250]$			
Data/restraints/parameters	3694/1/229			
Goodness-of-fit on F ²	1.077			
Final R indexes [I>= 2σ (I)]	$R_1 = 0.0275, wR_2 = 0.0684$			
Final R indexes [all data]	$R_1 = 0.0285, wR_2 = 0.0690$			

 Table S1. Crystal data and structure refinement for compound 9.

Identification code	rs091117_1_1
Empirical formula	$C_{17}H_{15}BrClF_4IO_2$
Formula weight	569.55
Temperature/K	100.0(1)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	11.35480(10)
b/Å	8.05860(10)
c/Å	21.0488(2)
$\alpha/^{\circ}$	90
β/°	95.6110(10)
$\gamma/^{\circ}$	90
Volume/Å ³	1916.82(3)
Z	4
$\rho_{calc}g/cm^3$	1.974
μ/mm^{-1}	17.295
F(000)	1096.0
Crystal size/mm ³	$0.145\times0.087\times0.03$
Radiation	$CuK\alpha \ (\lambda = 1.54184)$
2Θ range for data collection/°	8.442 to 159.458
Index ranges	$-14 \le h \le 14, -8 \le k \le 9, -26 \le l \le 26$
Reflections collected	68822
Independent reflections	$4118 \ [R_{int} = 0.0362, R_{sigma} = 0.0130]$
Data/restraints/parameters	4118/1/240
Goodness-of-fit on F ²	1.090
Final R indexes [I>= 2σ (I)]	$R_1 = 0.0202, wR_2 = 0.0491$
Final R indexes [all data]	$R_1 = 0.0206, wR_2 = 0.0494$

Table S2. Crystal data and structure refinement for compound 10.

Identification code	rs090418_1_2			
Empirical formula	$C_{15}H_{11}BrF_5IO$			
Formula weight	509.05			
Temperature/K	100.0(1)			
Crystal system	orthorhombic			
Space group	Fdd2			
a/Å	38.2117(7)			
b/Å	18.5754(5)			
c/Å	9.3073(3)			
$\alpha/^{\circ}$	90			
β/°	90			
$\gamma/^{\circ}$	90			
Volume/Å ³	6606.3(3)			
Z	16			
$\rho_{calc}g/cm^3$	2.047			
μ/mm^{-1}	4.408			
F(000)	3872.0			
Crystal size/mm ³	$0.241 \times 0.068 \times 0.032$			
Radiation	MoKa ($\lambda = 0.71073$)			
2Θ range for data collection/° 5.848 to 69.356				
Index ranges	$-56 \le h \le 58, -27 \le k \le 25, -12 \le l \le 14$			
Reflections collected	18693			
Independent reflections	5672 [$R_{int} = 0.0383$, $R_{sigma} = 0.0432$]			
Data/restraints/parameters	5672/4/213			
Goodness-of-fit on F ²	1.022			
Final R indexes [I>= 2σ (I)]	$R_1 = 0.0359, wR_2 = 0.0861$			
Final R indexes [all data]	$R_1 = 0.0496, wR_2 = 0.0906$			

 Table S3. Crystal data and structure refinement for compound 12.

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6. ¹H, ¹⁹F and ¹³C spectra:











