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Activation of the hypervalent fluoroiodane reagent by hydrogen bonding to hexafluoroisopropanol

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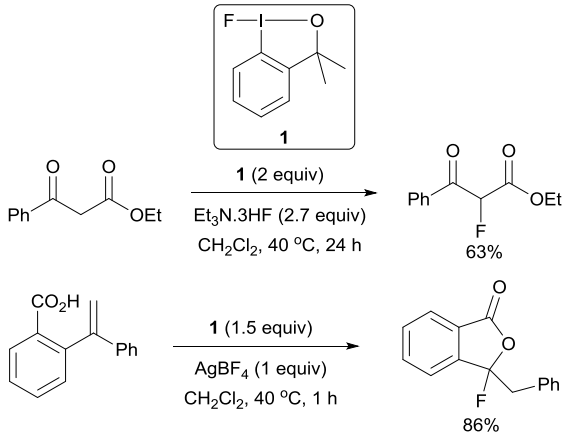
Hexafluoroisopropan-2-ol (HFIP) is an excellent solvent for promoting fluorinations with the hypervalent fluoroiodane reagent 1 and crucially, it removes the need for transition metals or TREAT-HF activators. The fluoroiodane reagent 1 was used in HFIP to monofluorinate 1,3-ketoesters and to fluorocyclise unsaturated carboxylic acids in excellent yields under mild reaction conditions.

An important strategy in the development of new pharmaceutical and agrochemical products is the incorporation of fluorine because it can increase their effectiveness, biological half-life and bioavailability.[1] Consequently, the chemical industry still needs more efficient methods for fluorination. The desire for new fluorination methodology is also fuelled by the rapidly growing, non-invasive medical imaging technique of positron emission tomography (PET). Fluorine-18 (β+ 0.635 MeV, t½ 109.7 min)[2] is often the radionuclide of choice for PET imaging which is widely used in oncology for diagnosis, staging and management of patients, accurate treatment planning and monitoring the response to therapy.

In 2013 we reported the synthesis of the new air- and moisture-stable fluorinating reagent **1** (Scheme 1).[3a] The key feature of **1** is that it is easily prepared by nucleophilic fluorinations, but it can simulate electrophilic fluorinations to create new C-F bonds.[3-5] Initially, **1** was used to monofluorinate 1,3-ketoesters and difluorinate 1,3-diketones in good yields, but the addition of TREAT-HF ($Et_3N.3HF$) was essential for these reactions.[3a] Subsequently, by using **1** in combination with $AgBF_4$, unsaturated carboxylic acids underwent a fluorination, aryl migration and a cyclisation cascade to produce a new class of fluorinated lactones.[3c]

Szabó has increased the substrate scope of reagent **1** and demonstrated that it can be used for the geminal difluorination of styrenes, the 1,3-difluorination of cyclopropanes, the geminal oxyfluorination of diazocarbonyl compounds and the intramolecular fluorocyclisations of unsaturated alcohols, amines and malonates.[4]



Scheme 1 Previous fluorinations with the fluoroiodane reagent **1**

However, these reactions only proceed in the presence of a transition metal. Gulder and Lu have also developed fluoro-cyclisations of unsaturated amides and carbamates respectively, undergoing a fluorination, aryl migration and cyclisation cascade.[5] The mechanisms of these fluorocyclisations have been investigated using density functional theory (DFT) calculations,[6] which revealed that the Lewis acids ($AgBF_4$ or $Zn(BF_4)_2.xH_2O$) activated the hypervalent fluoroiodane reagent by coordinating to its fluorine atom and elongating the I-F bond. Similarly, the fluorocyclisations of unsaturated amides proceeded without using a Lewis acid catalyst because the amide group activated the fluoroiodane by hydrogen bonding to its fluorine atom.

In this paper we propose that the strong hydrogen bond donating ability of hexafluoroisopropanol (HFIP), combined with its reduced nucleophilicity and good oxidative stability,[7] make it the ideal solvent to perform fluorinations with the hypervalent fluoroiodane reagent **1** without any transition metals or TREAT-HF activators. Recently, Hammond proposed that HFIP can form a hydrogen-bonded network which can activate KF for the synthesis of α-fluoroenamides.[8a] The activation of benzylic fluorides by hydrogen bonding in HFIP has also been reported by Paquin[8b] and Doyle has established that the combination of benzoyl fluoride and HFIP serves as a latent source of

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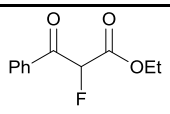
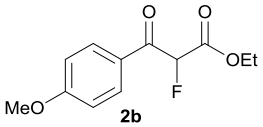
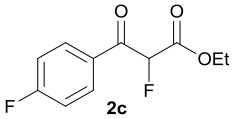
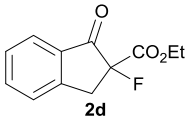
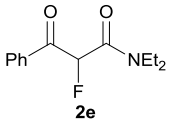
HF.[8c-d] In 2018 Crousse and Gulder independently published that HFIP is an excellent solvent for promoting electrophilic halogenations (X = Cl, Br and I) because it activates the respective *N*-halosuccinimides by hydrogen bonding.[9] Hypervalent iodine reagents have also been used in HFIP for oxidative cross-couplings of electron-rich arenes with protected anilines and phenols,[10] as well as oxidative ring expansions of secondary and tertiary alcohols.[11] In the hypervalent iodine-initiated [2+2] cycloadditions of styrenes, NMR spectroscopy revealed the formation of a strong hydrogen-bonded adduct between HFIP and phenyliodine(III) diacetate.[12] Herein, we report the fluorinations of 1,3-dicarbonyl compounds and the metal-free fluorocyclisations of unsaturated carboxylic acids by using HFIP to activate the fluoroiodane reagent through hydrogen bonding.

In our preliminary communication, the optimum reaction conditions for the fluorination of ethyl 3-oxo-3-phenylpropanoate used 2 equivalents of fluoroiodane **1** and 2.7 equivalents of TREAT-HF in dichloromethane at 40 °C for 24 hours to deliver the monofluorinated product **2a** in 63% yield (Entry 1, Table 1).[3a] When the same reaction is now performed in HFIP using 1.5 equivalents of fluoroiodane **1**, the TREAT-HF is no longer required and the reaction time is reduced to 4 hours at 60 °C to deliver **2a** in an improved 73% yield. The results from our original reaction conditions using TREAT-HF are compared directly in Table 1 with the results from our new reaction conditions using HFIP for a small series of 1,3-dicarbonyl compounds. Both ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate and ethyl 3-(4-fluorophenyl)-3-oxo-propanoate were monofluorinated in HFIP to form **2b** and **2c** in 90% and 93% yield respectively. The fluorination of ethyl 1-indanone-2-carboxylate was more efficient in HFIP (81% yield in 4 h) than using TREAT-HF in dichloromethane (55% yield in 48 h). *N*,*N*-Diethyl-3-oxo-3-phenylpropanoate was also fluorinated under milder reaction conditions in HFIP (RT for 1 h) to produce **2e** in 71% yield (entry 5). In these fluorinations we propose that the fluoroiodane is being activated by hydrogen bonding to HFIP and so, the TREAT-HF is no longer required.

The fluorinated lactones (**4a** to **4e**) were prepared originally by the intramolecular fluorocyclisations of unsaturated carboxylic acids (**3a** to **3e**) by using fluoroiodane **1** (1.5 equivalents), $AgBF_4$ (1 equivalent) and powdered 4Å molecular sieves in dichloromethane at 40 °C for 1 hour (Table 2).[3c] We now demonstrate that the same fluorocyclisations can proceed without a metal catalyst by performing the reactions in HFIP at 40 °C for 1 hour. Table 2 compares the results from these new reaction conditions with the results from the original reaction conditions using $AgBF_4$. In entries 1-4 the silver-catalysed fluorocyclisations formed the fluorinated lactones in 69-86% yield, whilst the metal-free fluorinations in HFIP produced the same products in 79-84% yield. Although HFIP is considered a poor nucleophile, it can react to form the hexafluoro-isopropoxy-substituted lactone as a minor side product (<5% in the crude product), but it is separated easily by column

Table 1 Fluorination of 1,3-dicarbonyl compounds using **1** with and without $Et_3N.3HF$

Entry	Product	Yield with $Et_3N.3HF$ (%)[a,b]	Yield in HFIP (%)[b,c]
1	 **2a**	63[d]	73
2	 **2b**	67[d]	90
3	 **2c**	-[e]	93
4	 **2d**	55[d,f]	81
5	 **2e**	88[g]	71[h]

[a] Reaction conditions: substrate (0.72 mmol), fluoroiodane **1** (1.44 mmol), $Et_3N.3HF$ (1.94 mmol) and dry CH_2Cl_2 (1.2 mL) at 40 °C for 24 h. [b] Isolated yield. [c] Reaction conditions: substrate (0.72 mmol), fluoroiodane **1** (1.08 mmol) and HFIP (1.2 mL) at 60 °C for 4 h. [d] Result taken from reference 3a. [e] Not part of original study. [f] 60 °C for 48 h. [g] Result taken from reference 13. [h] RT for 1h.

chromatography.[8a,9b,14] The silver-catalysed fluorocyclisation of 5-phenyl-5-hexenoic acid **3e** (entry 5) was investigated previously in order to prepare δ-lactones, but **4e** was only isolated in a moderate 38% yield. Here, when 5-phenyl-5-hexenoic acid was reacted with fluoroiodane **1** in HFIP, the fluorocyclisation was more selective and delivered the fluorinated δ-lactone in a good 66% yield.[15]

The intramolecular fluorocyclisation of the monosubstituted alkene, 4-pentenoic acid **3f** (entry 6), was investigated using both sets of reaction conditions to produce the fluorinated lactone, 5-(fluoromethyl)dihydrofuran-2(3*H*)-one **4f**, but a much better 82% yield was achieved in HFIP. The *trans*-disubstituted alkene, (*E*)-4-phenylbut-3-enoic acid **3g** (entry 7), is a less reactive substrate than the geminal-disubstituted alkenes (**3a** to **3d**) and required 4 hours at 40 °C to produce the new fluorinated γ-lactone **4g** as a mixture of diastereomers in only 43 or 36% yield. Finally, the trisubstituted alkene, (*E*)-4-phenylpent-3-enoic acid **3h** (entry 8), also underwent an intramolecular fluorocyclisation to produce the new fluorinated lactone, 5-fluoro-5-methyl-4-phenyldihydrofuran-2-one **4h**, which was isolated as a mixture of diastereomers in 86% yield in HFIP compared to a 69% yield with $AgBF_4$. As expected,[3c] the fluoro-

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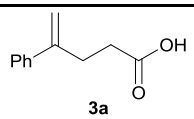
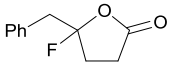
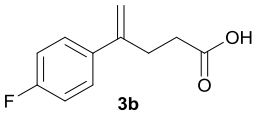
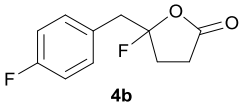
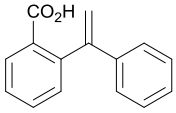
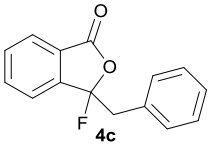
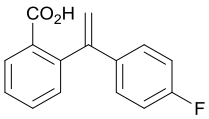
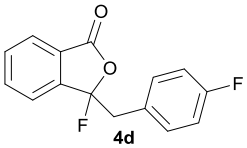
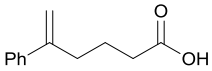
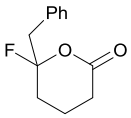
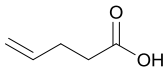
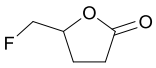
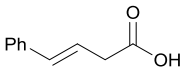
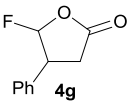
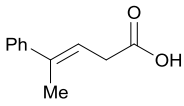
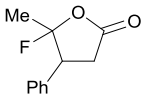
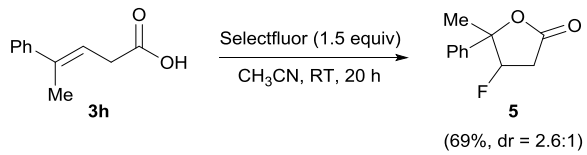
Table 2 Fluorocyclisations using **1** with and without $AgBF_4$

Entry	Substrate	Product	Yield with $AgBF_4$ (%)[a,b]	Yield in HFIP (%)[b,c]
1	 **3a**	 **4a**	81[d]	84
2	 **3b**	 **4b**	77[d]	80
3	 **3c**	 **4c**	86[d]	79
4	 **3d**	 **4d**	69[d]	81
5	 **3e**	 **4e**	38[d]	66
6	 **3f**	 **4f**	40	82
7	 **3g**	 **4g**	43[e] dr = 1.8:1	36[e] dr = 1.6:1
8	 **3h**	 **4h**	69 dr = 1:2	86 dr = 2.2:1

[a] Reaction conditions: substrate (0.7 mmol), fluoroiodane **1** (1.1 mmol), $AgBF_4$ (0.7 mmol), 4Å molecular sieves (0.18 g) and dry CH_2Cl_2 (0.4 mL) at 40 °C for 1 h. [b] Isolated yield. [c] Reaction conditions: substrate (0.9 mmol), fluoroiodane **1** (1.36 mmol), 4Å molecular sieves (0.11 g) and HFIP (3 mL) at 40 °C for 1 h. [d] Result taken from reference 3c. [e] 40 °C for 4 h.

cyclisation of the same substrate **3h** with Selectfluor™ gave different regioselectivity and 4-fluoro-5-methyl-5-phenyldihydro-furan-2-one **5** was formed as a mixture of diastereomers in 69% yield (Scheme 2). One of the advantages of using fluoroiodane **1** is these unusual transformations that are not possible with traditional electrophilic fluorinating reagents such as Selectfluor™. The (4*S*,5*R*)/ (4*R*,5*S*)- and (4*S*,5*S*)/(4*R*,5*R*)-diastereomers of **4h** and **5** were separated by column chromatography. In each case the major diastereomer was confirmed as the (4*S*,5*R*)/(4*R*,5*S*)-diastereomer by X-ray crystallography and the molecular structures are shown in the ESI.

The role of HFIP in activating the fluoroiodane was investigated using NMR spectroscopy. The ^1H, ^{19}F and ^{13}C NMR spectra were recorded for (a) fluoroiodane **1** and (b) HFIP separately, as well as for (c) a 1:1 mixture of fluoroiodane:HFIP (see ESI for full characterisation). Figure 1 shows the three ^1H NMR spectra and (c) the 1:1 mixure of fluoroiodane and HFIP is predominantly the sum of the two individual spectra (a) and (b). The red star, however, highlights that there was a significant downfield shift of the OH signal from 2.80 in HFIP to 4.92 ppm in the 1:1 adduct and the OH signal changed from a broad singlet in HFIP to a doublet in the 1:1 adduct



Scheme 2 Fluorination of **3h** with Selectfluor

($^3J_{HH}$ = 7.5 Hz). This provided good evidence for the formation of a hydrogen-bonded adduct between the HFIP and fluoroiodane.

In conclusion, we have demonstrated that HFIP is an excellent solvent for promoting fluorinations with the hypervalent fluoroiodane reagent **1** and crucially, it removes the need for transition metals or TREAT-HF activators. NMR data revealed the formation of a hydrogen-bonded adduct between the solvent and fluoroiodane, showing that the fluoroiodane reagent **1** is activated by hydrogen bonding to HFIP. 1,3-Ketoesters and a 1,3-ketoamide were monofluorinated in excellent yields in HFIP in 1-4 hours compared to 24 hours in dichloromethane using TREAT-HF. The metal-free fluorocyclisations of unsaturated carboxylic acids also proceeded well in HFIP to deliver the fluorinated lactones in excellent yields.

We would like to thank Vanessa Timmermann for assistance with the NMR experiments and Kuldip Singh for X-ray crystallography.

Conflicts of Interest

There are no conflicts to declare.

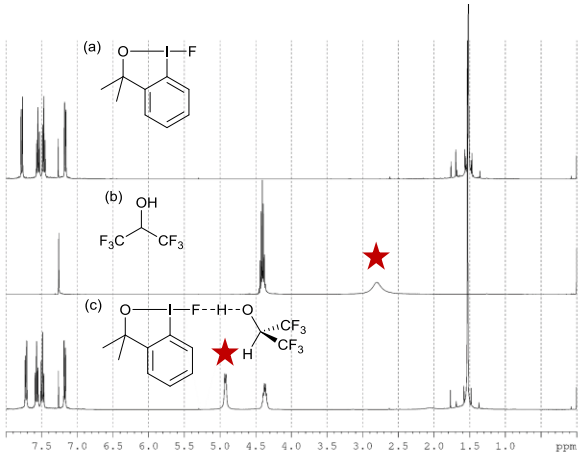


Figure 1. ^{1}H NMR spectra of (a) fluoroiodane **1**, (b) HFIP and (c) a 1:1 mixture of fluoroiodane:HFIP, showing a plausible structure of an adduct. The red star indicates the position of the deshielded OH signal of interest.

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