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Electrophilic Fluorination Using A Hypervalent Iodine Reagent Derived From Fluoride†

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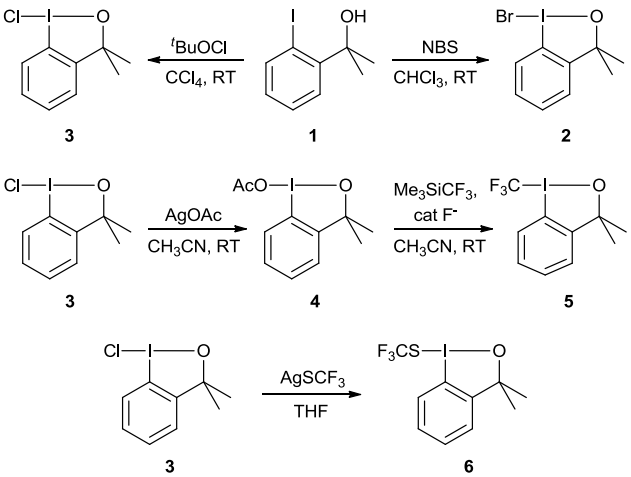
The air and moisture stable fluoroiodane 8, readily prepared on a 6 g scale by nucleophilic fluorination of the hydroxyiodane 7 with TREAT-HF, has been used as an electrophilic fluorinating reagent for the first time to monofluorinate 1,3-ketoesters and difluorinate 1,3-diketones in good isolated yields.

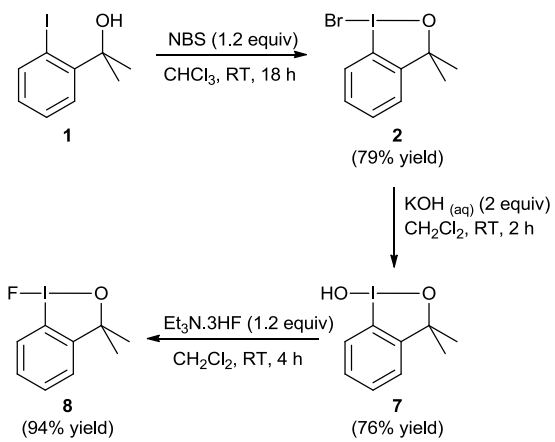
In late 2011, Ritter reported the first electrophilic fluorination using the fluoride anion in a transfer fluorination between two palladium species.[1] An alternative, non-metal based strategy could be envisaged using cyclic hypervalent iodine(III) compounds which have been shown to be mild, non-toxic and selective reagents for halogenation.[2-4] These reagents are normally prepared by oxidation of iodine(I) species with electrophilic reagents such as *tert*-butyl hypochlorite (**1** → **3**) and *N*-bromosuccinimide (**1** → **2**),[2] but Togni cleverly designed the synthesis of the electrophilic trifluoromethylated hypervalent iodine reagent **5** using a formal umpolung of the trifluoromethyl group (Scheme 1).[3a] Ruppert's reagent was used as the nucleophilic source of the trifluoromethyl anion in order to displace the acetate and form an electrophilic trifluoromethylating reagent. Togni's reagent now has widespread applications including the electrophilic trifluoromethylation of β-ketoesters, α-nitroesters, thiols, phosphines and heteroaromatic compounds.[3] Using an analogous nucleophilic route, Lu and Shen reported in 2013 the new electrophilic hypervalent iodine reagent **6** for the trifluoromethylthiolation of β-ketoesters, alkynes, aryl and vinyl boronic acids.[4]

Our research group is interested in designing new methods for introducing fluorine into organic molecules[5] because of the importance of incorporating fluorine into drug candidate molecules.[6] Since Banks first reported SelectFluor in 1992,[7] the fluoraza reagents have become increasingly popular electrophilic fluorinating reagents because they are commercially-available, shelf-stable powders that can be used to fluorinate a wide variety of substrates.[8] The main disadvantage of these electrophilic fluorinating reagents, however, is that they are very expensive because they are normally made from elemental fluorine.



Scheme 1 Syntheses of hypervalent iodine reagents

Alternative reagents such as (difluoroiodo)arenes have been prepared from aqueous HF, but they are extremely moisture sensitive and are commonly used as a freshly prepared solution, without isolation, or they can be generated *in situ*.[9] Inspired by Togni's seminal work on electrophilic trifluoromethylation,[3] we were interested in developing a new class of stable fluorinating reagents based on the cyclic hypervalent iodine(III) skeleton, but generated from cheap sources of fluoride. Here, we will report three different methods for the preparation of an air and moisture stable fluorinated hypervalent iodine reagent **8** and preliminary results on its' fluorination of a series of 1,3-dicarbonyl substrates.



Scheme 2 Synthesis of the fluoroiodane **8** using TREAT-HF

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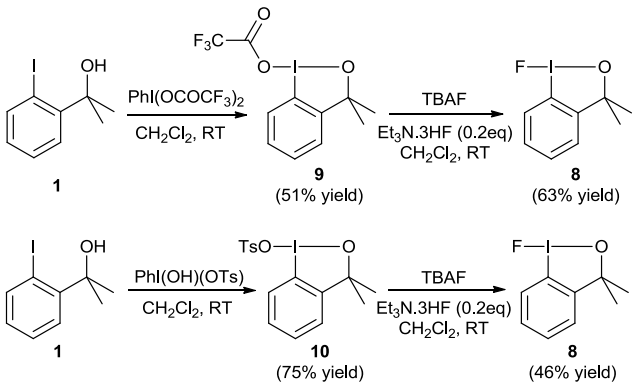
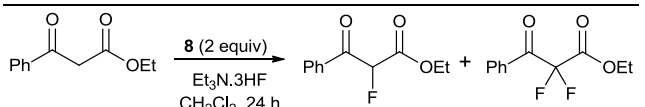


Scheme 3 Syntheses of the fluoroiodane **8** using TBAF

The fluoroiodane **8** was first prepared in 2012 by the electrophilic fluorination of 2-(2-iodophenyl)propan-2-ol **1** with 1.3 equivalents of Selectfluor in acetonitrile.[10] Whilst this manuscript was in the final stages of preparation, Togni reported a nucleophilic route to the fluoroiodane **8** by halogen exchange of the chloroiodane **3** with 1.5 equivalents of spray-dried potassium fluoride in acetonitrile,[11] but both the reaction and the work up were carried out under argon. We have developed an alternative three step synthesis that also uses a nucleophilic fluorination (Scheme 2). The bromoiodane **2**, synthesised using *N*-bromosuccinimide, was reacted with potassium hydroxide at room temperature in order to produce the hydroxyiodane **7** under mild reaction conditions. In the key step the hydroxyiodane **7** was reacted with 1.2 equivalents of triethylamine tris(hydrogen fluoride) (TREAT-HF) at room temperature to give the fluoroiodane **8** in a 94 % isolated yield after recrystallization from hexane. This is an excellent method for the preparation of **8** because there are no time-consuming purifications by column chromatography, each of the steps have been performed routinely on a 6-10 g scale and the reactions do not require either dry or inert conditions.

Since one of the long term aims of this project is to prepare a new fluorinating agent that is suitable for the production of ^{18}F-labelled radiotracers for Positron Emission Tomography (PET) imaging, we were also interested in developing a nucleophilic route to the fluoroiodane **8** using sources of fluoride, such as potassium fluoride or tetrabutylammonium fluoride (TBAF), that can be applied to PET chemistry. Our synthetic strategy was to introduce a good leaving group onto the hypervalent iodine reagent in order to facilitate nucleophilic displacement by fluoride (Scheme 3). To this end, the new hypervalent iodine reagents, trifluoroacetoxyiodane **9** and tosyliodane **10**, were synthesised by the reaction of 2-(2-iodophenyl)propan-2-ol **1** with either PhI(OCOCF$_3$)$_2$ or PhI(OH)(OTs) following Koser's procedure[12] and the solid-state structures of both compounds are presented in the supplementary information. When the trifluoroacetoxyiodane **9** was reacted with 1.2 equivalents of TBAF in dichloromethane, a mixture of the fluoroiodane **8** and the hydroxyiodane **7** was obtained in a 3:1 ratio. Since neither **9** nor **8** are hydrolysed in the presence of water, the formation of the hydroxyiodane **7** is believed to be due to the presence of tetrabutylammonium hydroxide in the TBAF. Therefore, since tetrabutylammonium hydroxide reacts with aqueous HF to give TBAF[13] and the hydroxyiodane **7** reacts with TREAT-HF to form the fluoroiodane **8**, the addition of TREAT.HF was investigated. With just 0.2 equivalents of TREAT-HF (Scheme 3) the fluoroiodane **8** was isolated in a 63% yield on a 1.0 g scale. The reaction between the tosyliodane **10** and TBAF in the presence of TREAT-HF was also successful giving a 100% conversion to the fluoroiodane **8** and a 46 % yield after recrystallization from hexane. Neither the trifluoroacetoxyiodane **9** nor the tosyliodane **10** react with TREAT-HF (1.2 equivalents) at room temperature and in both cases unreacted starting material was recovered at the end of the reaction showing that it is the fluoride ion from the TBAF that is undergoing the nucleophilic substitution to form the fluoroiodane **8**.

Table 1 Optimisation of fluorination of ethyl-3-oxo-3-phenylpropanoate



Entry	Concent[a] [M]	Temp (^{o}C)	TREAT-HF (no. equiv.)	Yield of **12**[b,c] (%)	Yield of **13**[b,c] (%)
1	0.12	60	0	8	0
2	0.12	60	0.9	30	4
3	0.12	60	1.8	48	7
4	0.12	60	2.7	65	19
5[d]	0.12	60	2.7	54	28
6[e]	0.12	60	2.7	0	0
7	0.12	40	2.7	54	4
8	0.12	80	2.7	49	36
9	**0.24**	**40**	**2.7**	**89 (63)**	**6**
10[d]	0.24	40	2.7	83	11
11	0.24	60	2.7	67(49)	25 (13)

[a] Concentration of substrate. [b] Determined by ^{1}H and ^{19}F NMR spectroscopy. [c] Isolated yield in parenthesis. [d] Reaction time was 48 h. [e] Control reaction without fluoroiodane **8**.

The reactivity of the fluoroiodane **8** as an electrophilic fluorinating reagent was first investigated using ethyl 3-oxo-3-phenylpropanoate **11** as the model substrate (Table 1). When 2 equivalents of the fluoroiodane **8** was reacted with ethyl 3-oxo-3-phenylpropanoate **11** at 60 ^{o}C for 24 hours (entry 1), only an 8% conversion to the monofluorinated product **12** was obtained. The addition of TREAT-HF is essential for the fluorination and on increasing the amount from 0.9 to 2.7 equivalents the conversion to both the monofluorinated and difluorinated products increased to 65% and 19% respectively (entry 4). On extending the reaction time to 48 hours in entry 5, more of the difluorinated product **13** was produced. However, the fluorination of ethyl 3-oxo-3-phenylpropanoate **11** with 2.7 equivalents of TREAT-HF does not proceed in the absence of the fluoroiodane **8** (entry 6). Interestingly, the temperature of the reaction is an important factor with a more selective reaction towards the monofluorinated product **12** observed at 40 ^{o}C (entry 7), whilst the amount of the competing difluorinated product **13** increased at 80 ^{o}C (entry 8).

The concentration of the reaction mixture is also an important factor in these fluorinations. When the concentration of the substrate was doubled from 0.12 M to 0.24 M, there was a dramatic improvement in the fluorination performed at 40 ^{o}C and the conversion to the monofluorinated product **12** increased from 54% (entry 7) to 89% (entry 9). The reaction was purified by column chromatography and ethyl 2-fluoro-3-oxo-3-phenylpropanoate **12** was isolated in 63% yield. When either the reaction time was extended to 48 hours (entry 10) or the reaction

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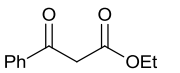
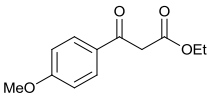
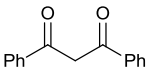
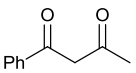
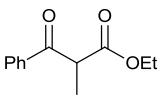
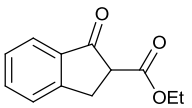
Table 2 Fluorination of 1,3-dicarbonyl compounds[a]

Entry	Substrate	Temp (°C)	Time (h)	Monofluoro Product[b,c] (%)	Difluoro Product[b,c](%)
1		40	24	89 (63)	6
2		40	24	95 (67)	5
3		40 60 60[d]	24 24 24	30 11 0	55 76 100 (71)
4		60[d]	24	0	100 (45)
5[e]		60	168	62 (55)	-
6[e]		60	48	100 (55)	-

[a] Reaction conditions: substrate (0.72 mmol), fluoroiodane **8** (1.44 mmol), $Et_3N.3HF$ (1.94 mmol) and dry CH_2Cl_2 (1.2 mL). [b] Determined by ^1H and ^{19}F NMR spectroscopy. [c] Isolated yield in parenthesis. [d] Fluoroiodane **8** (3 equiv). [e] No solvent.

was performed at 60 °C (entry 11), the amount of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **13** increased.

The scope of the reaction was established with a series of 1,3-dicarbonyl compounds and the results are presented in Table 2. The relative reactivity of the different substrates could be directly correlated with their enol content as observed previously for electrophilic fluorinations.[7c,14] When ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate was reacted with the fluoroiodane **8** under the optimum reaction conditions from Table 1 (entry 9: 40 °C, 24 hours), the monofluorinated product was isolated in 67% yield (entry 2). Under the same reaction conditions the more reactive substrate, 1,3-diphenyl-1,3-propanedione (entry 3), gave a mixture of the monofluorinated (30%) and difluorinated (55%) products. In order to convert the 1,3-diketone into the difluorinated product, the reaction was repeated at 60 °C for 24 hours but there was still a small amount of the monofluorinated product present (11%) at the end of the reaction. Finally, the reaction was repeated with 3 equivalents of the fluoroiodane **8** at 60 °C resulting in a 100% conversion to 1,3-diphenyl-2,2-difluoro-1,3-propanedione which was isolated in 71% yield. The other 1,3-diketone, 1-phenyl-1,3-butanedione (entry 4), was also reacted with 3 equivalents of the fluoroiodane **8** at 60 °C for 24 hours producing 1-phenyl-2,2-difluoro-1,3-butanedione in 45% yield. Due to its extremely low enol content (100% ketone in $CDCl_3$ by ^1H NMR spectroscopy), the fluorination of the monosubstituted 1,3-ketoester, ethyl 2-methyl-3-oxo-3-phenylpropanoate (entry 5) took 7 days at 60 °C without solvent to give the fluorinated product in 55% isolated yield. On the other hand, the fluorination of ethyl 1-indanone-2-carboxylate was much more efficient and 100% conversion to ethyl 1-indanone-2-fluoro-2-carboxylate was obtained in 48 hours (55% yield) because of its higher enol content (17% in $CDCl_3$ by ^1H NMR spectroscopy).

In summary, we have prepared fluoroiodane **8** by three different methods using either TREAT-HF or TBAF as the source of the fluoride ion. Preliminary reactivity studies have revealed that it can be used to fluorinate 1,3-diketones and 1,3-ketoesters in good isolated yields and we are currently investigating further applications of **8** as an electrophilic fluorinating reagent with a range of different organic substrates.

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