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PhIO/$Et_3N \cdot 3HF$-Mediated Formation of Fluorinated 2*H*-Azirines via Domino Fluorination/Azirination Reaction of Enamines

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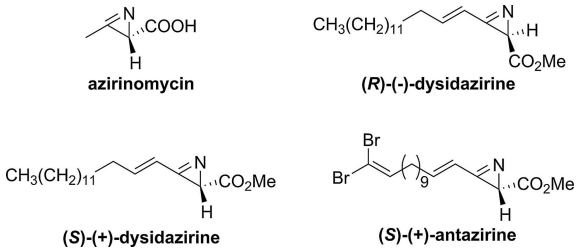
Abstract: A variety of enamine carboxylic esters and enaminones were converted to the biologically interesting fluorinated 2*H*-azirines through reactions with $PhIF_2$ generated in situ by PhIO and $Et_3N \cdot 3HF$ in 1,2-dichroloethane, which features the hypervalent iodine reagents-mediated introduction of fluorine atom and formation of the 2*H*-azirine skeleton under metal-free conditions. The domino reaction is postulated to proceed via a $PhIF_2$-mediated oxidative fluorination and a subsequent azirination of the fluorinated enamine intermediates.

Keywords: enamine; difluoroiodoarene generated *in situ*; domino reaction; fluorination; azirination

Organofluorine compounds are extremely scarce in natural organohalides, as only five natural fluorinases have been discovered.[1] Fluorine substitution in organic compounds enables many valuable properties, which are applicable to pharmaceuticals, agrochemicals, and materials bearing an outstanding property.[2] It has also been well known that the introduction of fluorine atoms into pharmaceuticals can increase their metabolic stability, lipophilicity, and overall biological activity, and thus more than 150 commercially available pharmaceutical agents contain at least one fluorine atom.[3]

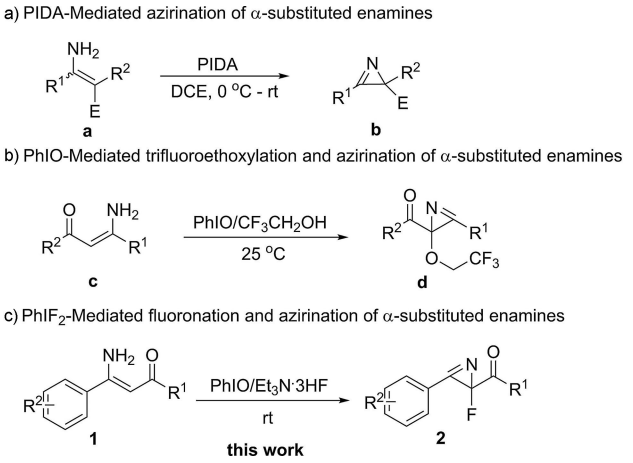
2*H*-azirines, the smallest heterocyclic compounds with an imino-type C=N bond incorporated into a three-membered ring, have been studied extensively for their presence in natural products.[4] Furthermore, 2*H*-azirines have been applied to the synthesis of various N-containing heterocycles via strain-driven ring expansion.[5] For example, azirinomycin was isolated from *Streptomyces aureus* by Miller and coworkers in 1970 as the first example of a natural product containing an azirine ring, which was found to exhibit a broad range of *in vitro* antibiotic activities against both gram-positive and gram-negative bacteria.[4] Other azirine-containing natural products include (*R*)-(−)- and (*S*)-(+)-dysidazirine and (*S*)-(+)-antazirine, isolated from *dysidea fragilis* (Scheme 1).

The predominant synthetic methods developed for the construction of this interesting class of compounds include the classic Neber rearrangement of proper imine substrates,[6] azirination of vinyl azides,[7] elimination or oxidation of aziridines,[8] ring contraction of isoxazoles,[9] oxazaphosphole derivatives,[10] and coupling reactions between nitriles and carbenes[11] or between nitrenes and acetylenes.[12] In 2009, our group reported that 2*H*-azirines could also be obtained via direct oxidative azirination of enamine compounds (Scheme 2a).[13] Although the above approach enables the synthesis of various 2*H*-azirine compounds bearing



Scheme 1. Representatives of naturally-occuring 2*H*-azirines.

different substitution, to the best of our knowledge, there have been scarce reports on the synthesis of F-containing 2*H*-azirines.[14] As both the 2*H*-azirine framework and F atom are important pharmacores in medicinal chemistry, it should be highly desirable to develop methodologies for synthesis of F-containing 2*H*-azirines.



Scheme 2. Formation of 2*H*-azirines via I(III)-mediated oxidative azirination of enamines.

Recently, the chemistry of hypervalent iodine compounds has accomplished remarkable progress,[15] and it has been proven that this class of "green" oxidant compounds have shown many synthetically useful characteristics, including mild oxidizing property, similar chemical behaviors to transition metals, and the environmentally benign feature. Among them, difluoroiodoarenes ($ArIF_2$), bearing two fluorine atoms, have been widely used in synthetic applications.[16] For example, difluoroiodoarenes have shown to be an efficient fluorinating reagent in the fluorination reactions of 1,3-dicarbonyl compounds and have been applied to the fluorination of β-ketoesters, β-ketoamides, and β-diketones.[17] Besides, difluoroiodoarenes have also been used to fluorinate various alkenes and diazocompounds, leading to the synthesis of various organofluorine compounds.[18] It has also been well documented that the combined use of PhIO and amine·HF complex could generate $PhIF_2$ *in situ* and the use of such oxidative system could be applied to fluorination reactions.[19]

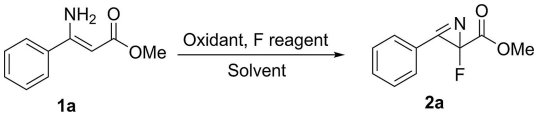
In 2013, we reported that enaminones and enamine carboxylic esters could be converted to the trifluoroethoxylated 2*H*-azirines via PhIO-mediated oxidative trifluoroethoxylation and the subsequent intramolecular azirination (Scheme 2b).[20] As this work allowed the introduction of trifluoromethyl moiety into 2*H*-azirine product to be achieved, we were also interested to realize the introduction of the biologically interesting F atom into the 2*H*-azirine products by using difluoroiodobenzene, generated *in situ* from the reaction of PhIO and $Et_3N \cdot 3HF$.

We began our investigation by choosing compound **1a**, a relatively easily prepared product from commercially available acetophenone and dimethyl carbonate in a straightforward two step process, as the model substrate.

We first attempted the reaction by subjecting enamino ester **1a** to various solvents in the presence of PhIO as oxidant and $Et_3N \cdot 3HF$ as fluorine reagent (Table 1). Solvents including CH_3CN, DMF and DMSO were studied, however, TLC analysis indicated that no desired product was formed in each case (Table 1, entries 1–3). To our delight, we found that the reaction in toluene furnished the desired product, albeit in a low yield of 35% (Table 1, entry 4). DCE was latter proved to be a more effective solvent as the reaction gave the desired product in 67% yield (Table 1, entry 6). The use of other fluorine reagents including amine·4HF, amine·5HF (amine means the mixture of Et_3N and pyridine) also afforded the desired products in moderate yield, respectively (Table 1, entries 8–9), while HF (40% aqueous solution) and Olah reagent did not provide any desired product under the conditions (Table 1, entries 7 and 10). Finally, screening of the dosage of $Et_3N \cdot 3HF$ showed that when the amount of $Et_3N \cdot 3HF$ was increased to 3.0 equiv. or decreased to 1.0 equiv. no improvement was obtained in each case (Table 1, entries 11–12). Subsequently, the other commonly used I(III) oxidants were also examined, while PIDA gave an even lower yield and PIFA was detected to be ineffective for the reaction (Table 1, entries 13–14). Combining all the testing results, the optimized conditions are finally determined to be PhIO (2.2 equiv.) as oxidant and $Et_3N \cdot 3HF$ (2.0 equiv.) as fluorine reagent in DCE (Table 1, entry 6).

Under the optimized reaction conditions, the scope and limitation of this cascade fluorination and azirination reaction was investigated (Table 2). A series of reactions of enamino esters containing electron-rich or electron-deficient aryl groups all reacted smoothly, providing the corresponding fluorinated 2*H*-azirine products in moderate to good yields (**2a–k**, 52–78%). Specifically, enamines bearing both electron-donating and electron-withdrawing groups in the phenyl ring afforded the desired products in good yields while substrates possessing a strong electron-donating methoxy group at *para* position could not afford the products (not shown). Meanwhile, enamines bearing substituents at *para* position gave the products in higher yields than the corresponding *meta*- and *ortho*-substituted enamines, except for the *meta* methoxy substituted substrates. An enamine bearing a naphthyl group also furnished the corresponding fluorinated product (**2l**) in good yield (81%).

Table 1. Optimization of reaction conditions.[a]

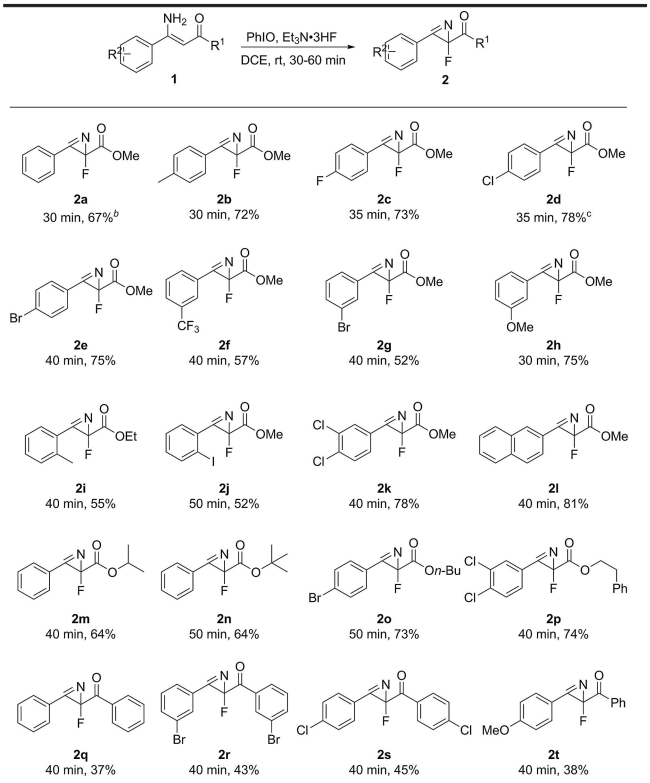


1a 2a

Entry	Oxidant	F reagent	Solvent	Yield (%)[a]
1	PhIO	$Et_3N·3HF$	CH_3CN	ND
2	PhIO	$Et_3N·3HF$	DMF	ND
3	PhIO	$Et_3N·3HF$	DMSO	ND
4	PhIO	$Et_3N·3HF$	toluene	35
5	PhIO	$Et_3N·3HF$	DCM	58
6	PhIO	$Et_3N·3HF$	DCE	67
7	PhIO	40% HF	DCE	ND
8	PhIO	amine·4HF[c]	DCE	51
9	PhIO	amine·5HF[d]	DCE	55
10	PhIO	Olah reagent	DCE	ND
11	PhIO	$Et_3N·3HF$[e]	DCE	55
12	PhIO	$Et_3N·3HF$[f]	DCE	43
13	PIDA	$Et_3N·3HF$	DCE	15
14	PIFA	$Et_3N·3HF$	DCE	ND

[a] Reaction conditions: all reactions were carried out by mixing the I(III) oxidant (2.2 mmol) and F reagent (2 mmol) in solvent (10 mL) at rt for 15 min and then **1a** was added (1 mmol in 1 mL of solvent) dropwise at rt unless otherwise stated.
[b] Isolated yield.
[c] Mixture of pyr·9HF 0.467 mmol (0.110 mL) and $Et_3N·3HF$ 2.39 mmol (0.390 mL).
[d] Mixture of pyr·9HF 0.870 mmol (0.205 mL) and $Et_3N·3HF$ 1.81 mmol (0.295 mL).
[e] 3.0 equiv. of $Et_3N·3HF$ was used.
[f] 1.0 equiv. of $Et_3N·3HF$ was used.

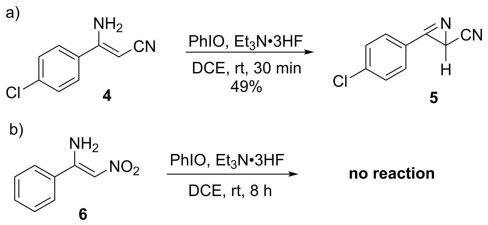
Table 2. Synthesis of 2-fluoro-2*H*-azirine derivatives through PhIO-mediated fluorination and azirination of Enamines.[a]



[a] all reactions were carried out by mixing the oxidant (2.2 mmol) and F reagent (2 mmol) in DCE (10 mL) at rt for 15 min and then adding **1a** (1 mmol in 1 mL of DCE) dropwise at rt unless otherwise stated.
[b] Isolated yields.
[c] The structure of **2d** was confirmed by X-ray crystallography.[21]

Next, a series of substrates bearing different ester moieties were tested. Enamino esters bearing *n*-butyl ester, *i*-propyl ester, *t*-butyl ester and phenylethyl ester also reacted smoothly to afford the corresponding fluorinated 2*H*-azirines in good yields (**2m–p**). Further experiments showed that this method worked moderately for a broad range of enaminones although the corresponding products were obtained in relatively lower yields (**2q–t**).

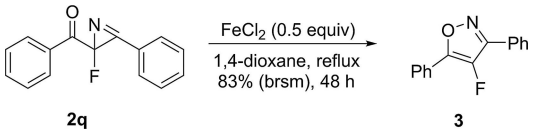
In order to investigate whether the carbonyl group in the substrate is indispensable for this reaction, we had the carbonyl group in substrate **1d** replaced with an electron-withdrawing cyano group and subjected the corresponding 3-amino-3-(4-chlorophenyl)acrylonitrile **4**[22] to the standard conditions. However, the reaction underwent solely the intramolecular azirination leading to the formation of 3-(4-chlorophenyl)-2*H*-azirine-2-carbonitrile **5** in 49% yield, without any detection of the fluorinated 2*H*-azirine product (Scheme 3a). Disappointingly, when enamine substrate bearing a strong electron-withdrawing nitro group **6**[23] was subjected to the optimal reaction conditions, no reaction occured and the starting material was recovered in 93% yield (Scheme 3b).



Scheme 3. Investigation the reaction scope by changing the carbonyl group with different electron-withdrawing groups.

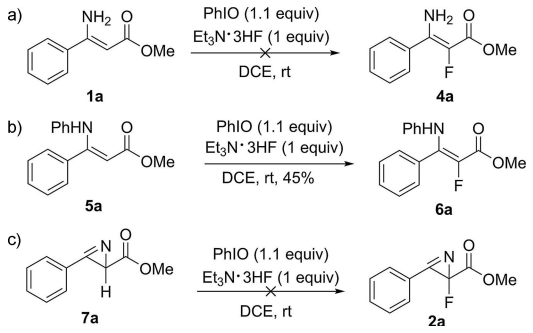
One important application of the obtained fluorinated-2*H*-azirine derivatives is their potential to be transformed into various isoxazole compounds via intramolecular ring expansion.[5,13,20] For example, upon treatment **2q** with $FeCl_2$ in refluxing 1,4-dioxane at 101 °C, fluorinated 2*H*-azirine **2q** could be effi-

ciently turned into the corresponding isoxazole **3** in good yield through an intramolecular rearrangement reaction (Scheme 4).



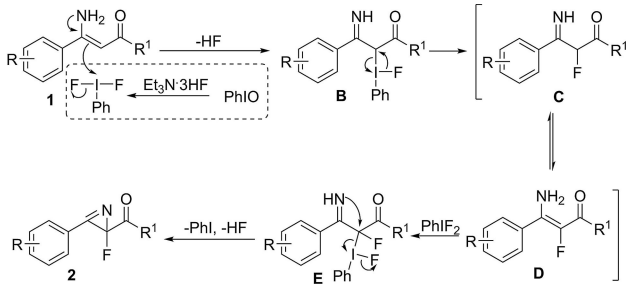
Scheme 4. Conversion of fluoronated 2*H*-azirine **2q** to isoxazole **3** via $FeCl_2$-mediated intramolecular ring expansion.

In order to gain insights into the reaction mechanism, we tried to isolate and confirm the structure of the proposed enamine intermediate. When the amount of PhIO was decreased to 1.1 equiv., the reaction of substrate **1a** did not afford any isolable α-fluoro enamine carboxylic ester intermediate **4a** (Scheme 5a). This result may indicate that the α-fluoro enamine intermediate may not be stable under the reaction conditions.[24] Fortunately, when the phenyl-protected enamine carboxylic ester **5a**[25] was used, the corresponding α-fluoro enamine carboxylic ester intermediate **6a** could be obtained in 45% yield by using PhIO (1.1 equiv.) and $Et_3N{\cdot}3HF$ (1.0 equiv.) (Scheme 5b). Furthermore, when α-hydrogen 2*H*-azirine **7a** prepared by a known procedure[26] was subjected to the standard conditions, no α-fluorinated 2*H*-azirine **2a** could be obtained (Scheme 5c). This result obviously ruled out the alternative mechanistic pathway in which the azirination occurs prior to the fluorination.



Scheme 5. Control experiments to probe on the reaction mechanism.

Based on the results of the above control experiments as well as the previous reports,[19b,20] we postulated a plausible mechanistic pathways for this PhIO/$Et_3N{\cdot}3HF$-mediated tandem oxidation reaction, described in Scheme 6. Initially, the reaction between PhIO and $Et_3N{\cdot}3HF$ gave $PhIF_2$ species, which reacts with the enamine substrate **1** to give the α-iodo imine **B**. The reductive removal of PhI from **B** affords fluorinated imine **C**, which tautomerizes into its enamine isomer **D**. Further reaction of **D** with the second molecule of $PhIF_2$ provides intermediate **E**, which undergoes intramolecular azirination to give the title compound **2**.[27]



Scheme 6. Proposed mechanistic pathway.

In conclusion, we have developed an approach to the construction of the fluorinated 2*H*-azirines through the reaction between the α-unsubstituted enamines and $PhIF_2$ which was generated *in situ* from PhIO and $Et_3N{\cdot}HF$ in DCE. The process features a domino reaction of a metal-free intermolecular oxidative C–F bond formation and a subsequent intramolecular oxidative azirination. The significance of the method is tied together with the unique features of the products formed, in that they possess not only the biologically important 2*H*-azirine skeleton but also the biologically interesting fluorine atom.

Acknowledgments

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[21] CCDC 1815122 (**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Formula: $C_{10}H_7C_{l1}$ $F_1N_1O_2$, unit cell parameters: a = 4.1467(12) b = 10.253(4) c = 12.251(4) P-1.

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[27] It can not be ruled out that intermediate E also undergoes reductive elimination to give a α,α-difluorinated imine intermediate, which undergoes intramolecular S_N2 reaction to give the fluorinated 2*H*-azirine product **2**.

COMMUNICATIONS

PhIO/$Et_3N \cdot 3HF$-Mediated Formation of Fluorinated 2*H*-Azirines via Domino Fluorination/Azirination Reaction of Enamines

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