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Formation of Functionalized 2*H*-Azirines through PhIO-Mediated Trifluoroethoxylation and Azirination of Enamines

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ABSTRACT

A variety of enaminones and enamine carboxylic esters were converted to trifluoroethoxylated 2*H*-azirines through reactions with PhIO in trifluoroethanol (TFE). The cascade reaction is postulated to proceed via a PhIO-mediated oxidative trifluoroethoxylation and a subsequent azirination of the α-trifluoroethoxylated enamine intermediates.

2*H*-Azirines, the smallest unsaturated nitrogen heterocycles,[1] represent a highly valuable class of compounds found in several natural products. For example, azirinomycin,[2] isolated from *Streptomyces aureus*, was found to exhibit a broad range of antibiotic activities *in vitro* against both gram-positive and gram-negative bacteria.[3] Other azirine-containing natural products include (*R*)-(−)- and (*S*)-(+)-dysidazirine and (*S*)-(+)-antazirine, isolated from *dysidea fragilis*.[4]

In addition, the characteristic high ring strain of this particular functional group has rendered 2*H*-azirines widely applicable in the synthesis of substituted allenes, alkynes, heterocycles, and other important synthetic intermediates.[5] A survey of the literature reveals that the predominant strategies adopted 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

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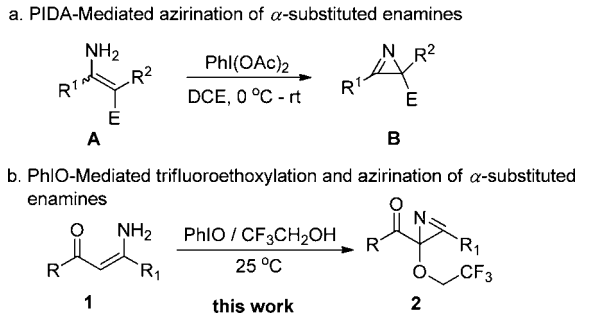
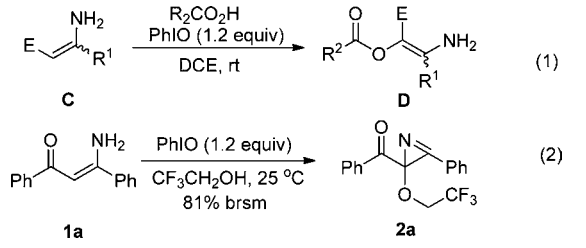
Scheme 1. Formation of 2*H*-Azirines via I(III)-Mediated Oxidative Azirination of Enamines



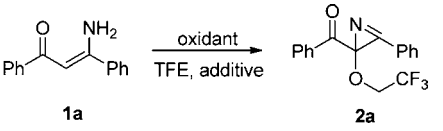
Scheme 2. Discovery of the Formation of Trifluoroethoxylated 2*H*-Azirines



between nitrenes and acetylenes.[12] In 2009, we reported that various enamine compounds **A** could be oxidized by a hypervalent iodine reagent, i.e., phenyliodine(III) diacetate, into a series of 2-functionalized 2*H*-azirine derivatives **B** via direct intramolecular azirination (Scheme 1a).[13] This method is in general well suitable for the synthesis of α-substituted enamine compounds. In this communication, we report a similar type of reactions where a series of α-unsubstituted enamine compounds **1** are directly converted to trifluoroethoxylated 2*H*-azirines **2** by reacting with PhIO in trifluoroethanol (TFE) as solvent, a process involving an intermolecular oxidative C−O bond formation followed by a subsequent intramolecular oxidative azirination (Scheme 1b).

Quite recently, we reported that the α-unsubstituted enaminone compounds **C** could undergo direct *β*-acyloxylation

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	temp (°C)	time (min)	additive	yield[b]
1	PhIO	25	30	none	60%[c]
2	PhIO	0	60	none	50%[c]
3	**PhIO**	**25**	**30**	**none**	**77%**
4	PhIO	25	30	none	30%[d]
5	PhIO	25	45	NaOAc[e]	66%
6	PhIO	25	30	$BF_3 \cdot Et_2O$[e]	ND
7	PIDA	25	20	none	35%
8	PIFA	25	10	none	ND
9	IBX	25	180	none	NR
10	DMP	25	180	none	NR

[a] Reaction conditions: all reactions were carried out by mixing the oxidant (2.1 mmol) in TFE (5 mL) at rt for 15 min and then adding **1a** (1 mmol in 5 mL of TFE) dropwise at rt unless otherwise stated. [b] Isolated yields. [c] PhIO (2.1 mmol) was added to a solution of **1a** in TFE (10 mL) in one portion. [d] The reaction was conducted in the presence of 2 equiv of TFE in DCM (5 mL). [e] 2 equiv of additive was used.

by reacting with carboxylic acids in the presence of iodosobenzene (PhIO) and give *β*-acyloxy enamines **D** (Scheme 2, eq 1).[14] Inspired by the results of this work, we set out to see if a parallel reaction would take place between enamine **1a** and an alcohol compound which could result in the C(sp^2)−O bond formation via the expected intermolecular oxidative coupling reaction. To our delight, the test result was positive such that the reaction of enamine **1a** (1 mmol) with trifluoroethanol as the solvent provided *β*-trifluoroethoxylated 2*H*-azirine compound **2a**, in a good yield of 81% (brsm) (Scheme 2, eq 2). It is obvious that the reaction sequence involves not only the C(sp^2)−O bond formation but also a subsequent intramolecular azirination process. Undoubtedly, this new finding led us to the establishing of a new protocol for accessing functionalized 2*H*-azirines, namely, from α-unsubstituted enaminones through a cascade reaction involving oxidative trifluoroethoxylation ensued by the intramolecular azirination of the generated α-trifluoroethoxylated enamine intermediate.

Enaminone **1a** was used as the model substrate in further screening tests in search of the optimal conditions for this newly discovered tandem reaction. Results show that the addition of PhIO to a solution of enaminone **1a** in TFE (0.1 M) in a one-portion manner at room temperature afforded **2a** in 60% yield, while the same reaction conducted at 0 °C became relatively sluggish and the yield of **2a** was decreased by over 15%. On the other hand, a satisfactory yield of 77% was obtained when enaminone **1a** was added to a solution of PhIO in TFE (0.1 M), premixed and

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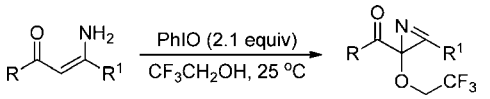
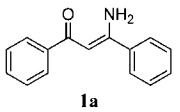
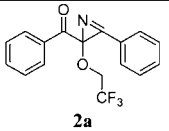
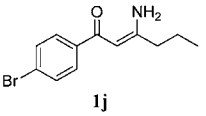
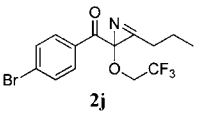
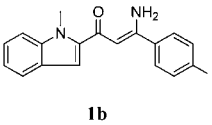
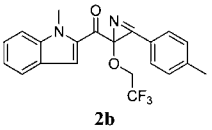
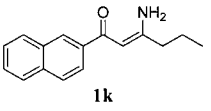
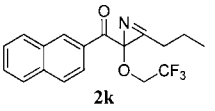
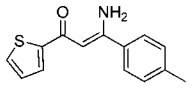
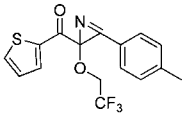
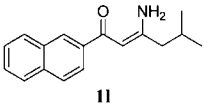
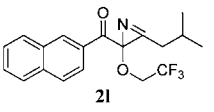
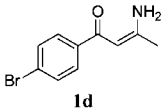
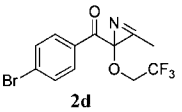
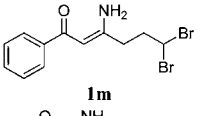
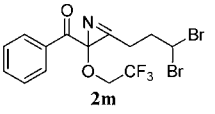
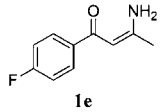
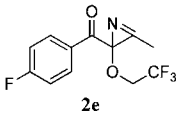
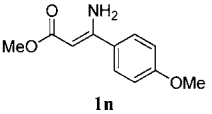
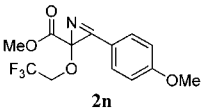
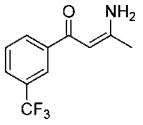
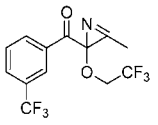
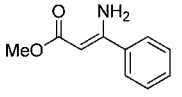
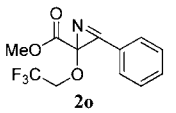
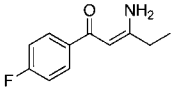
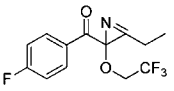
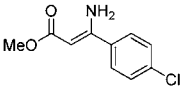
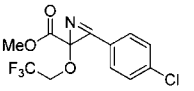
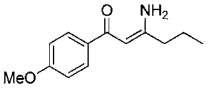
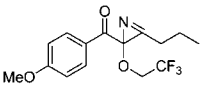
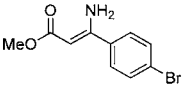
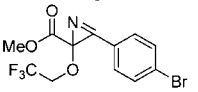
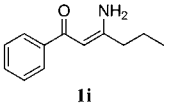
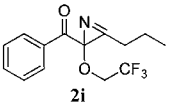
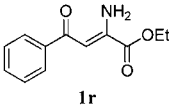
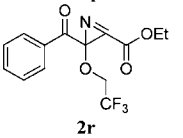
Table 2. Synthesis of 2-Trifluoroethoxyl-2*H*-azirine Derivatives through PhIO-Mediated Trifluoroethoxylation and Azirination of Enamines[a]



1 2

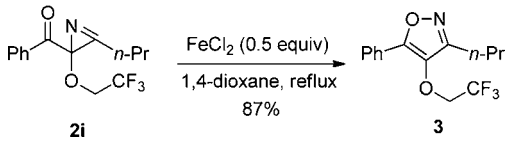
entry	substrate **1**	product **2**	yield (%)[b]	Entry	substrate **1**	product **2**	yield(%)[b]
1	 **1a**	 **2a**	77	10	 **1j**	 **2j**	71
2	 **1b**	 **2b**	40	11	 **1k**	 **2k**	80
3[c]	 **1c**	 **2c**	66	12	 **1l**	 **2l**	63
4	 **1d**	 **2d**	71	13	 **1m**	 **2m**	85
5	 **1e**	 **2e**	53	14	 **1n**	 **2n**	45
6	 **1f**	 **2f**	46	15	 **1o**	 **2o**	77
7	 **1g**	 **2g**	66	16	 **1p**	 **2p**	65
8	 **1h**	 **2h**	85	17	 **1q**	 **2q**	50
9	 **1i**	 **2i**	87	18	 **1r**	 **2r**	65

[a] General conditions: PhIO (2.1 mmol) in TFE (5 mL) was stirred at rt for 15 min, and then substrate **1** (1 mmol in 5 mL of TFE) was added dropwise. [b] Isolated yields. [c] The structure of **2c** was determined by X-ray crystallography.

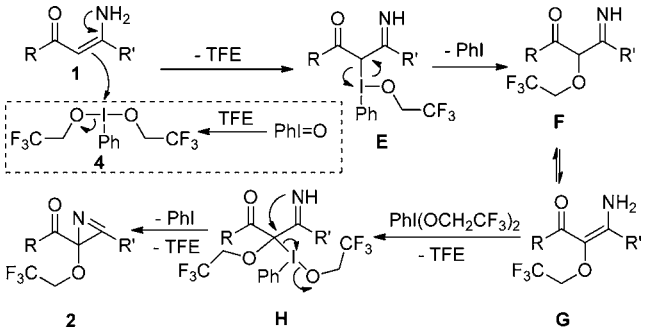
stirred at room temperature for 15 min. Carrying out the same reaction by applying 2 equiv of TFE and using DCM as the solvent only afforded the desired product in 30% yield (Table 1, entry 4). Attempts to further increase the yield by adding additives, such as NaOAc and $BF_3 \cdot Et_2O$, were found unsuccessful in either case, specifically, with a decreased yield of 66% for the former, and no desired product in the latter case (Table 1, entries 5–6). Other hypervalent iodine reagents including PIDA, PIFA, IBX, and DMP were also tested for the conversion. The results indicated that a 35% yield in the case of PIDA (Table 1, entry 7), no desired product of PIFA (Table 1, entry 8), and no reaction at all of either IBX or DMP (Table 1, entries 9–10).

Under the optimal conditions, various enamines were prepared and examined to probe the scope and generality of this method. For the enaminone substrates with both R and R^1 being aryl groups, the reaction proceeded smoothly to afford the corresponding 2-trifluoroethoxyl-2*H*-azirine products (Table 2, entries 1–3). The method was shown to be also well applicable to the enaminone substrates with R

Scheme 3. Conversion of 2-Trifluoroethoxyl-2*H*-azirine **2i** to Isoxazole **3** via $FeCl_2$-Mediated Intramolecular Ring Expansion



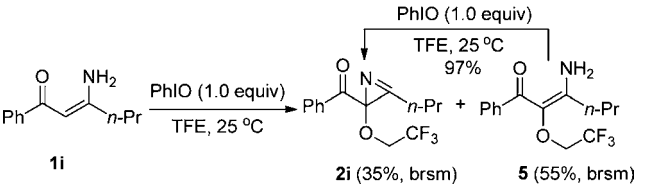
Scheme 4. Proposed Mechanistic Pathway



being an aryl group and R^1 being an alkyl group, including a relatively long-chained propyl group and a bulky isobutyl group (Table 2, entries 4−12). Additional experiments show that this method is applicable to a broad range of enaminones containing a variety of R or R^1 groups, yields are between 45 and 85%, R can be an ester group (Table 2, entries 14−17), and R^1 can be a terminally dibromo substituted alkyl group (Table 2, entry 13) or even an α-ethoxycarbonyl group (Table 2, entry 18).

One important application of the obtained 2-trifluoroethoxyl-2*H*-azirine derivatives **2** is their potential to be transformed into various isoxazole compounds via intramolecular ring expansion. For example, upon treatment with $FeCl_2$ in refluxing 1,4-dioxane at 101 °C, 2-trifluoroethoxyl-2*H*-azirine **2i** could be efficiently turned into the corresponding isoxazole **3** in excellent yields through an intramolecular rearrangement (Scheme 3).[15]

Scheme 5. Further Probe on the Reaction Mechanism



A plausible mechanistic pathway for the above trifluoroethoxylation and azirination process is described in Scheme 4. Initially, the reaction between PhIO and TFE undergoes condensation to give the $PhI(OCH_2CF_3)_2$ intermediate **4**,[16] which reacts with the enamine substrate **1** to give the α-iodo imine **E**. The reductive removal of PhI from **E** affords α-triflouroethoxy imine **F**, which tautomerizes into its enamine isomer **G**. Further reaction with the second molecule of $PhI(OCH_2CF_3)_2$ provides intermediate **H**, which undergoes intramolecular azirination to give the title compound **2**.

In order to gain further insights into the reaction mechanism, we undertook the task of isolating and verifying the structure of the proposed enamine intermediate **G**. When the amount of PhIO was decreased to 1.0 equiv, the reaction regarding substrate **1i** afforded a 55% yield of the α-triflouroethoxy enaminone **5**, in addition to the cyclized 2*H*-azirine **2i**. After separating the two compounds, exposure of enaminone **5** to 1.0 equiv of PhIO in TFE at rt led to the formation of the azirinated product in nearly quantitative yield (Scheme 5). This result indisputably supports the reaction sequence proposed above.

In conclusion, we have reported a novel method for the synthesis of the trifluoroethoxylated 2*H*-azirines through reactions between the α-unsubstituted enamines and PhIO in trifluoroethanol (TFE). The process features a cascade reaction of a metal-free intermolecular oxidative C−O 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[3,17] but also the biologically interesting trifluoroethoxyl moiety.[18] Further study on the reaction mechanism is in progress in our lab.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds and X-ray structural data of **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(16) In our control experiment, $PhI(OCH_2CF_3)_2$ was isolated and characterized from the reaction of PhIO and TFE (see Supporting Information for details). For the previous proposed in situ formation of $PhI(OCH_2CF_3)_2$, see: (a) Kajiyama, D.; Inoue, K.; Ishikawa, Y.; Nishiyama, S. *Tetrahedron* **2010**, *66*, 9779–9784. (b) Kidwai, M.; Sapra, P. *Org. Prep. Proced. Int*. **2001**, *33*, 381–386. (c) Bell, R.; Morgan, K. J. *J. Chem. Soc*. **1960**, 1209–1214. (d) Baker, G. P.; Mann, F. G.; Sheppard, M. N.; Tetlow, A. J. *J. Chem. Soc*. **1965**, 3721–3728. (f) Leffler, J. E.; Ward, D. C.; Burduroglu, A. *J. Am. Chem. Soc*. **1972**, *94*, 5339–5341.

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