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Achieving Regio- and Stereo-Control in the Fluorination of Aziridines under Acidic Conditions

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Abstract

We developed an efficient fluorination protocol that converts easily accessible aziridines into β -fluoroamines, which are important motifs in biologically active molecules. In contrast with traditional fluorination approaches, DMPU-HF has shown both higher reactivity and regioselectivity and good functional group tolerance; thus, a wide scope of β -fluoroamines can now be accessed conveniently. The stereochemical behavior of ring opening depends on the substitution pattern of the aziridine substrates.

Graphical Abstract

DMPU-HF demonstrates good reactivity and regioselectivity in conversion of aziridines into biologically important β -fluoroamines. The stereochemistry of aziridine-opening was found to be depend greatly on substitution pattern.

The ring-opening of small ring heterocycles (epoxides and aziridines) by a nucleophile is an important method for the preparation of vicinal di-functionalized compounds.¹ Although this reaction appears in any beginners' course in organic chemistry, the factors that control the selectivity of the ring opening, especially under acidic conditions, are ambiguous.^{2–4} Although the mechanism for most acid-mediated nucleophilic substitutions approximates that of an S_N1 pathway, in aziridines, for example, a free carbocation (**A** in Scheme 1) is

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hardly expected to form because the nearby amino group will strongly coordinate to a β -carbocation; therefore, the nucleophilic displacement will not follow the S_N1 pathway of traditional acid catalyzed nucleophilic substitutions. Thus, the acid-mediated ring opening of epoxides or aziridines probably traverses a path somewhere between a S_N2 and S_N1 mechanisms, leading to products with lack of regio- and stereo-control (Scheme 1b).¹ This may be one reason why, compared to the well-defined base-mediated aziridine opening, the acid mediated ring-opening of aziridines is under-utilized in synthesis. Additionally, because the absolute stereochemistry is not easy to establish unequivocally, studies on the absolute stereochemistry of the products derived from the acid-catalyzed ring-opening of epoxides or aziridines are sketchy at best.^{1, 5–8}

Nowhere is the lack of selectivity more consequential than in the ring opening fluorination of aziridines by hydrogen fluoride given that β -fluoroamines (Scheme 1b) are important building blocks and motifs in medicinal chemistry;⁹ therefore, efficient synthetic approaches toward β -fluoroamines are highly sought after. Among these methods, the nucleophilic ring-opening of aziridines (Scheme 1b) by HF is ideal because of the low cost of reagents, mild reaction conditions, and general accessibility of substrates,^{10, 11} but the production of regioisomers and stereoisomers makes this approach problematic (Scheme 1b).^{6, 12–15} Early work by Wade¹⁶ and Laurent¹⁷ demonstrated the use of anhydrous hydrogen fluoride as well as HF-amine reagents^{18–22} to open the aziridine ring (Scheme 1b). However, in addition to the inconvenience related to use of hazardous anhydrous HF, aziridine ring-opening suffers from low yields, production of isomeric mixtures, and side products. Furthermore, bicyclic aziridines usually give rise to the formation of a mixture of diastereomers. Coutts and co-workers also reported the ring-opening of *N*-tosylaziridines employing pyridine-HF-KF system.²³ However, their yields were not improved significantly, and the scope of reactive substrates was limited. Recently, Doyle and co-workers reported opening aziridines with hydrogen fluoride generated *in situ* from acyl fluoride, but their method only worked with symmetrical *cis*-2,3-disubstituted aziridines, which also needed expensive hexafluoroisopropanol as reaction medium.^{24, 25}

Recently, we developed a new HF-based reagent—DMPU-HF (DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidin-9-one, now commercially available²⁶), and demonstrated that it was an efficient nucleophilic fluorination reagent in the gold-catalyzed hydrofluorination of alkynes²⁷ and fluoro-Prins cyclization reactions.²⁸ We chose the hydrofluorination of 2-methyl *N*-tosylaziridine **1a** as our model reaction (Table 1). We found that, by treating **1a** with 65% HF-DMPU in DCE under room temperature, **1a** was regioselectively converted into the desired 2-fluoropropyl-*N*-tosylamine **2a** in high yield and with the tosyl protecting group intact (Table 1, entry 1). The reaction did not take place in tetrahydrofuran (entry 2), and the addition of scandium triflate significantly reduced the yield (entry 3). No substantial changes were observed when the amount of DMPU-HF was doubled (Table 1, entry 4). Shortened reaction times caused an incomplete conversion, but the material balance remained good (Table 1, entry 5). Elevating the reaction temperature did not reduce the yield (Table 1, entry 6). In comparison, Olah's reagent (70% HF in pyridine) provided an incomplete conversion within the same time frame, and the material

balance and regioselectivity were not as good (Table 1, entry 7). Another common HF-based reagent, triethylamine trihydrofluoride, gave no reaction at all (Table 1, entry 8).

The effectiveness of this method was confirmed in the ring opening of various *N*-tosyl aziridines (Scheme 2). Hydrofluorination of the mono alkyl-, aryl-, and benzyl-substituted *N*-tosylaziridines **1a–1g** occurred at the most substituted carbon and delivered primary alkyl amines **2a–2g** in good yields (Scheme 2). 2-Ethyl-3-methyl-1-tosylaziridine **1h** yielded an inseparable mixture of regioisomers and diastereomers under these conditions (Table 1, 2h). *gem*-Disubstituted aziridine **1i** decomposed significantly under these conditions, without providing isolable amount of product **2i**. Bicyclic aziridine **1j** was converted into *trans*- β -fluoroamines **2j** in good yield and diastereoselectivity.²⁹ The reaction of β -hydroxyl bicyclic aziridine **1k** took place at the less hindered side leaving the hydroxyl group untouched; X-ray crystallography confirmed the stereo configuration of **2k**.³⁰

Trisubstituted aziridines **1l** and **1m** were fluorinated also at the more substituted carbon in moderate-to-good efficiency (Table 1, 2l and 2m). Bicyclosubstituted aziridine **1n** yielded the *trans*-substituted product **2n** with the same regioselectivity.

Next, we tested aziridines with various *N*-protecting groups (Scheme 3). Aziridines protected by Cbz (**1o**), Fmoc (**1p**) and benzoyl (**1q**) groups were well tolerated under the reaction conditions, affording the corresponding β -fluoroamines **2o**, **2p** and **2q** in excellent yields and regioselectivity under the standard reaction conditions (Scheme 3). It should be noted that in reaction of **1q**, the re-cyclized Heine product³¹ that was the major side product in Laurent's report¹⁷, was not observed at all under our reaction conditions. The benzyl-protected aziridine **1r** was only partially converted into **2r**, even after an extended reaction time. We think that even though the more basic NBn in **1r** can be easily protonated, the protonated NBn is not a good leaving group, so **1r** is less reactive.

An idealized S_N2 pathway would foster the α -attack (less hindered position) product (Scheme 4a). In our case, fluorination at the more substituted internal carbon renders a carbocation-like intermediate, which follows an S_N1-type regioselectivity accompanied with inversion of stereochemical configuration, even though a free carbocation does not actually form (**TS-2**, Scheme 4b). Our proposed mechanism can also explain the poor results obtained with pyridine-HF and Et₃N-HF (Table 1). In the case of Et₃N-HF, the acidity of the system was low due to the high basicity of Et₃N and only an S_N2 like pathway was allowed, but, due to the poor nucleophilicity of HF, no conversion took place (Table 1, entry 7). On the other hand, pyridine-HF has a higher acidity than Et₃N-HF but it is less acidic than DMPU-HF, therefore nucleophilic substitution with pyridine-HF will exhibit a higher tendency towards a classic S_N2 attack (Scheme 4a) with diminished regioselectivity (Table 1, entry 8). Of course, steric factors may also influence the regioselectivity of the reaction but because HF is a small nucleophile, the influence of steric factors is negligible.

We also studied the stereochemical outcome of aziridine opening by DMPU-HF and observed a substrate-dependent stereochemical behavior. Reaction of bicyclic aziridines yielded stereoconfigurational inversion products (see Scheme 5a and also Scheme 2).

For example, alkyl aziridine (*R*)-**1a** furnished the configurational inversion product (*S*)-**2a** (Scheme 5a). This result can be rationalized by a quasi-S_N2 concerted pathway (see **TS-2** in Scheme 4). In contrast, phenyl-substituted (*S*)-**1c** gave a completely racemized product (Scheme 5b). This result could be rationalized by a quasi-S_N1 step-wise pathway due to fact that the corresponding carbocation intermediate **B** can be strongly stabilized by the phenyl group. More surprisingly, (*S*)-**1d**, under standard conditions, yielded (*S*)-**2d** with almost perfect retention of stereoconfiguration (Scheme 5c). The stereochemistry of both starting material and product was confirmed by X-ray crystallography (Scheme 5c). Neighboring group participation by the phenyl group in (*S*)-**1d** could help forming a highly delocalized phenonium ion-like transition structure, hence preventing racemization from taking place (**TS-3**, Scheme 5). Fluoride was delivered internally from the same enantiomeric face of nitrogen assisted by an N-H hydrogen bond, which resulted in retention of stereoconfiguration (a quasi-S_Ni mechanism). This pathway was supported by DFT analysis and further rationalized by the fact that HF itself is a very strong hydrogen-bond donor (underscored by the relative acidity of DMPU-HF).^{31–34} These results indicated that the stereochemical outcome depended on the relative stability of the carbocation-like intermediate (e.g. **B** in Scheme 5). With only alkyl groups attached, there is no real carbocation-like intermediate, so the reaction mechanism is close to an S_N2 concerted pathway with inversion of stereoconfiguration (Scheme 5a). With a strong carbocation stabilizing group (phenyl), a semi-free carbocation intermediate is formed, so the mechanism is close to a step-wise S_N1 mechanism (Scheme 5b). And the reaction of (*S*)-**1d** lies between the two extremes (Scheme 5c).

In sum, DMPU-HF is a very effective reagent for the ring-opening hydrofluorination of aziridines, giving products with both high regioselectivity and high stereoselectivity. The scope of the β-fluoroamines produced in this fashion includes cyclic and acyclic structures with diverse sets of functional groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
 Synthetic routes toward β -fluoroamines.

Scheme 2.

Scope of *N*-tosylaziridines. Only major regioisomers are presented. Numbers are isolated yields. Numbers in parenthesis are regioisomeric ratio determined by ^{19}F NMR. Reaction conditions: aziridine **1** (0.5 mmol), 65% HF-DMPU (98 μL , 3.6 mmol HF), DCE (1 mL), room temperature for 18 h.

Scheme 3.

Scope of *N*-protective groups. Only major regioisomers are presented. Reaction conditions: aziridine **1** (0.5 mmol), 65% HF-DMPU (98 μ L, 3.6 mmol HF), DCE (1 mL), room temperature for 18 h, all yields are isolated yields. ^[a] Numbers in parenthesis are regioisomeric ratio determined by ¹⁹F NMR.

Scheme 4.
 Regioselectivity in ring-opening of aziridine by DMPU-HF.

Scheme 5.

Substrate-dependent stereochemical behavior of hydrofluorination of aziridine. **TS-3** was computed at the M062X/aug-cc-pVDZ level of theory.

Table 1Development of reaction conditions.^a

Entry	Variation on standard conditions	Conversion(%)	Yield(%) ^b	Ratio of 2a:3a ^c
1	None	> 99	93 (87 ^d)	>30:1
2	In THF	0	N/A	N/A
3	Add 10 mol% of Sc(OTf) ₃	97	69	>30:1
4	15 equiv of HF	99	86	>30:1
5	9 h	54	43	>30:1
6	55 °C	> 99 ^e	88	>30:1
7	70% HF-Pyridine	85	78	7:1
8	3HF·NEt ₃	0	N/A	N/A

^aStandard reaction conditions: **1** (0.2 mmol), HF (7.5 equiv, 1.5 mmol) in 0.5 mL of dichloroethane (DCE) at room temperature in a sealed polypropylene vial over for 18 h.

^bDetermined by ¹⁹F NMR using benzotrifluoride as an internal standard.

^cDetermined by ¹⁹F NMR.

^dIsolated yield.

^eReaction time was shortened to 12 h.