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Synthesis of 3-Fluoroazetidines

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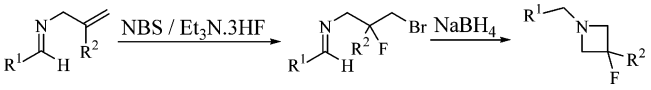

N-(Alkylidene or 1-arylmethylidene)-2-propenylamines were regiospecifically functionalized to novel *N*-(alkylidene or 1-arylmethylidene)-3-bromo-2-fluoropropylamines, which were proven to be excellent precursors for 3-fluoroazetidines.

Introduction

The selective fluorination of biologically important compounds often results in a profound modification of their biological activity.[1−3] These distinctive properties of specifically fluorinated compounds have significantly contributed to the growing interest in the field of organofluorine chemistry in the past decade. Although β-fluorinated amines have been the subject of considerable attention because of their interesting pharmaceutical properties,[1−3] their small ring heterocyclic analogues have barely been described in the literature. 3-Monofluorinated azetidines are very rare compounds, the chemistry of which is virtually unknown, apart from some isolated transformations. Perfluoroazetidines have been prepared by thermolysis of the corresponding perfluoro-1,2-oxazines or by photolysis of perfluorinated triazines,[4−7] while 3-fluoroazetidine *N*-oxides have been involved in the synthesis of isoxazolidines via thermal ring enlargement.[8] Photofluorination of azetidines with fluoroxytrifluoromethane has been used in the preparation of L-*cis*-3-fluoroazetidine-2-carboxylic acid.[9−11] 3-Fluoroazetidines have been synthesized via a ring opening of 1-azabicyclo-[1.1.0]butanes with Olah's reagent (pyridine.10 HF) or liquid hydrogen fluoride.[12] Although good yields were obtained for the ring opening, the drawback of this synthesis is the use of a multistep preparation of the labile starting material, that is, 1-azabicyclo[1.1.0]butanes. A very peculiar example of a reduction of a 3-fluorinated β-lactam with diisobutyl aluminum hydride toward the corresponding 3-fluoro-2-azetidinol is also known.[13] At present, a rapidly growing interest in 3-fluorinated azetidines exists, as these compounds apparently possess interesting biological activities. The inhibition of specific enzymes such as dipeptidyl peptidase IV constitutes a promising feature of fluorinated azetidines which can be applied in the treatment of type 2 diabetes.[14−18] In addition, the recent patents concerning fluorinated azetidines emphasize the possibilities of these compounds as substituents to modulate the activity of different active compounds.[19−22] In the latter publications, 3-fluorinated azetidines are mainly synthesized by treatment of 3-azetidinols or 3-azetidinones with diethylaminosulfur trifluoride (DAST). Until now, this synthetic method is the only procedure to obtain 3-fluorinated azetidines. However, no examples of the synthesis of 3- or 4-substituted 3-fluoroazetidines via this method are known. As a result, new syntheses toward the highly attractive 3-fluoroazetidines are of considerable interest for organic, agrochemical, and medicinal chemists.

Results and Discussion

In the present article, we report an efficient and facile three-step procedure for the synthesis of 3-fluoroazetidines **4** and **11** using *N*-(alkylidene or 1-arylmethylidene)-γ-bromo-β-fluoroamines **3**. Imines bearing reactive halogens in the side chain have not been frequently used in organic synthesis because of the lability of this type of bifunctional compounds. However,

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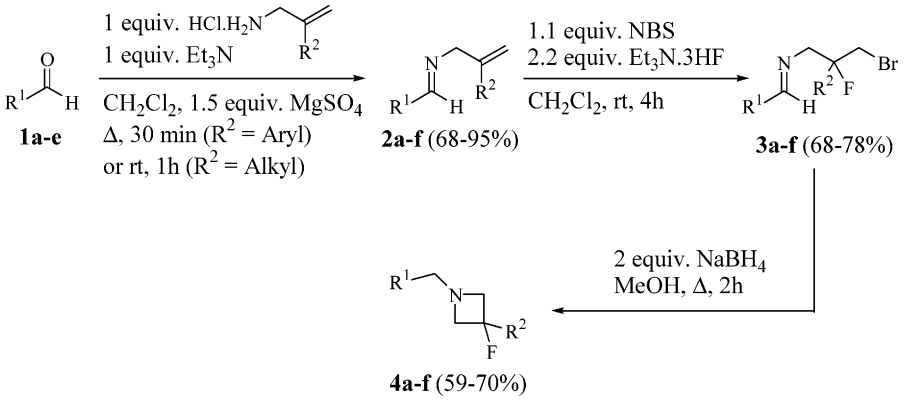
SCHEME 1. Synthesis of 3-Fluoroazetidines



SCHEME 2. Attempts of Bromofluorination Reactions

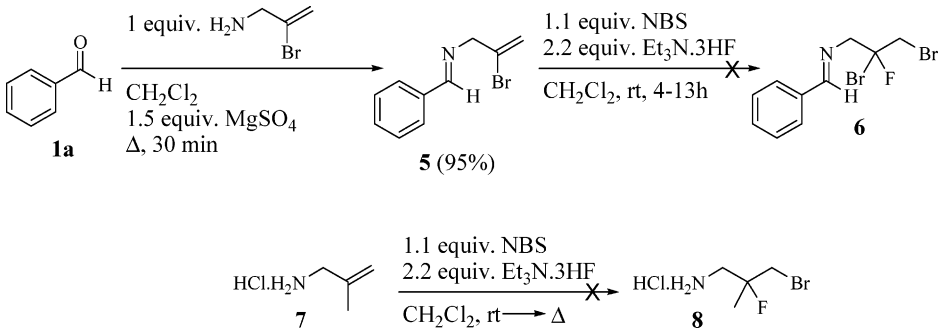


TABLE 1. Synthesis of *N*-(Alkylidene)- and *N*-(1-Arylmethylidene)-3-bromo-2-fluoropropylamines 3a−f and 3-Fluoroazetidines 4a−f

	R^1	R^2	yield of **3**	bp of **3** °C/mmHg	yield of **4**
a	C_6H_5	Me	76%	69−71/0.05	70%
b	4-MeC_6H_4	Me	78%		61%
c	4-MeOC_6H_4	Me	71%	73−75/0.05	65%
d	$CHEt_2$	Me	68%	51−55/0.03	61%
e	*t*-Bu	Me	73%		59%
f	C_6H_5	C_6H_5	77%		60%

former research demonstrated the synthetic potential of *N*-(ω-haloalkyl)imines in the synthesis of azaheterocycles.[23,24] Here we describe the first functionalization of olefinic imines into novel bromofluorinated imines **3**, which are easily converted to 3-fluoroazetidines **4**.

Imination of aromatic and aliphatic aldehydes **1a**−**e** with 2-substituted 2-propenylamines afforded the corresponding imines **2a**−**f**, which were subsequently regiospecifically bromofluorinated to *N*-(1-arylmethylidene)- or *N*-(alkylidene)-3-bromo-2-fluoropropylamines **3a**−**f** using triethylamine trihydrofluoride and *N*-bromosuccinimide in dichloromethane (Scheme 1, Table 1). This is the first report on the tolerance of an imino functionality to the bromination and fluorinating reagent, which has been shown previously to halogenate olefins.[25] Although all compounds **3a**−**f** were pure enough (>95%) to be used in further reactions, imines **3a** and **3c**,**d** could be distilled easily at high vacuum to remove the minor amounts of impurities. It should be noted that, based on ^{1}H NMR analysis, no α-bromination took place during bromofluorination of aldimine **2d**.

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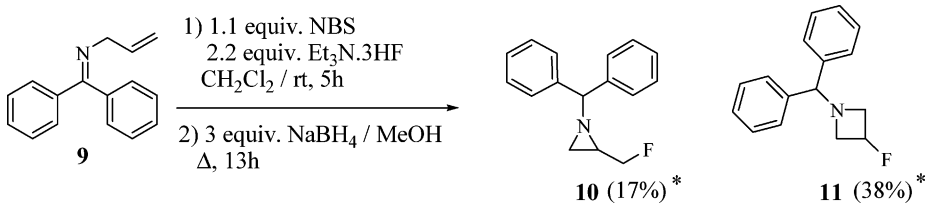
The methodology described above was also evaluated for the synthesis of interesting 3-bromo-3-fluoroazetidines (Scheme 2). However, the bromofluorination of *N*-(benzylidene)-2-bromo-2-propenylamine **5** proved unsuccessful and yielded mainly benzaldehyde owing to hydrolysis during the aqueous workup (Scheme 2). This lack of reactivity can be attributed to the low nucleophilicity of the vinyl bromide unit and the higher reactivity of the imino function toward *N*-bromination, the latter resulting in hydrolysis during aqueous workup. Different attempts to perform a functionalization of 2-methyl-2-propenylamine hydrochloride **7** did not give any constructive result, demonstrating the need to perform an imination of the amine **7**. In other words, the imino function is a suitable protective group for alkenylamines which undergo electrophilic addition reactions.

The reaction of the functionalized imines **3a**−**f** with sodium borohydride in methanol under reflux afforded the corresponding 3-fluoroazetidines **4a**−**f**, which were purified by flash chromatography (Table 1). No change in reactivity was observed when *N*-alkylidene- (**3d**,**e**) or *N*-(1-arylmethylidene)amines (**3a**−**c**,**f**) were used as substrates for the cyclization reaction toward azetidines **4**. As almost no side products were formed during the hydride induced cyclization, the moderate yields are due to the affinity of 3-fluoroazetidines **4** toward silica gel in the purification step, a classical problem in the purification of *N*-containing heterocycles (while the use of alumina did not result in the separation of the minor amounts of impurities from the azetidines **4**).

To investigate the regioselectivity of the bromofluorination, attempts were made to perform the functionalization of *N*-(benzylidene)allylamine. As the only reactivity observed was the decomposition of the starting compound because of prolonged reaction times, the suitability of the more stable

SCHEME 3. Regioselectivity of Bromofluorination of 9



* Isolated yield after column chromatography.

N-(diphenylmethylidene)allylamine **9** was evaluated (Scheme 3). Hydride induced cyclization of the reaction mixture, obtained by bromofluorination of ketimine **9**, led to the formation of 1-benzhydryl-2-(fluoromethyl)aziridine **10** and 1-benzhydryl-3-fluoroazetidine **11** in a 1:3 ratio, respectively, as determined by ^{1}H NMR. 2-(Fluoromethyl)aziridine **10** originates from the formation of *N*-(2-bromo-3-fluoropropyl)-*N*-(diphenylmethylidene)amine during the bromofluorination reaction of imine **9**, which proves the lack of regioselectivity of this reaction in this particular case. Upon chromatographic separation by column chromatography, 17% of the novel 1-(benzhydryl)-2-(fluoromethyl)aziridine **10** and 38% of 1-(benzhydryl)-3-fluoroazetidine **11** were isolated.

In conclusion, a new and efficient three-step synthesis of 3-fluoroazetidines was developed from aldehydes via hitherto unknown bromofluoroimines.

Experimental Section

General Procedure for the Bromofluorination of *N*-(Alkylidene- or 1-Arylmethylidene)-2-propenylamines 2a−f. At 0 °C, 4.4 mmol of triethylamine tris(hydrofluoride) and 2.2 mmol of *N*-bromosuccinimide were added to a solution of 2 mmol of *N*-(allyl)imine **2a**−**f** in dichloromethane under nitrogen atmosphere. After 4 h of stirring at room temperature, the solvent was evaporated, and the residue was washed three times with 10 mL of pentane. After evaporation of the solvent, *N*-(3-bromo-2-fluoropropyl)imines **3a**−**f** were obtained, sufficiently pure (>95%) for further use in the next step. Imines **3a**,**c**,**d** were distilled under vacuum.

***N*-Benzylidene-3-bromo-2-fluoro-2-methylpropylamine 3a.** Yield: 76%. Boiling point: 69−71 °C/0.05 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.51 (3H, d, J = 21.5 Hz), 3.59 (2H, d, J = 16.8 Hz), 3.70−3.88 (2H, m), 7.31−7.73 (5H, m), 8.18 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.1 (d, J = 22.0 Hz), 37.07 (d, J = 26.9 Hz), 65.83 (d, J = 25.6 Hz), 93.72 (d, J = 177.0 Hz), 127.9, 128.2, 130.6, 135.4, 163.1. IR (NaCl, cm^{-1}): 1649. MS (70 eV) *m*/*z* (%): 257/9(M^+, 3), 178(4), 158(1), 149(3), 118(100), 117(12), 104(5), 91(70), 90(11), 89(11), 77(9), 65(9), 63(6), 59(9), 51(10), 41(7). Anal. Calcd for $C_{11}H_{13}BrFN$: C, 51.18; H, 5.08; N, 5.43. Found: C, 51.05; H, 5.23; N, 5.30.

General Procedure for the Synthesis of 3-Fluoroazetidines 4a−f. At 0 °C, 0.1 mol of sodium borohydride was added to a solution of 0.05 mol of imine **3a**−**f** in 50 mL of methanol. After reflux for 2 h, the resulting mixture was triturated with water and three times extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), and, after evaporation of the solvent, 3-fluoroazetidines **4a**−**f** were obtained. Further purification was performed by flash chromatography over silica gel.

1-Benzyl-3-fluoro-3-methylazetidine 4a. Yield: 70%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.58 (3H, d, J = 22.4 Hz), 3.25 (2H, d × d, J = 22.8 Hz, J = 8.4 Hz), 3.35 (2H, d × d × d, J = 13.3 Hz, J = 8.4 Hz, J = 1.9 Hz), 3.66 (2H, s), 7.23−7.33 (5H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 23.1 (d, J = 25.7 Hz), 63.5, 65.3 (d, J = 20.7 Hz), 89.8 (d, J = 203.9 Hz), 127.1, 128.3, 128.4, 137.9. IR (NaCl, cm^{-1}): 1381, 1364, 1323, 1271, 1230, 938. MS (70 eV) *m*/*z* (%): 179 (M^+, 7), 178(8), 164(3), 119(3), 118(5), 104(3), 102-(3), 91(100), 65(10), 44(6), 42(5), 41(5). Anal. Calcd for $C_{11}H_{14}$-FN: C, 73.71; H, 7.87; N, 7.81. Found: C, 73.58; H, 7.99; N, 7.73.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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