SYNTHESIS OF (TRIFLUOROMETHYL)AZIRIDINES IN 1,1,1,3,3,3-HEXAFLUOROPROPAN-2-OL: FIRST EXAMPLE OF COUPLING REACTIONS OF FLUORAL, AN AMINE AND A DIAZO COMPOUND

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This paper is dedicated to the memory of Professor Miloš Hudlický.

The influence of solvent on the $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$-catalyzed reaction of (trifluoromethyl)aldimines with ethyl diazoacetate has been investigated. The reaction of fluoral ethyl hemiacetal, an aromatic amine, and ethyl diazoacetate could be performed in 1,1,1,3,3,3-hexafluoropropan-2-ol to provide the corresponding (trifluoromethyl)aziridines.
Keywords: Aziridines; Aziridination; Fluorine; Hexafluoropropan-2-ol; Imines; Diazo compounds.

Aziridines are versatile building blocks for the synthesis of a variety of biologically important compounds, such as amino alcohols, unnatural amino acids and nitrogen-containing heterocyclic compounds[1]. A number of methods are available for the synthesis of aziridines. The simplest approach is either the addition of a nitrene to an alkene, or the addition of a carbene to an imine[2]. In both cases transition metals (copper, rhenium) have been found to act as effective catalysts by favoring the formation of the nitrene or carbene species. In the case of reaction between ethyl diazoacetate (EDA) and imines, Lewis acids such as $BF_3{\cdot}Et_2O$ or $AlCl_3$ are also excellent catalysts by increasing the electrophilicity of the imine[3].

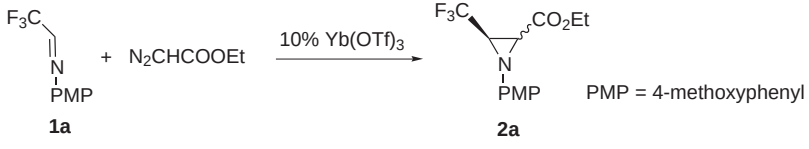
Utilisation of these methods for the preparation of (trifluoromethyl)aziridines had received no attention before our recently reported preliminary results[4]. $BF_3{\cdot}Et_2O$, and, to a lesser extent, $Yb(OTf)_3$, appeared to be good catalysts for the nucleophilic addition of ethyl diazoacetate to

(trifluoromethyl)imines leading to 3-(trifluoromethyl)aziridine-2-carboxylic acids[4a]. We now describe our effort to perform the catalyzed coupling reactions of a fluoral hemiacetal, amines and ethyl diazoacetate.

First, taking into account that $Yb(OTf)_3$-catalysed aziridination reactions can be performed in various solvents, including aqueous and protic, we investigated the influence of solvent on the $Yb(OTf)_3$-catalysed aziridination of aldimine **1a** with EDA. The results are summarised in Scheme 1 and Table I.

Compared to hexane, no solvent allowed an improvement of the reaction and even when the reaction was performed in alcohols[5], no trace of aziridine could be detected. Due to its great electrophilicity, the fluorinated aldimine **1a** readily added EtOH and MeOH to afford the corresponding hemiaminal **3** isolated in quantitative yield. In order to avoid this parasitic reaction, EtOH was replaced by 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), which is known to be a non-nucleophilic alcohol. The value of nucleophilicity of HFIP is –4.23 whereas that of EtOH is considered the zero reference[6].

The reaction was performed with imine **1a** and ethyl diazoacetate in the presence of $Yb(OTf)_3$ as catalyst (10 mole %) in HFIP, and under these conditions a *cis*/*trans* mixture of aziridine **2a** was obtained in high yield after



SCHEME 1

TABLE I
Aziridination reactions of fluoral imine

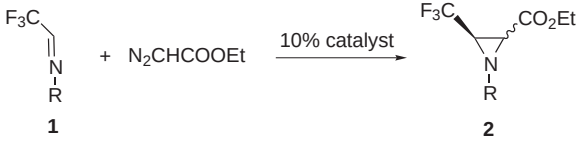
Entry	Solvent	Time, h	*cis/trans*	Recovered, %	Yield, %
1	hexane	20	70/30	0	83
2	Et_2O	20	75/25	5	68
3	CH_3CN	20	54/46	14	55
4	MeOH or EtOH	20	–	0	0[a]

[a] 100% yield of $CF_3(OR)NH$-PMP, R = Me, Et (**3**).

only 3 h. The reaction was also efficient with other (trifluoromethyl)aldimines: from **1b** and **1c**, aziridines **2b** and **2c** could be obtained in 85% (*cis*/*trans* = 64/36) and 82% (*cis*/*trans* = 70/30) yields, respectively (Table II). As expected, HFIP did not react with aldimines and, furthermore, its use as solvent significantly improved the aziridination reaction (yield and reaction time) compared to hexane[4]. This efficiency prompted us to also investigate this reaction in HFIP with $BF_3{\cdot}Et_2O$ as catalyst (Scheme 2 and Table II).

With $BF_3{\cdot}Et_2O$, the aziridination was less effective in HFIP than in ether: the yields of aziridines were slightly lower and the stereoselectivity was lower (*ca* 65/35 instead of 85/15 in ether). The great improvement of the reaction with $Yb(OTf)_3$ could be due to the enhancement of its Lewis acid power through hydrogen bonding between the sulfonate function and HFIP.

The three-component reactions were then investigated of fluoral ethyl hemiacetal (**4**) using 4-methoxyaniline as amine (0.95 equivalent) under four system conditions: 10% $Yb(OTf)_3$ in hexane and in HFIP, 10% $BF_3{\cdot}Et_2O$ in ether and in HFIP (Scheme 3 and Table III). The reaction was performed as a two-step one-pot reaction. The first step of these reactions was performed at room temperature with or without a drying agent and the reac-



1 **2**

SCHEME 2

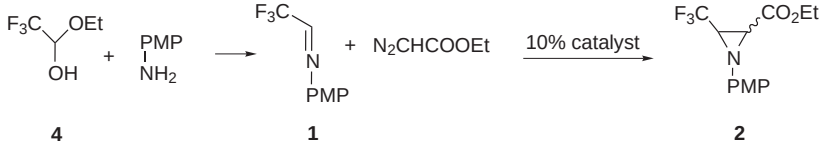
TABLE II
Aziridination reactions of fluoral imine in 1,1,1,3,3,3-hexafluoropropan-2-ol

Imine	R	Catalyst	Time, h	Yield, %	*cis/trans*
1a	PMP	$Yb(OTf)_3$	3	90	57/43
1b	Bn	$Yb(OTf)_3$	1.5	85	64/36
1c	Ph_2CH	$Yb(OTf)_3$	18	82	70/30
1a	PMP	$BF_3{\cdot}Et_2O$	1	88	60/40
1b	Bn	$BF_3{\cdot}Et_2O$	1.5	73	64/36
1c	Ph_2CH	$BF_3{\cdot}Et_2O$	24	64	66/33

tion was followed by ^{19}F NMR. After disappearance of fluoral hemiacetal **4**, the ethyl diazoacetate (1.5 equivalents) was added.

The two systems $Yb(OTf)_3$ in hexane and $BF_3{\cdot}Et_2O$ in ether, provided only traces of aziridines **2a**. Conversely, in HFIP, with both $Yb(OTf)_3$ and $BF_3{\cdot}Et_2O$, aziridines **2a** were obtained in 65% (*cis*/*trans* = 55/45) and 72% (*cis*/*trans* = 60/40) yields, respectively (Table III).

This essential influence of HFIP in the formation of aziridines in the three-component reaction, compared to its weak influence on the reaction of the imine **1a** with EDA prompted us to follow the course of these sequential reactions by ^{19}F NMR. In ether and in hexane, fluoral hemiacetal **4** reacted with the amine providing a mixture of several tetrahedral intermediates (^{19}F NMR, δ from –79 to –89 ppm) with only a small amount of imine **1a** (δ –71 ppm). The formation of **1a** could not be enhanced when the reaction was conducted in the presence of a drying agent. In HFIP, with both catalysts, the imine **1a** was the major compound (*ca* 60%) in a mixture of tetrahedral adducts. This predominant formation of imine **1a** in HFIP is not the only reason for successful preparation of aziridines in the three-component reaction since, after addition of ethyl diazoacetate, the tetrahedral adducts also disappeared, and at the end of the reaction only aziridines were obtained. Unlike in the reactions performed with non-fluorinated aldehydes[7], the rate-determining step in these sequential reactions is not the aziridination itself, but the slow formation of aldimines due to the stabilisa-



4 **1** **2**

SCHEME 3

TABLE III
Three-component aziridination of fluoral imine

Entry	Solvent	Catalyst	Yield, %	*cis/trans*
1	hexane	$Yb(OTf)_3$	traces	–
2	HFIP	$Yb(OTf)_3$	65	55/45
3	ether	$BF_3{\cdot}Et_2O$	traces	–
4	HFIP	$BF_3{\cdot}Et_2O$	72	60/40

tion of tetrahedral intermediates by the CF_3 substituent. Although not well understood, HFIP appeared to be essential to solve this difficulty.

In conclusion, we have shown that the $Yb(OTf)_3$- or $BF_3{\cdot}Et_2O$-catalyzed three-component reaction of fluoral ethyl hemiacetal, an aromatic amine, and ethyl diazoacetate is efficient in 1,1,1,3,3,3-hexafluoropropan-2-ol as solvent. (Trifluoromethyl)aziridines **2** could be prepared in good yields but with moderate diastereoselectivity. The role of HFIP is crucial in the product limiting step of these sequential reactions which is the formation of an aldimine and the reactivity of tetrahedral adducts. More investigations are required to determine parameters governing the chemical and stereochemical course of different steps of these three-component reactions.

EXPERIMENTAL

General Procedure for the Aziridination of Imines

To a solution of imine **1** (1 mmol) in HFIP (3 ml) were added the Lewis acid (0.01 mmol) and EDA (1.5 mmol, 0.16 ml) at room temperature. The reaction was followed by GC. When starting material was no more detected, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution (10 ml). The aqueous layer was extracted with diethyl ether (3 × 5 ml), then the organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The products were purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 4 : 1).

trans-1-(4-Methoxyphenyl)-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2a**): pale yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): 6.82 (4 H, m); 4.08 (2 H, q, J = 7.0); 3.75 (3 H, s); 3.42 (2 H, m); 1.14 (3 H, t, J = 7.0). ^{13}C NMR ($CDCl_3$): 166.1, 157.2, 140.4, 124.1, 121.4, 115.4, 62.9, 56.4, 43.4, 40.4, 14.8. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –71.4 (d, J = 4.0). IR: 1 736 (CO). For $C_{13}H_{14}F_3NO_3$ calculated: 53.98% C, 4.88% H, 4.84% N; found: 53.88% C, 5.02% H, 4.83% N.

cis-1-(4-Methoxyphenyl)-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2a**): pale yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): 6.96 (2 H, d, J = 9.0); 6.81 (2 H, d, J = 9.0); 4.32 (2 H, q, J = 7.0); 3.77 (3 H, s); 3.07 (1 H, d, J = 6.5); 2.89 (1 H, q, $J_{H\text{-}F}$ = 4.5, $J_{H\text{-}H}$ = 6.5); 1.33 (3 H, t, J = 7.0). ^{13}C NMR ($CDCl_3$): 166.7, 157.5, 144.1, 121.4, 123.2, 115.5, 62.9, 56.3, 43.9, 42.3, 14.8. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –68.3 (d, J = 4.5). IR (neat): 1 753 (CO).

trans-1-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2b**): pale yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.31 (4 H, m); 4.14 (2 H, q, J = 7.0); 3.93 (2 H, q); 2.95 (2 H, m); 1.21 (3 H, t, J = 7.0). ^{13}C NMR ($CDCl_3$): 167.5, 138.6, 129.3, 129.1, 128.3, 124.2, 62.7, 55.2, 44.5, 38.5, 14.6. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –68.3 (d, J = 5.0). IR: 1 732 (CO). For $C_{13}H_{14}F_3NO_2$ calculated: 57.14% C, 5.16% H, 5.13% N; found: 56.95% C, 5.25% H, 5.10% N.

cis-1-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2b**): ^{1}H NMR ($CDCl_3$, 200 MHz): 7.35 (2 H, m); 4.26 (2 H, m); 3.77 (3 H, s); 2.56 (1 H, d, J = 6.5); 2.43 (1 H, q, $J_{H\text{-}F}$ = 5.5, $J_{H\text{-}H}$ = 6.5); 1.26 (3 H, t, J = 7.0). ^{13}C NMR ($CDCl_3$): 166.9, 136.6, 129.5, 129.2, 128.8, 124.2, 63.1, 62.6, 43.9, 42.2, 14.8. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –67.3 (d, J = 5.5). IR: 1 751 (CO).

trans-1-Diphenylmethyl-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2c**): white powder, m.p. 136 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.56 (2 H, d, J = 8.0); 7.44 (2 H, d, J = 8.0); 7.39–7.20 (6 H, m); 4.91 (1 H, s); 4.23 (2 H, q, J = 7.0); 3.13 (1 H, d, J = 2.0); 3.08 (1 H, q, $J_{H\text{-}F}$ = 3.5,

J_{H-H} = 2.0); 1.25 (3 H, t, *J* = 7.0). ^{13}C NMR ($CDCl_3$): 166.5, 141.8, 128.5, 127.7, 127.4, 127.0, 122.8, 67.4, 61.5, 43.3, 38.3, 13.6. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –71.2 (d, *J* = 3.5).

cis-1-Diphenylmethyl-3-trifluoromethyl-2-ethoxycarbonylaziridine (**2c**): white powder, m.p. 131 °C. ^1H NMR ($CDCl_3$, 200 MHz): 7.56 (2 H, d, *J* = 8.0); 7.44 (2 H, d, *J* = 8.0); 7.39–7.20 (6 H, m); 4.23 (2 H, q, *J* = 7.0); 3.85 (1 H, s); 2.66 (1 H, d, *J* = 7.0); 2.54 (1 H, q, J_{H-F} = 5.0, J_{H-H} = 7.0); 1.25 (3 H, t, *J* = 7.0). ^{13}C NMR ($CDCl_3$): 165.7, 141.0, 128.5, 127.8, 127.5, 125.8, 76.9, 61.5, 43.3, 42.0, 13.8. ^{19}F NMR ($CDCl_3$, $CFCl_3$): –67.3 (3 F, d, *J* = 5.0). IR: 1 741. For $C_{19}H_{18}F_3NO_2$ calculated: 65.32% C, 5.19% H, 4.01% N; found: 64.77% C, 4.99% H, 3.87% N.

General Procedure for Three-Components Coupling Reactions of Fluoral, 4-Methoxyaniline and Ethyl Diazoacetate

A mixture of trifluoroacetaldehyde ethyl hemiacetal (TFAE) (1.2 mmol, 0.12 ml), 4-methoxyaniline (1 mmol, 123 mg) and catalyst (0.01 mmol) in 3 ml of HFIP was stirred at room temperature for 1 h (^{19}F NMR was used to check the composition of the mixture), then EDA (1.5 mmol, 0.16 ml) was added, and the reaction was treated as previously described.

With $Yb(OTf)_3$: the starting mixture was composed by imine (63%), (1-ethoxy-2,2,2-trifluoroethyl)-(4-methoxyphenyl)amine (20%) and other tetrahedral intermediates (7%). After reaction with EDA, aziridines **2a** were recovered in an overall 65% yield (188 mg) and a 55/45 *cis*/*trans* ratio.

With $BF_3{\cdot}Et_2O$: the starting mixture was composed by imine (44%), (1-ethoxy-2,2,2-trifluoroethyl)-(4-methoxyphenyl)amine (53%) and traces of other tetrahedral intermediates. After reaction with EDA, aziridines **2a** were recovered in an overall 72% yield (208 mg) and a 60/40 *cis*/*trans* ratio.

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