Cyclisation/fluorination of nitrogen containing dienes in superacid HF–SbF_5: a new route to 3- and 4-fluoropiperidines†‡

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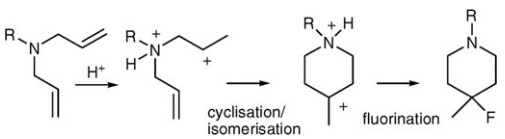
Various *N*,*N*-diallylic amines and amides were rapidly converted to fluorinated piperidines after a novel cyclisation/fluorination reaction in superacid HF–SbF_5.

Selectively (poly)fluorinated analogues of biologically active compounds have attracted significant interest among synthetic and medicinal chemists over the years, mainly due to a fluorine atom's unique specificities.[1] In addition, nitrogen heterocycles and especially piperidine are ubiquitous structural features of many alkaloid natural products.[2] As a consequence, fluorinated piperidines became important synthetic building blocks in the design of antimetabolite and drug candidates.[3] Despite its importance for application related to life sciences, the synthesis of fluoropiperidines has not been largely explored. Such fluorinated heterocycles are usually prepared by using the common dehydroxyfluorination of hydroxypiperidines with (diethyl)aminosulfur trifluoride (DAST) but this method suffers from rearranged[4] and dehydrated[3,5] side products, difficulty already encountered by Middleton.[6] Other routes such as the use of *N*-fluoro-derivatives, ring opening of aziridines or electrochemical process are also mentioned but remain very specific.[7] In this communication, we demonstrate a novel reaction of cyclisation/fluorination in superacid HF–SbF_5 as an alternative route to 4-fluoropiperidines from easily accessible dienes. During the past decades, Jacquesy *et al*. extensively studied nitrogen compounds behavior in superacid HF–SbF_5, showing the ability to perform reactions that cannot occur in conventional media.[8] As a part of our ongoing research in superacid HF–SbF_5, we recently reported that hydrofluorination of unsaturated amines can be performed, as an entry to β-fluoroamines.[9] It has been demonstrated that this novel methodology was based on the formation of a highly reactive electrophilic intermediate. The postulated ammonium–carbenium dicationic intermediate can undergo nucleophilic attack even in the presence of a poor nucleophilic partner. Based on these promising results, we decided to explore the ability to perform intramolecular nucleophilic substitution of such a dicationic intermediate, using a double bond as nucleophile (Scheme 1).

The cyclisation/fluorination reaction was firstly attempted with several amines and amides (Table 1).§

After reaction in HF–SbF_5 (molar ratio 8 : 1, 3 min, 0 °C), amines **1a,b** and amides **1f–h** (entries 1, 2 and 9–11) afforded the expected fluorinated products in moderate to good yields. In all cases no other products could be detected by ^{1}H NMR of the crude reaction mixture suggesting that compounds **2f,g** might be sensitive to purification. These first attempts showed the ability to use our methodology from either secondary or tertiary amines but also from aliphatic amides. Benzylic amine and aromatic amide reactivity has also been tested (entries 3, 13). Whatever the reaction conditions, substrates **1c** and **1i** gave a complex mixture of compounds, probably due to a possible competition between the double bond and the aromatic ring as nucleophilic partner. Indeed, when the aromatic ring is polysubstituted (entry 4) or deactivated (entries 5, 14) the desired fluorinated cyclic products are isolated. The substitution with a nitro group in *ortho* position (entry 15) allowed the formation of the desired fluorinated compound in 53% yield beside a side product **2k′** in 17% yield. The formation of this non-cyclic compound might be the fact of a possible steric hindrance between the *ortho*-nitro group and the double bond, preventing partially from the intramolecular trapping of the carbocationic center. At this stage it should be pointed out that hydroxy analogues can also be obtained from amides, depending on acidity conditions. When the acidity of the media is higher (entry 12), fluoro and hydroxy derivatives were formed in 28 and 31%, respectively. The formation of a 3-fluoropiperidine **2e′** after reaction of amine **1e** at −78 °C, and the formation of a mixture of 3- and 4-fluoroisomers at −50 °C (entries 6, 7) encouraged us to postulate a mechanism (Scheme 2). Mild conditions are clearly needed to obtain selectively the 3-fluoropiperidine, which seems to indicate that this isomer could be an intermediate in the reaction course. Indeed, the formation of compound **2e** starting from the 3-fluoropiperidine **2e′** confirmed this hypothesis (entry 8).



Scheme 1 Strategy to obtain fluorinated piperidines.

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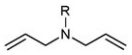
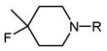
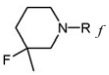
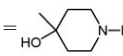
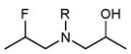
† For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719309b

‡ Electronic supplementary information (ESI) available: All experimental procedures and spectral data. See DOI: 10.1039/b719309b

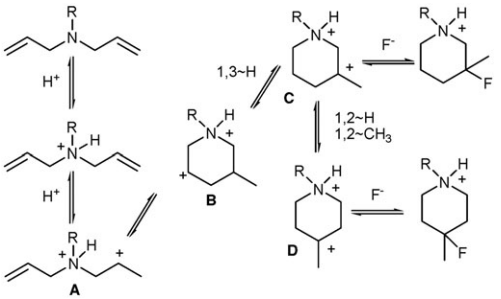
Table 1 Cyclisation/fluorination of amines and amides[a]

Entry	Substrate		Product	Yield[b] (%)
				
1	R = H	**1a**	**2a**·HCl	70
2	R = Me	**1b**	**2b**·HCl	85
3	R = Bn	**1c**	—[c]	/[c]
4	R = $CH_2C_6F_5$	**1d**	**2d**	68
5	R = *p*-NO_2Bn	**1e**	**2e**	35
6[d]	R = *p*-NO_2Bn	**1e**	**2e′**[e]	52
7[f]	R = *p*-NO_2Bn	**1e**	**2e**	32
			2e′[e]	21
8	**2e′**[e]		**2e**	100[g]
9	R = CHO	**1f**	**2f**	34
10[h]	R = $COCH_3$	**1g**	**2g**	30
11	R = $COCF_3$	**1h**	**2h**	69
12[i]	R = $COCF_3$	**1h**	**2h′**[j]	28
				31
13	R = Bz	**1i**	—[b]	—[b]
14[h]	R = *p*-NO_2Bz	**1j**	**2j**	55
15[h]	R = *o*-NO_2Bz	**1k**	**2k**	53
			2k′[k]	17

[a] Standard conditions: HF–SbF_5 molar ratio 8 : 1, 3 min, 0 °C. [b] Chemical yield after column chromatography. [c] Complex mixture. [d] Reaction performed at −78 °C. [e] **2e′** =  [f] Reaction performed at −50 °C. [g] Conversion.[10] [h] Reaction performed at −30 °C. [i] HF–SbF_5 molar ratio 4 : 1. [j] **2h′** =  [k] **2k′** = 

After protonation of the nitrogen atom, the strong acidity of the medium allows the formation of the ammonium–carbenium dication **A**. It has been previously showed that such dication can be considered as a superelectrophilic intermediate.[11] The proximity of the charges strongly activates its electrophilic character, allowing nucleophilic substitution with poor nucleophile partners.[12] In our case, the non-protonated double bound can act as a nucleophile, despite its electronic deactivation by the strong withdrawing effect of the proximal ammonium ion, and undergoes intramolecular cyclisation to form **B**. Such diene intramolecular cyclisation could be compared to previously postulated mechanism for the formation of azabicyclo[3,2,1]octenes in strong acidic conditions.[13] The formation of the 3-fluoropiperidine **2e′** starting from **1e** in mild conditions, confirmed the possible 1,3-hydride shift, leading to inductively more stabilized intermediate **C** precursor of 3-fluoropiperidine. In usual conditions (HF–SbF_5 molar ratio 8 : 1, 0 °C, 3 min) the more stabilized intermediate **D** (optimal charges repulsion and inductive stabilization) is obtained after 1,2-hydride and methyl shifts and then trapped by fluoride ion to give the precursor of the 4-fluoropiperidine. To complete the understanding of this novel process, a series of dienes has been submitted to reaction (Table 2).§

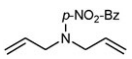
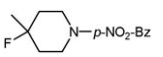
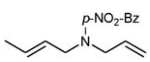
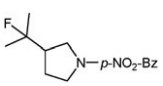
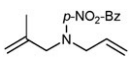
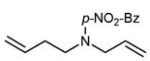
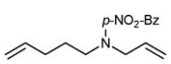
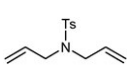
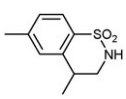
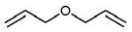
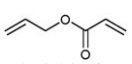
A preliminary study of the influence of the double bond substitution on the reaction course was attempted using **1j** as model substrate. Whatever the position of the methyl substitution a novel cyclic fluorinated pyrrolidine derivative **2l** was obtained in good yield (entries 2, 3). The influence of the distance between the unsaturation and the function has also



Scheme 2 Proposed mechanism.

been studied. Indeed starting from homoallylic substrate **1n** only 28% of pyrrolidine **2l** was formed among a large amount of side products, and whatever reaction conditions, substrate **1o** gave only a complex mixture of compounds (entries 4, 5). All these results seem to comfort our previously proposed mechanism based on the strong reactivity of the dicationic superelectrophilic intermediate. It appears that the extension of the distance between the protonated function and the carbenium decreases the reactivity of the intermediate and so the selectivity of the reaction, whereas substitution of the double bond with a methyl inductive donating group opens new possibilities toward the formation of new fluorinated nitrogen containing cyclic products. It has to be pointed out that the formation of this novel fluorinated pyrrolidine remains unclear. Isomerisation after intramolecular cyclisation could be postulated, but extended additional work is currently under progress to propose a reasonable hypothesis for the formation of compound **2l**. The formation of cyclic sulfonamide **2p** starting from *N*-tosyl diene (entry 6) confirmed the possible competition between double bond and aromatic ring attack, in accordance with previous results.[9] At this stage the

Table 2 Cyclisation/fluorination of various dienes

Entry	Substrate		Product		Yield (%)[a]
1		**1j**		**2j**	55
2		**1l**		**2l**	50
3		**1m**		**2l**	86
4		**1n**		**2l**	28
5		**1o**	—[b]		—[b]
6		**1p**		**2p**	81
7		**1q**	—[b]		—[b]
8		**1r**	—[b]		—[b]

[a] Chemical yield after column chromatography. [b] Complex mixture.

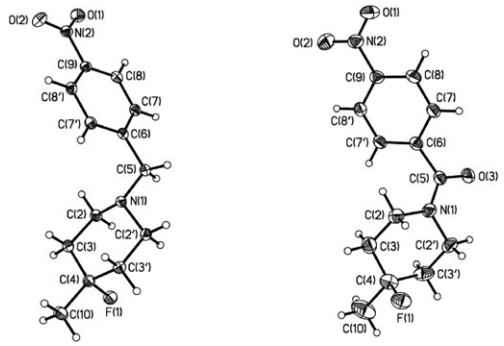


Fig. 1 ORTEP drawings of **2e** and **2j**.[15]

deallylation process remains unclear and is currently studied. First attempts to obtain fluorinated cyclic ethers or esters were unsuccessful (entries 7, 8). Whatever conditions used, the reaction was not selective leading to a complex mixture of compounds, showing that this novel process seems not to be consistent with non-nitrogen containing dienes. For all 4-fluoropiperidines, similarly to 3-fluoropiperidines,[14] a preferred axial orientation of the fluorine atom in the six-membered ring chair can be postulated, confirmed by X-ray analysis of amine **2e** and amide **2j** (Fig. 1).

In conclusion, we have developed a novel superacidic cyclisation/fluorination reaction as a new route to fluorinated piperidines starting from easily accessible starting materials. In addition, we have also showed that this novel concept could be applied to substituted dienes as an entry to more elaborated fluorinated nitrogen containing cyclic derivatives. The identification of a product intermediate allowed us to postulate a mechanism based on the intramolecular nucleophilic trapping of a superelectrophilic dication. This investigation sets the stage for the rapid access to high biologically valued fluorinated building blocks. Further work is now directed at carrying on the scope and limitations study of this innovative process and at extending it to more elaborated dienes.

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Notes and references

§ *Procedure* for the production of **2j**: To a mixture of HF–SbF_5 (6 mL, 8 : 1 molar ratio) maintained at −30 °C was added 500 mg of **1j** (2.03 mmol). The mixture was magnetically stirred at the same temperature for 5 min. The reaction mixture was then neutralized with water–ice–Na_2CO_3 and extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (70 : 30 petroleum ether–ethyl acetate) gave the product as a colourless powder (296 mg, 55%). All experimental procedures and spectral data are reported in ESI.‡

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10 The term "conversion" is used here to mean the total percentage of product detected in the reaction mixture by ^{1}H NMR before isolation.

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15 Thermal ellipsoids represent 30% probabilities. *Crystal structure analysis* of **2e**: $C_{13}H_{17}FN_2O_2$, 100 K, triclinic, space group $P\bar{1}$; a = 6.3802(11), b = 7.2136(11), c = 14.245(3) Å, α = 96.205(7), β = 93.734(8), γ = 103.868(7)°, V = 629.95(19) Å^3; Z = 2; total reflections collected: 26 662; independent reflections: 3642 (2993 $F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 60.16° (98.6% coverage). Number of variables: 164; R_1 = 0.0380, wR_2 = 0.1125, S = 1.075; highest residual electron density 0.454 e Å^{-3}. CCDC 670158. *Crystal structure* analysis of **2j**: $C_{13}H_{15}FN_2O_3$, room temperature, triclinic, space group $P\bar{1}$; a = 6.6927(3), b = 8.2566(3), c = 12.1565(5) Å, α = 79.479(2), β = 80.510(2), γ = 78.922(2)°, V = 642.26(5) Å^3; Z = 2; total reflections collected: 13 438; independent reflections: 2260 (1917 $F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 50° (100% coverage). Number of variables: 173; R_1 = 0.0366, wR_2 = 0.1177, S = 1.136; highest residual electron density 0.163 e Å^{-3}. CCDC 670159†.