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Synthesis of *gem*-difluoroamines from allylic or halogenoamines

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Abstract—In HF–SbF_5, in the presence of *N*-bromosuccinimide, allylic or halogenoamines yield *gem*-difluoroamines, through bromofluorointermediates.

Introduction of fluorine atom(s) into a molecule can modify its physical and chemical properties and its original biological activity.[1–3]

Synthesis of *gem*-difluoro derivatives has been extensively studied. Direct *gem*-difluorination can be carried out using fluorinating agents, sources of either nucleophilic or electrophilic fluorine.[4,5]

We have previously reported a novel oxidative *gem*-difluorination carried out on *Vinca* alkaloids in superacid HF–SbF_5, in the presence of either *N*-bromosuccinimide (NBS) or chloromethanes ($CHCl_3$ or CCl_4), fluorination occurring selectively at the cleavamine moiety.[6] We would like to report the difluorination of acyclic allylic or halogenated amines under similar conditions, confirming the generality of this new reaction.

A typical experimental procedure is as follows. To a mixture of HF–SbF_5 (7:1 molar ratio, 20 mL) at 0°C in a Teflon® flask was slowly added at first NBS (320 mg, 18 mmol) then, after 2 min the amine **1** (Fig. 1) (342 mg, 6 mmol). The mixture was magnetically stirred at the same temperature for 10 min then neutralized with water/ice (60 mL) and sodium carbonate (40 g). The aqueous phase is then treated with acetic anhydride (4 mL) 3 h, then with an additional 2 mL for 24 h. The mixture was then extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were finally dried and evaporated. Flash chromatography over basic alumine provided acetylated compound **9** (378 mg, 46%). A similar procedure was carried out with amines **2**, **3**, **5**–**7**, but starting from the less volatile amines **4** and **10**, products can be separated without acylation. The results reported in Table 1 deserve several comments:

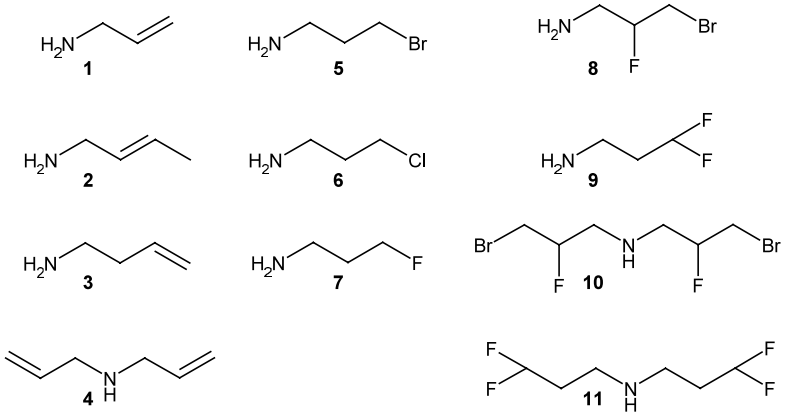

Figure 1.

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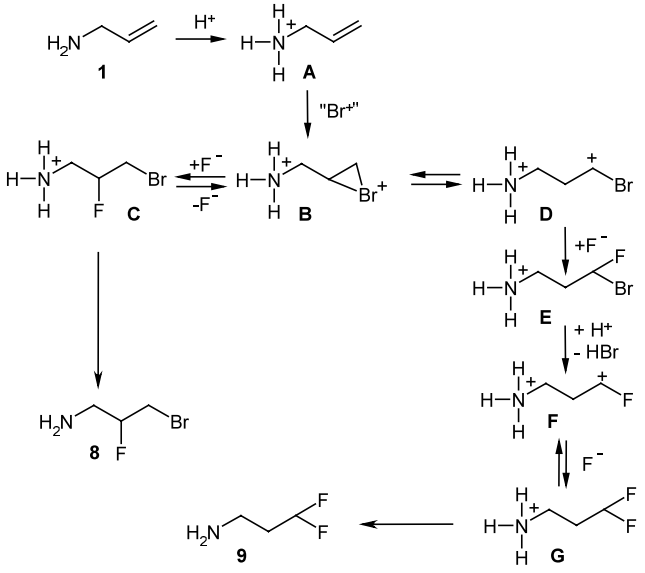
Table 1. *gem*-Difluorination of allylic or halogenated amines

Entry	Compound	Time (min)	Temperature (°C)	Products (% yield)
1	**1**	2	−35	**8**[b] (41)
2	**1**	10	0	**9**[b] (46)
3	**2**	1	−20	Complex mixture
4	**3**	1	−20	Complex mixture
5	**4**	2	−35	**10** (50)
6	**4**	5	0	**11** (55)
7	**10**[a]	3	0	**11** (70)
8	**5**	1	−30	(**8**+**9**)[b] (39) (2/1)
9	**5**	10	−20	**9**[b] (43)
10	**6**	1	0	(**8**+**9**)[b] (26) (2/1)
11	**6**	10	0	**9**[b] (33)
12	**7**	20	20	**8**+**9**[b] (34) (51/3.5)

[a] Reaction carried out without NBS.
[b] Separated after acylation of the reaction mixture using acetic anhydride.

– Bromofluoroderivatives **8** and **10**, obtained at low temperature and short reaction time from **1**, **5**–**7** and **4**, respectively, are intermediates in the *gem*-difluorination, leading to the corresponding compounds **9** and **11** obtained at a higher temperature. This is confirmed by reaction of compound **10** without NBS at 0°C (entry 7).
– In HF–SbF_5–NBS difluoroamine **9** is obtained at −20°C from bromoamine **5**, at 0°C from chloroamine **6** and only at ambient temperature from the fluoro analog **7**, implying reactivity order **5**>**6**>**7**. Furthermore, compound **9** is also obtained (44% yield) at −20°C in HF–SbF_5 without using NBS from bromoamine **5**, implying that the substrate is the source of electrophilic bromine 'Br^+' like NBS in the reaction conditions.[7,8] The chloro and fluoro analogs **6** and **7** are unreactive in HF–SbF_5 without NBS.
– Butenylamines **2** and **3** lead only to complex mixtures.



Scheme 1.

Yields are for isolated products after chromatography. Products gave satisfactory spectral data (MS, ^1H, ^{13}C NMR) and the expected analytical (HRMS) results.[12]

Taking into account these data, the postulated mechanism is outlined in Schemes 1 and 2. In HF–SbF_5, amines are *N*-protonated. For example, starting from amine **1**, the resulting ion **A** can react with electrophilic bromine to give cyclic bromonium ion **B** which is trapped by a complex fluoride ion (SbF_6^-, $Sb_2F_{11}^-$…) to **C**, precursor of compound **8**. Though bridged bromonium ions are more stable than α-bromonium ions,[9] ion **B** is destabilized by the protonated amino groups, favoring formation ion **D** which might react with a fluoride ion to give ion **E**.[10] This ion would lead irreversibly to ion **F** then to ion **G**, precursor of compound **9**. The intermediate α-fluoronium ion **F** is stabilized by back donation of the unbound electron pair into the vacant p orbital of the carbocationic carbon atom.[11]

Such a mechanism might also account for the formation of compounds **10** and **11** from amine **4**.

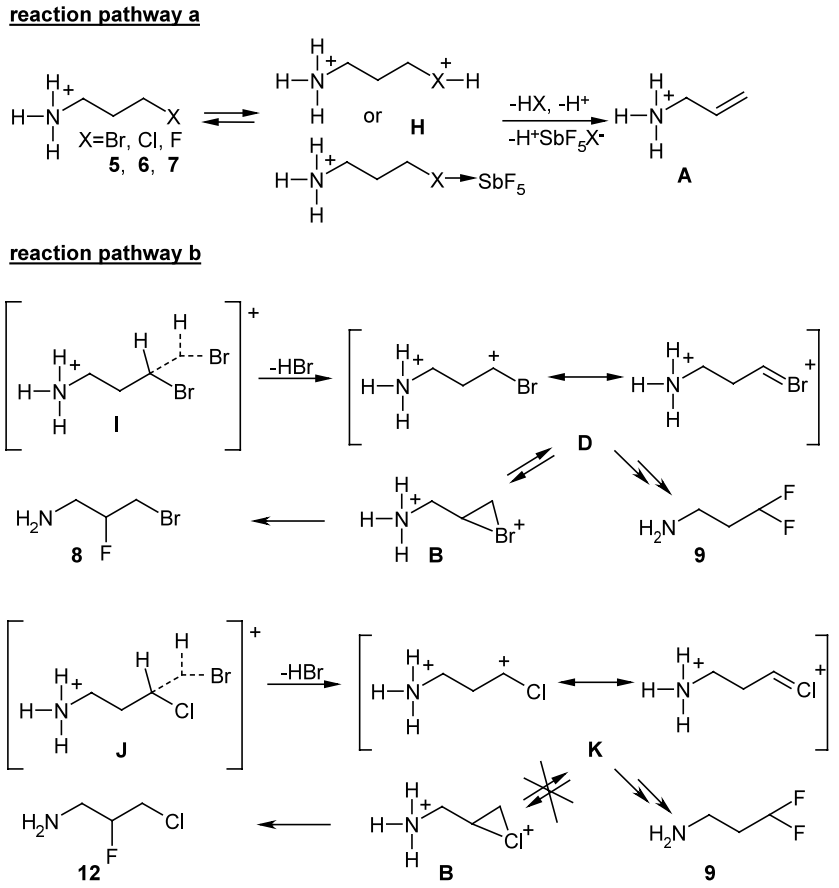
Starting from halogenated amines **5**–**7**, two mechanisms can be considered (Scheme 2).

The first one (reaction pathway a) implies elimination of HX from ion **H**, obtained after protonation (or complexation with SbF_5) of the halogen atom, to yield the ion **A** which can react as previously described. This might account for the relative reactivity of compounds **5**, **6** and **7**, the larger halogen atoms accommodating more protonation then the smaller ones.

The alternative mechanism (reaction pathway b) involves hydride abstraction by electrophilic bromine through a carbonium ion. Starting from amine **5**, loss of HBr from carbonium ion **I** yields ion **D**, in equilibrium with ion **B**, precursors of compounds **9** and **8**, respectively.

Such a mechanism, starting from amine **6** would involve an α-chloronium **K** accounting for the formation of difluoroamine **9**, but not of the bromofluoro amine **8** (instead formation of chloroamine **12** would be expected). It has been shown that α-chloronium ions are stabilized by chlorine atom which becomes both a π and σ donor,[11] and a tertiary α-chloronium ion has been postulated in the fluorination of alkaloids.[6] Such a mechanism can also be ruled out with the fluoroamine **7**, intervening of α-fluoronium would lead only to difluoroamine **9**. Finally, starting from amines **5**, **6** and **7** the most likely mechanism implies elimination of HX, but a hydride abstraction from protonated amines **5** and **6** might also be operative.

Our results confirm that this *gem*-difluorination initially reported on alkaloids is a general process. Extension of



Scheme 2.

this novel reaction to other polyfunctional bioactive products will be reported in a near future.

Acknowledgements

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12. Selected spectral data for:
Compound **8** after acylation: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (s, $\underline{CH_3}CO$), 3.52 (dd, $J_{H-F}=20.0$ Hz, $J_{H-H}=6.0$ Hz, 2H, CH_2N, H-1), 3.55 (dd, $J_{H-F}=17.6$ Hz, $J_{H-H}=5.6$ Hz, CH_2, CH_2Br, H-3), 4.64 (dq^5, $J_{H-F}=47.6$ Hz, $J_{H-H}=5.5$ Hz, CH, CHF, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (s, $\underline{CH_3}CO$), 30.4 (d, $J=26.6$ Hz, CH_2, C-3), 44.1 (d, $J=22.3$ Hz, CH_2, C-1), 93.2 (d, $J=173.4$ Hz, CH, C-2), 170.8 (s, C=O); GC–EIMS m/z: 118 (M^+–Br); HR-MS: calcd for $C_5H_{10}NOF$ (M+1–Br)+: 119.07464, obsd: 119.0753.
Compound **9** after acylation: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H, $\underline{CH_3}CO$), 1.98–2.15 (massif, 2H, CH_2, H-2), 3.45 (q^4, $J=6.4$ Hz, 2H, H-1), 5,92 (tt, $J_{H-F}=56.1$ Hz, 1H, $J_{H-H}=4.1$ Hz, 1H, CHF_2, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1 (s, $\underline{CH_3}CO$), 33.2 (t, $J=6.5$ Hz, CH_2N, C-1), 33.9 (t, $J=20.5$ Hz, CH_2, C-2), 116.3 (t, $J=238.0$ Hz, CHF_2, C-3), 170.6

(s, C=O); GC–EIMS m/z: 137 (M^+); HR-MS: calcd for ($C_5H_9NOF_2$) 137.06522, obsd: 137.0653

Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$): 3.02 (dd, $J_{H-F}=20.0$ Hz, $J_{H-H}=6.0$ Hz, 2H, CH_2N, H-1), 3.56 (dd, $J_{H-F}=19.0$ Hz, $J_{H-H}=5.7$ Hz, 2H, CH_2Br, H-3), 4.76 (dq^5, $J_{H-F}=47.0$ Hz, $J_{H-H}=5.0$ Hz, 1H, CHF, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): 30.9 (d, $J=23.4$ Hz, CH_2, C-3), 51.2 (d, $J=20.9$ Hz, CH_2, C-1), 91.5 (d, $J=174.2$ Hz, CH, H-2); EIMS m/z: 293(5), 295(10), 297(4) (M^+); HR-FABMS: calcd for ($C_6H_{12}N(79)Br_2F_2$) 293.93045, obsd: 293.9303.

Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (ttd, $J_{H-F}=17.4$ Hz, $J_{H2-H1}=6.8$ Hz, $J_{H2-H3}=2.1$ Hz, 2H, CH_2, H-2), 2.80 (t, $J=6.8$ Hz, 2H, CH_2N, H-1), 5.94 (tt, $J_{H-F}=56.7$ Hz, $J_{H-H}=4.4$ Hz, 1H, CHF_2, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.4 (t, $J=20.5$ Hz, CH_2, C-2), 42.9 (t, $J=6.2$ Hz, CH_2N, C-1), 116.5 (t, $J=237.0$ Hz, CHF_2, C-3); HR-FABMS: calcd for ($C_6H_{12}NF_4$) 174.09059, obsd: 174.0909.