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Superelectrophilic Activation in Superacid HF/SbF_5 and Synthesis of Benzofused Sultams

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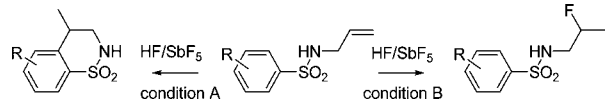
ABSTRACT



The synthesis of benzofused sultams and/or fluorinated sulfonamides, starting from *N*-allylic sulfonamides, was performed in superacid HF/SbF_5, through superelectrophilic activation. A dramatic effect of superacid composition on the selectivity of the reaction was shown and applied to the synthesis of cyclic 4-aminobenzenesulfonamides.

The sulfonamides constitute an important class of drugs with several types of pharmacological agents possessing antibacterial, diuretic, hypoglycemic, antithyroid, and antitumor activity.[1] High interest has also been directed to their cyclic counterparts, the sultams, with the development of nonsteroidal antiinflammatory agents[2] (e.g., piroxicam), antiepileptic agents[3] (e.g., sulthiame), and antiglaucoma agents[4] (e.g., brinzolamide). Recently, cyclic sulfonamides have been shown to display a vast array of biological activities.[5] At the same time, drug candidates with one or more fluorines have recently become common place.[6] Thus, on the basis of fluorine properties[7] and of the development of sulfonamides as selective inhibitors of the zinc carbonic anhydrase, broad-based studies linked increasing acidity of the heteroarene sulfonamides and fluoroalkane sulfonamides to their affinity for carbonic anhydrases.[8] Powerful methods have been developed for sultam synthesis by cyclization protocols, including Diels−Alder reactions,[9a] cycloadditions,[9b] and transition-metal-catalyzed approaches such as copper-,[9c] rhodium-,[9d] ruthenium-,[9e] and palladium-catalyzed cyclization.[10] Other methods such as gold-catalyzed hydroamina-

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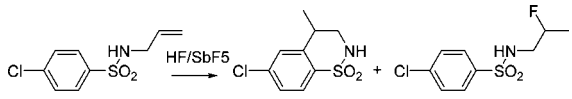
tion,[11] hydrogenation of *N*-sulfonylimines,[12] or Friedel−Crafts reactions[13] are also used. However, in the recently reported copper-catalyzed intramolecular carboamination, through an oxidative cyclization process,[14] no cyclization process starting from simple *N*-allylic sulfonamides has been reported to access benzofused sultams. We have recently reported the first hydrofluorination of unsaturated amines in superacid.[15] After polyprotonation and formation of a dicationic ammonium−carbenium superelectrophile,[16] fluorination led to the corresponding β-fluoroamines. Interestingly, a competition between the fluoride ions of the media and the aromatic sulfonamide was shown. Starting from *N*-tosyl-protected allylic amine, the corresponding benzofused sultam was formed in good yield. Owing to the ability to form ammonium−carbenium dications, able to react either in an intramolecular way with strongly deactivated aromatic ring (sulfonamide) or with fluoride ions in an intermolecular way, we conceived that superelectrophilic activation in superacid HF/SbF_5 might be used as a powerful synthetic method toward either benzofused sultams or fluorinated sulfonamide synthesis.

First, a study was performed to investigate whether the variation of the reaction conditions could influence the reaction course and could allow the selective formation of the desired sultams or the fluorinated sulfonamides. Our initial experiments showed that *N*-allylic-*p*-chlorobenzenesulfonamide **1a** yielded sultam **2a** and β-fluoro product **3a** after reaction in HF/SbF_5 (Table 1, entry 1). When the acidity of the medium was lower,[17] by decreasing SbF_5 content, the cyclization process decreased in favor of the hydrofluorination reaction (Table 1, entry 2). Moreover, when the acidity of the medium increased, sultam **2a** was formed in 64% yield, and no traces of fluorinated products could be detected in the crude reaction mixture (Table 1, entry 3).

It has to be noted that in all cases a deallylation process also occurred to give *p*-chlorobenzenesulfonamide as a side product of the reaction.[18] To test whether a dilution effect could influence the intramolecular cyclization, variation of the substrate's concentration was studied. As expected, higher dilution afforded sultam in better yield, and by using 0.16 mol·L^{-1} concentration of substrate, sultam **2a** could be obtained in 67% yield (Table 1, entry 5). Thus, starting from *N*-allylic sulfonamide, sultam or β-fluorinated product could be selectively obtained in optimized conditions: Friedel−Crafts intramolecular cyclization c = 0.16 mol·L^{-1}, % mol SbF_5 = 13.6, −20 °C, 10 min (condition A); hydrofluorination c = 0.33 mol·L^{-1}, % mol SbF_5 = 3.8, −20 °C, 10 min (condition B). Taking into account the preliminary results, we postulated the following mechanism (Scheme 1). Protonation of the sulfonamide function[19] and the double bond of substrate **1a** in superacid gives the dication **A**, which undergoes fluorination and leads to ammonium **B**, the precursor of the fluorinated product **3a** after hydrolysis. To explain the selective formation of sultam, a usual Friedel−Crafts type process involving the superelectrophile **A** could be reasonably postulated. Then, we investigated whether the fluorinated derivative could be considered as an intermediate in the cyclization process. Starting from fluoroderivative **3a**, after reaction in cyclization conditions, sultam **2a** was formed quantitatively, a result which confirmed our hypothesis. However, to discuss the displacement of equilibrium (**I**) toward ammonium−carbenium **A** in cylization condition, the composition of the media has to be analyzed.

Extensive reported studies of ionic composition in HF/SbF_5 solutions led to the accepted following conclusions.[17] For SbF_5 concentration lower than 10 mol %, SbF_6^- is practically the only anionic species present, and $H_3F_2^+$ is

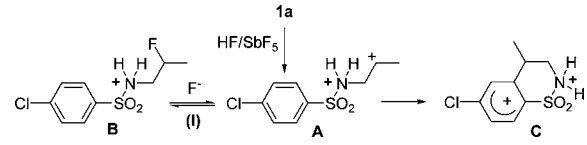
Table 1. Competition between Intramolecular Friedel−Crafts and Hydrofluorination Reactions in Superacid[a]



entry	concentration[b] (mol·L^{-1})	acidity (% mol SbF_5)	products (yield)[c]	
1	0.33	8.4	**2a** (55)	**3a** (17)
2	0.33	3.8	**2a** (13)	**3a** (71)
3	0.33	27	**2a** (64)	**3a** (0)
4	0.66	13.6	**2a** (49)	**3a** (0)
5	0.16	13.6	**2a** (67)	**3a** (0)

[a] 10 min reaction time at −20 °C. [b] Substrate concentration. [c] After column chromatography.

Scheme 1. Reaction of **1a** in Superacid HF/SbF_5



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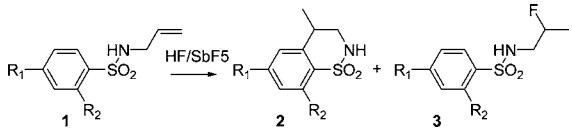
(18) To the best of our knowledge, no similar deallylation has been encountered yet in superacid. However, Stamm reported a similar behavior of *N*-allylsulfonamide in the presence of Lewis acid $AlCl_3$, through in situ enamide formation. Stamm, H.; Ornitschenko, A.; Buchholz, B.; Mall, T. *J. Org. Chem.* **1989**, *54*, 193.

the predominant cationic species. From 10 to 22 mol % SbF_5 in HF, the anions are essentially SbF_6^- and $Sb_2F_{11}^-$ in slow equilibrium, and only $H_3F_2^+$ is observed. Taking into account these conclusions, we can consider that the nucleophilicity of the fluoride ion source strongly decreases by SbF_5 concentration increase. Furthermore, it has now largely been shown that increasing the amount of SbF_5 increases the acidity strength of the media. In cyclization conditions, the fluorinated intermediate **B**, after protonation and HF elimination, could give **A**, which could be trapped by the more nucleophilic species (aromatic ring) to give dication **C**, precursor of the sultam after hydrolysis.

Then, a variety of substrates with different aromatic patterns were submitted to the reaction, to evaluate the scope of these reactions and the influence of the nucleophilic character of the aromatic ring on the selectivity of the reaction (Table 2). As expected, the inductive donating methyl group increased the nucleophilic character of the aromatic ring, leading to the exclusive formation of sultams, even in fluorination conditions (Table 2, entries 1−3). However, ortho substitution seemed to disfavor the cyclization (Table 2, entry 4). Deactivation of the aromatic ring with electron mesomeric withdrawing groups led only to the formation of fluorinated products, even in cyclization conditions (Table 2, entries 13−18). As already observed in superacid,[17e] methoxy and acetamido groups must be protonated, changing the substituent from electron donor to a strong attracting one (Table 2, entries 9−12). Surprisingly, trifluoromethyl substitution did not completely deactivate the aromatic ring toward substitution, and an equal amount of sultam and fluorinated product was formed in cyclization condition (Table 2, entry 5). The divergent synthetic character of this method was well emphasized by halogen-substituted substrate behavior. In almost all cases, reaction in cyclization conditions led exclusively to sultams in good yields, whereas using fluorination conditions fluorinated sulfonamides were obtained (Table 2, entries 19−28). The obtained low yields after reaction of substrate **1n** confirmed the versatility of iodo compounds in superacid.

Table 2. Selective Sultam Synthesis and Hydrofluorination[a]



entry		substrate	method[b]	products (yield)[c]	
1	**1b**	R_1 = Me	A	**2b** (64)	
2		R_2 = H	B	**2b** (90)	
3	**1c**	R_1 = H	A	**2c** (69)	
4		R_2 = Me	B	**2c** (58)	**3c** (23)
5	**1d**	R_1 = CF_3	A	**2d** (20)	**3d** (20)
6		R_2 = H	B		**3d** (84)
7	**1e**	R_1 = H	A		**3e** (46)
8		R_2 = CF_3	B		**3e** (86)
9	**1f**	R_1 = OMe	A		**3f** (73)
10		R_2 = H	B		**3f** (90)
11	**1g**	R_1 = NHAc	A		**3g** (42)
12		R_2 = H	B		**3g** (59)
13	**1h**	R_1 = $COCH_3$	A		**3h** (28)
14		R_2 = H	B		**3h** (78)
15	**1i**	R_1 = NO_2	A		**3i** (74)
16		R_2 = H	B		**3i** (93)
17	**1j**	R_1 = H	A		**3j** (19)
18		R_2 = CN	B		**3j** (67)
19	**1k**	R_1 = F	A	**2k** (54)	
20		R_2 = H	B		**3k** (88)
21	**1a**	R_1 = Cl	A	**2a** (67)	
22		R_2 = H	B		**3a** (71)
23	**1l**	R_1 = Br	A	**2l** (55)	
24		R_2 = H	B		**3l** (42)
25	**1m**	R_1 = H	A		**3m** (16)[d]
26		R_2 = Cl	B		**3m** (63)
27	**1n**	R_1 = I	A	**2n** (25)[d]	
28		R_2 = H	B		**3n** (39)[d]

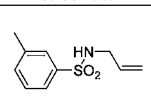
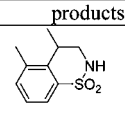
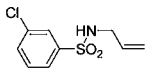
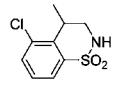
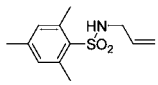
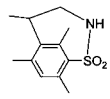
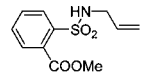
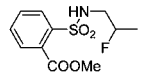
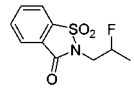
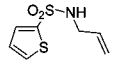
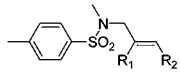
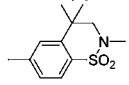
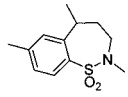
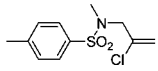
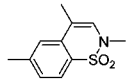
[a] 10 min reaction time at −20 °C. [b] Method A: c = 0.16 mol·L^{-1}, % mol SbF_5 = 13.6. Method B: c = 0.33 mol·L^{-1}, % mol SbF_5 = 3.8 [c] After column chromatography. [d] Side product formation.

We also examined the intramolecular Friedel−Crafts reaction of various substituted sulfonamides, to evaluate if this methodology could be applied toward the synthesis of original sultam derivatives (Table 3). The ability to access sterically hindered sultams was confirmed by the reaction of sultams **4a** and **4b** (Table 3, entries 1, 2). When ortho positions were already substituted with an electron-donating group, seven-membered ring sultams could also be formed (Table 3, entry 3). However, the reaction was not selective, and the formation of a large amount of side products was observed. Moreover, deactivated substrate **4d** was found to give only fluorinated products **5d** and **5′d**. As *N*-(2-fluoropropyl)-saccharin derivative **5′d** probably came from base-catalyzed cyclization of **4d** during a workup procedure,[20] hydrolysis time was increased, and fluorinated saccharin derivative **5′d** could be formed quantitatively (Table 3, entries 4, 5).

In addition, sultam **5f** could be formed in excellent yield starting from methyl-substituted substrate (Table 3, entry 7). Despite the stabilizing effect of the methyl substituent, the formed dicationic intermediate still showed a superelectrophilic character, to give the desired sultam. More notably, the reaction was applied to the synthesis of a seven-membered ring sultam **5g** in good yield (Table 3, entry 8). However, the cyclization of phenyl-substituted substrate **4h** was unsuccessful, and the reaction was not possible when the double bond was too deactivated (Table 3, entries 9, 10). We also found that 2*H*-1,2-benzothiazine 1,1-dioxide **5j** could be synthesized after cyclization and elimination in superacid (Table 3, entry 11). The compatibility of the superelectrophilic activation reaction with heteroaromatic sulfonamide was confirmed by the formation of products **5e** and **5′e** starting from thiophene substrate **4e**. Original electrophilic substitution on the 3-position of the thiophene occurred,[21] probably due to the stabilizing effect of the formation of a six-membered ring product in this case (Table 3, entry 6).

On the basis of these results, we show that superelectrophilic activation in superacid could be a convenient method

Table 3. Reaction of Substituted Sulfonamides in Superacid[a]

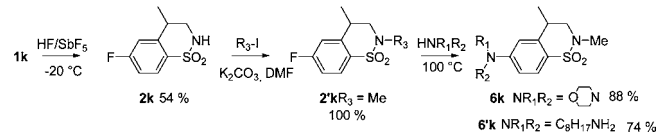
entry	substrate	products (Yield)[b]	
1	 **4a**	 **5a/5'a** (63:3/7)[c]	
2	 **4b**	 **5b/5'b** (72:1/1)[c]	
3	 **4c**		**5c** (17)[d]
4	 **4d**	 **5d** (58)	 **5'd** (15)
5[e]		**5d** (0)	**5'd** (100)
6	 **4e**	 **5e** (3)	 **5'e** (47)
7	 R_1=Me, R_2=H **4f**		**5f** (80)
8	R_1=H, R_2=Me **4g**		**5g** (73)
9	R_1=H, R_2=Ph **4h**	[f]	
10	R_1=COOEt, R_2=H **4i**	[g]	
11	 **4j**		**5j** (61)

[a] 10 min, − 20 °C, c = 0.16 mol·L^{-1}, % mol SbF5 = 13.6. [b] After column chromatography. [c] Molar ratio determined by ^{1}H NMR. [d] Side products formation. [e] Hydrolysis time: 24 h. [f] Complex mixture. [g] No reaction.

for the expeditious synthesis of original sultams. Then, we focused on the ability to use this methodology to access aminobenzene sulfonamides. Since the discovery of sulfa drugs, the aminobenzene sulfonamide core became very popular in medicinal chemistry research, which led recently to the discovery of potent antiprotozoal lead compounds.[22]

In addition to chemical libraries of sulfonamide compounds, efforts have to be made to access rapidly and efficiently a large variety of original cyclic sulfanilamide analogues. The absence of cyclic product formation starting from substrate **1g** (Table 2, entries 11, 12) led us to find an alternative toward 4-aminobenzofused sultam. A three-step procedure allowed the formation of 4-aminobenzofused sultam in overall good yield (Scheme 2). Starting from *N*-allylic

Scheme 2. 4-Aminobenzofused Sultam Synthesis



4-fluorobenzene sulfonamide **1k**, superacid intramolecular cyclization led to sultam **2k** in 54% yield. N-Methylation followed by a nucleophilic aromatic substitution of the fluorine atom with morpholine or octylamine (secondary or primary amine) yielded compounds **6k** (88% yield) and **6′k** (74% yield).

In conclusion, superelectrophilic activation in superacid has been demonstrated to be an efficient and divergent novel method to access either benzofused sultams or fluorinated sulfonamides, starting from easily accessible substrates. In HF/SbF_5, the reaction conditions were shown to be crucial for the selective formation of novel original sultam synthesis. A mechanism strongly based on the influence of the acidity and, so, on the influence of the nucleophilic character of fluoride ions source was postulated. We have also provided evidence that this chemistry could be used as a real synthetic tool, consistent with a multistep procedure. The ability to use this strategy toward the divergent synthesis of potent bioactive compounds was evaluated, and preliminary research is now focused in this area.

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Supporting Information Available: Experimental procedure, product characterization, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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