136. New Fluorinating Reagents

Part II[1])

Preparation and Synthetic Application of a Saccharin Derived *N*-Fluorosultam

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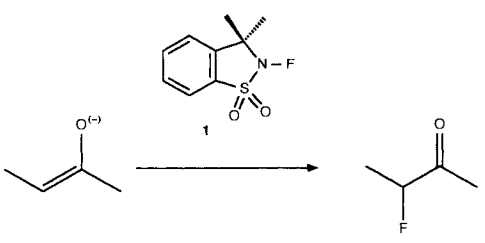
The synthesis of the new saccharin derived *N*-fluorosultam **1** is described. A comparative study with commercially available *N*-fluorosulfonamides shows **1** to be a superior fluorinating reagent for the synthesis of α-fluorocarbonyl compounds.

1. Introduction. – Fluorine substituents at biologically relevant positions of synthetic drugs and pesticides are extremely effective modifiers of their reactivity, a fact, which has initiated an ever growing interest in selectively fluorinated molecules [2]. Enormous efforts have been made in the past to solve the inherent synthetic problems and to search for new fluorination methodologies [3]. In particular, after years of using potentially hazardous perchloryl fluoride or fluorooxy compounds for the fluorination of carbanions, interesting new *N*-fluoro compounds have been developed for the same purpose [4]. Thus, *N*-fluoro-2-pyridone [5], *N*-fluoroquinuclidinium fluoride [6], as well as various *N*-fluorosulfonamides [7], *N*-fluorosultams [1], and *N*-fluoropyridinium triflates [8] are new fluorinating reagents, which are all effective to fluorinate a metal enolate and to transform it into an α-fluorocarbonyl compound *(cf. Scheme 1)*.

Scheme 1



A few of *Barnette's* *N*-alkyl-*N*-fluorosulfonamides [7] are commercially available. However, due to the presence of α-H-atoms on the *N*-alkyl residue, all of these reagents undergo a base-induced HF elimination as an undesired side reaction during fluorination

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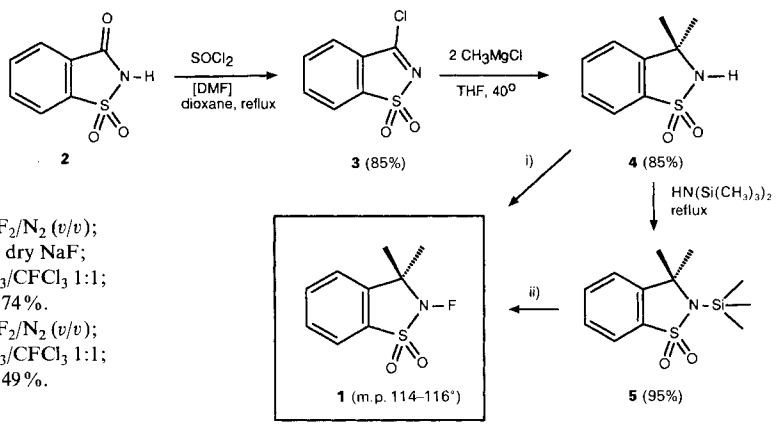
of carbanions *(vide infra)*[3]). In this paper, we describe the preparation and synthetic application of a very active *N*-fluorosultam **1**, derived from saccharin, which offers various advantages in fluorination reactions *(Scheme 1)*.

2. Synthesis of *N*-Fluorosultam 1. – Saccharin (**2**) can easily be transformed, *via* the 3-chloro compound **3**, into the well known 3,3-dimethyl-2,3-dihydro-1,2-benzothiazol 1,1-dioxide (**4**) by modifying the literature procedure [9] (see *Exper. Part*). According to [10], **4** can be *N*-silylated quantitatively by using hexamethyldisilazane to give white crystalline **5**. Two different fluorination procedures yield the new *N*-fluorosultam **1** as a colourless, thermally stable (< 200°) solid of m.p. 114–116°. *Method A* starts from **5** by using 10% (*v/v*) F_2 in N_2[4]) and, thus, avoiding the generation of HF which itselfs may cleave the sulfonamide bond in an undesired side reaction (*e.g.* [12]). However, the reaction stops after 50% conversion yielding **1** and **4** after workup. Using *Method B*, purification by column chromatography can be avoided, if one directly fluorinates the sultam **4** in the presence of well-dried NaF as the HF scavenger. Thus, for large-scale preparation, *Method B* seems to be the method of choice (*cf. Scheme 2* and *Exper. Part*).

Scheme 2



i) 10% F_2/N_2 (*v/v*); excess dry NaF; $CHCl_3/CFCl_3$ 1:1; –40°; 74%.

ii) 10% F_2/N_2 (*v/v*); $CHCl_3/CFCl_3$ 1:1; –40°; 49%.

3. Fluorination Reactions with *N*-Fluorosultam 1. – The fluorination potential of **1** is shown in a comparative study with commercially available *Barnette*-type *N*-fluorosulfonamides **6a–c** (*Scheme 3* and *Table*). The enolates **10a–c** were generated under standard conditions by treatment of the corresponding carbonyl compounds with LDA in THF at –78° (**10a** and **10b**), and with NaH in Et_2O at 0°, respectively (**10c**). After the addition of the fluorinating reagent, the cooling bath was removed, and after reaching room temperature, the reaction mixture was quenched with saturated aq. NH_4Cl, and analyzed by high-field ^{1}H-NMR. The yields of crude material were calculated based on the integration of the CH_3 signals of the tolyl group of all detectable sulfonamide derivatives in the

[3]) A *N*-(*tert*-butyl) group as the *N*-alkyl residue has its drawback by giving very low yields on preparation of the corresponding *N*-fluorosulfonamide (*cf.* [7]).

[4]) A precise description of the fluorination apparatus, which allows preparation of 100-g quantities of **1** will be published elsewhere [11].

Scheme 3

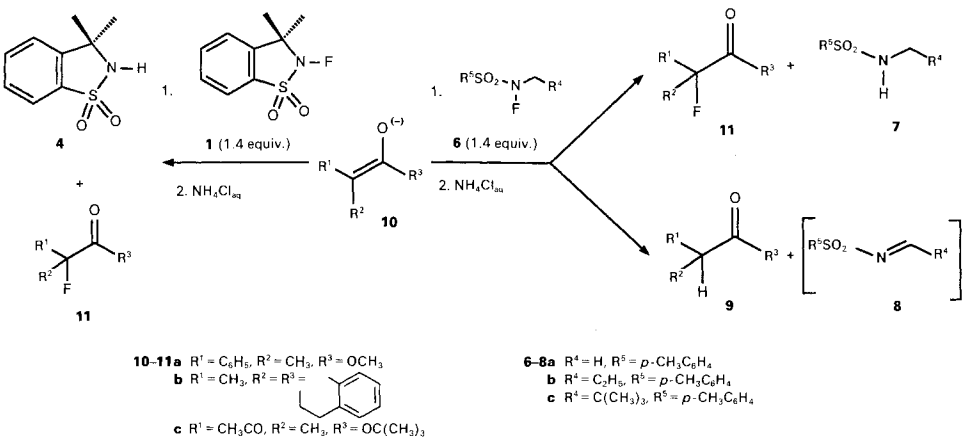


Table. *'F$^+$' Transfer* vs. *HF Elimination*[a])

Entry	Enolate	'F$^+$'	'F$^+$' Transfer		HF Elimination		6 [%][b])	
			11 [%]	**7** [%][b])	**9** [%]	**8** [%][b])		
a	**10a**	**6a**	21	17	30	83	0	
b		**6b**	33	30	67	66	4	
c		**6c**	72	73	20	25	2	
d		**1**	78 (55)[c])	67 (**4**)	– (11)[d])	–	25	(**1**)
e	**10b**	**6a**	13	10	50	82	8	
f		**6b**	20	21	80	63	16	
g		**6c**	57	45	43	37	18	
h		**1**	97 (90)[c])	77 (**4**)	– (3)[d])	–	23	(**1**)
i	**10c**	**6a**	48	45	4	37	18	
j		**6b**	43	51	4	22	27	
k		**6c**	40	75	3	15	10	
l		**1**	70 (21)[c])	65 (**4**)	– (2)[d])	–	35	(**1**)

[a]) Yields of crude material determined by ^{1}H-NMR.
[b]) Note that 100% refers to 1.4 equiv. of the reagent.
[c]) Yields of isolated material.
[d]) Arising probably from hydrolysis.

mixture. The range of HF elimination from the fluorinating reagent – followed by decomposition of the thus formed *N*-tosylimines – was estimated from the difference between the sum of the integration of *N*-F- and *N*-H-sulfonamides and the total of the integration of all tolyl-CH_3 signals. No attempts were made to characterize the degradation products of the tosylimines which are known to be very unstable intermediates [13]. Results are summarized in the *Table*.

The following observations can be made: the yields of the α-fluorocarbonyl compounds **11a** and **11b** strongly depend on the structure of the fluorinating reagent and increase from less than 20% to more than 90% in the order of **6a** < **6b** < **6c** ≪ **1**; the ratio of HF elimination at **6** *vs.* 'F$^+$' transfer to **7** depends on both the fluorinating reagent and the enolate structure: *i)* for a given enolate, the ratio decreases from *N*-fluoro-*N*-

methylsulfonamide (**6a**; *Entry a*) to *N*-fluoro-*N*-neopentylsulfonamide (**6c**; *Entry c*), and obviously becomes zero for the *N*-fluorosultam **1**. *ii)* For a given fluorinating reagent, the ratio decreases from the ester or ketone (*Entries b* and *f*) to the β-ketoester (*Entry j*). A connection between HF elimination and decomposition of the reaction mixture becomes obvious as indicated by the low yields of the recovered starting carbonyl compound **9** in particular with the *N*-fluoro-*N*-methylsulfonamide **6a**.

These results clearly indicate that, with ester or ketone enolates, HF elimination from the fluorinating reagents **6a–c** often becomes the main reaction, increasing from **6c** to **6b** to **6a**. This seems not to be restricted to strongly basic alkyl or aryl organometallics as suggested in [7]. In our hands, only β-ketoester enolates gave in some cases satisfactory results with commercially available *N*-alkyl-*N*-fluorosulfonamides. Therefore, a *N*-fluorosulfonamide lacking H-atoms in α-position to N-atom is of importance for a high-yield fluorine transfer. Thus, *N*-fluorosultam **1** appears to be the reagent of choice for such fluorine-transfer reactions.

4. Conclusion. – *N*-Fluorosultam **1** has proven to be an efficient, versatile, and easily accessible fluorinating reagent. It has considerable advantages over commercially available *N*-alkyl-*N*-fluorosulfonamides, in particular due to absence of H-atoms in the α-position of the N-atom and, thus, preventing base-induced HF elimination. Further applications of **1** for the fluorination of carbanionic species are currently under investigation and will be the subject of a subsequent paper.

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Experimental Part

1. *General.* See [14]. The *N*-alkyl-*N*-fluorosulfonamides **6a–c** are available from *Kali Chemie AG*, D-3000 Hannover.

2. *3-Chloro-1,2-benzothiazol 1,1-Dioxide* (**3**). A mixture of 54.9 g (0.3 mol) of saccharin (**2**), 90.0 ml (0.45 mol) of $SOCl_2$ and a catalytic amount of DMF (4 ml) was heated in 250 ml of dioxane for two days at reflux. Then, the clear brown soln. was concentrated *in vacuo* at 60° and the residue recrystallized from toluene: 51.4 g (85%) of yellow **3**. M.p. 140–145°.

3. *3,3-Dimethyl-2,3-dihydro-1,2-benzothiazol 1,1-Dioxide* (**4**). To a 3.0M soln. of MeMgCl in THF (100 ml) 20.6 g (0.1 mol) of **3** in 250 ml of THF was added at a rate to maintain the reaction temp. at *ca.* 40°. After stirring for additional 3 h at 40°, the mixture was poured onto ice, extracted with Et_2O, washed, and concentrated *in vacuo*. Chromatography on SiO_2/CH_2Cl_2 yielded 16.8 g (85%) of **4**. M.p. 106–107°.

4. *3,3-Dimethyl-2-(trimethylsilyl)-2,3-dihydro-1,2-benzothiazol 1,1-Dioxide* (**5**). A soln. of 43.8 g (0.22 mol) of **4** in 200 ml of hexamethyldisilazane was heated for 24 h at reflux in an Ar atmosphere. The mixture was then concentrated *in vacuo* at 70° and dried over night under a high vacuum. Compound **5** was thus obtained as a white powder in quant. yield (59.3 g). M.p. 144–146°. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.8–7.3 (*m*, 4 arom. H); 1.7 (*s*, $(CH_3)_2C$); 0.6 (*s*, $(CH_3)_3Si$).

5. N-*Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazol 1,1-Dioxide* (**1**). *Method A.* Excluding air and moisture, 10.6 g (40 mmol) of **5** in a mixture of 250 ml of $CHCl_3/CFCl_3$ 1:1 was reacted for 75 min at −40° with a mixture of 10% (*v/v*) F_2 in N_2. After blanketting with N_2 at r.t., the mixture was concentrated on a rotary evaporator *in vacuo* and the residue purified on SiO_2/CH_2Cl_2 and recrystallized from Et_2O/pentane yielding 4.1 g (49%) of white crystalline **1**. M.p. 114–116°. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.85–7.35 (*m*, 4 arom. *H*); 1.77 (*d*, $J = 4$, $(CH_3)_2C$). ^{19}F-NMR ($CDCl_3$): 9.796 (*sept.* $J = 3.51$). ^{13}C-NMR ($CDCl_3$): 144.0 (*s*); 135.1 (*s*); 131.0 (*s*); 129.7 (*s*); 123.9 (*s*);

122.7 (*s*); 69.8 (*d*, J(F,C) = 12, $C(CH_3)_2$); 26.3 (*d*, J(F,C) = 8, $C(CH_3)_2$). MS: 215 ($M^{+\cdot}$), 200, 182, 136, 133, 117, 109, 91, 89, 76, 63, 51, 50. Anal. calc. for $C_9H_{10}FNO_2S$ (215.24): C 50.22, H 4.68, N 6.51, S 14.90, F 8.83; found: C 50.12, H 4.68, N 6.55, S 14.99, F 8.99.

Method B. Excluding air and moisture, 4.93 g (25 mmol) of **4** in a mixture of 250 ml of $CHCl_3/CFCl_3$ 1:1 and *ca.* 5 g of well-dried NaF powder were reacted for 20 min at −40° with a mixture of 10% (*v/v*) of F_2 in N_2. After blanketting with N_2 at r.t. and filtration, the mixture was concentrated on a rotary evaporator *in vacuo*, and the residue recrystallized from Et_2O/pentane: 3.98 g (74%) of white crystalline **1**.

6. *Fluorination of 1-Methoxy-2-phenylprop-1-enolate* (**10a**) *and 1,2-Dihydro-3-methyl-3-naphtholate* (**10b**). 6.1. *General Procedure.* To a soln. of 0.17 ml (1.2 mmol) of $(i\text{-}Pr)_2NH$ in 15 ml of THF at −20° were added 0.75 ml (1.2 mmol) of 1.6N BuLi in pentane. After stirring for 30 min at −10°, the mixture was cooled to −78°, and **10a** or **10b** (1 mmol) in 2 ml of THF were added dropwise. After 1 h at −78°, the fluorinating reagent (1.4 mmol) in 2 ml of THF was added dropwise, the mixture then stirred for 1 h at −78°, and warmed up to r.t. After 1 h, the mixture was quenched by adding a sat. soln. of aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$), and analyzed as a crude mixture by ^{1}H-NMR.

6.2. *Fluorination of* **10a** *with* **1**. The crude mixture, which was obtained according to the procedure described above, was purified by flash chromatography on SiO_2 (cyclohexane/AcOEt 9:1) to give 100 mg (55%) of pure *methyl 2-fluoro-2-phenylpropionate* (**11a**). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.22 (*m*, 5 arom. H); 3.70 (*s*, CH_3O); 1.87 (*d*, J = 22.5, CH_3).

6.3. *Fluorination of* **10b** *with* **1**. The reaction mixture, as described above, was purified by flash chromatography on SiO_2 (cyclohexane/AcOEt 9:1) to give 160 mg (90%) of pure *2-fluoro-1,2,3,4-tetrahydro-2-methylnaphthalen-1-one* (**11b**). ^{1}H-NMR (250 MHz, $CDCl_3$): 8.06 (*dd*, J = 7.5, 1.8, 1 H); 7.52 (*td*, J = 7.5, 1.8, 1 H); 7.35 (*t*, J = 7.5, 1 H); 7.27 (*d*, J = 8, 1 H); 3.17 (*dt*, J = 18, 7.5, 1 H); 3.02 (*ddd*, J = 18, 12, 6, 1 H); 2.48 (*m*, 1H); 2.27 (*m*, 1 H); 1.60 (*d*, J = 22.5, CH_3).

7. tert-*Butyl 2-Fluoro-2-methyl-3-oxobutanoate* (**11c**). 7.1. *General Procedure.* To a soln. of 0.172 g (1 mmol) of *tert*-butyl 2-methyl-3-oxobutanoate in 10 ml of Et_2O at 0° were added 29 mg (1.2 mmol) of NaH, and the mixture was then stirred for 1 h at 0°. Then, the fluorinating reagent (1.4 mmol) in 5 ml of Et_2O was added dropwise. After stirring for 1 h at 0°, the mixture was warmed up to r.t., and after 2 h, quenched with sat. aq. NH_4Cl. Extraction with CH_2Cl_2 and drying ($MgSO_4$) gave the crude mixture which was analyzed by ^{1}H-NMR.

7.2. *Fluorination of* **10c** *with* **1**. The crude reaction mixture obtained according to the procedure described above was purified by flash chromatography on SiO_2 (cyclohexane/AcOEt 9:1) to give 40 mg (21%)[5] of pure **11c**. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.31 (*d*, J = 4.5, $COCH_3$); 1.63 (*d*, J = 22.5, CH_3); 1.49 (*s*, *t*-Bu).

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[5] Compound **11c** partially decomposes during purification.