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New Fluorinating Reagents from Acesulfam Sweeteners

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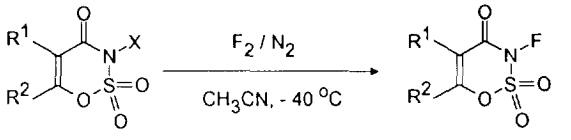
Abstract: Oxathiazinone dioxides, a group of well known sweetening agents, have been used for the synthesis of a new type of heterocyclic N-F reagents. Benz-1,2,3-oxathiazin-4(3F)-one 2,2-dioxide (1c), for example, is a stable crystalline compound, which can be used for the electrophilic fluorination of a variety of organic compounds under very mild conditions.

We wish to report our observations concerning the synthesis and reactivity of N-fluoro oxathiazinone dioxides (**1**), which we have found to be useful as electrophilic fluorinating agents. These are the first N-fluoro compounds in which both a carbonyl and a sulfonyl group have been used to decrease the electron density on the nitrogen and thus tune the fluorinating activity.



2 1

a: $R^1 = H$; $R^2 = CH_3$
b: $R^1 = CH_3$; $R^2 = CH_3$
c: $R^1 = R^2 = -(CH=CH)_2-$
X = H, Na, K

In many biologically active compounds, the introduction of a fluorine atom leads to a strong alteration of its properties. This has been especially useful in the pharmaceutical and agrochemical fields since the change in the physicochemical properties can be used to purposely vary the bioactivity of target molecules.[1] To modify such molecules, mild and selective methods for the incorporation of a fluorine atom are required. The development of such methods has, therefore, become an intensively active area of research.[2] In particular electrophilic fluorinating agents have received a lot of attention since they formally permit the replacement of a C-H bond by a C-F bond in one synthetic step.[3] However, the use of electrophilic fluorination reagents such as F_2, CF_3OF, C_2F_5OF, RCO_2F, $RfCO_2F$, $CsSO_4F$ has been very limited due to their disadvantageous properties: explosive, hygroscopic, gaseous, toxic, etc.

Since fluorine is the most electronegative element, it may be expected, that all those properties are unavoidable in reagents in which fluorine behaves as an electrophile. Many of the recently developed N-F

reagents — electrophilic reagents based on compounds containing N-F groups — prove, however, that this is not necessarily true.[4] These compounds can be often readily isolated and show excellent storage stability and fluorinating activity.

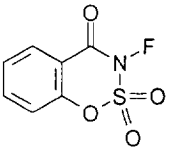
The development of neutral N-fluoro compounds has been based on two working principles: 1) enhancement of the fluorinating activity by decreasing the electron density on nitrogen, and 2) use of electron-withdrawing groups which can also stabilize the resulting anion formed by the loss of fluorine from nitrogen. Based on this strategy, two functional groups have been mainly used in the development of neutral N-F reagents: the sulfonyl and the carbonyl group. Since the sulfonamides show in general better stability and stronger fluorinating activity, most of the research activity has concentrated on this class of molecules and a variety of practical reagents of this type have already been prepared.

These include N-alkyl-N-fluoro-p-toluenesulfonamides,[5] N-fluoro-sultams,[6] N-fluoroperfluoralkyl sulfonimides,[7] N-fluorobenzenesulfonimide[8] and N-fluoro-o-benzenedisulfonimide.[9]

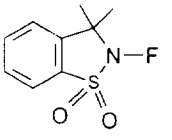
In contrast, only a few reports on N-fluoro amides as fluorinating agents have been published. These include 1-fluoro-2-pyridone[10] and several N-fluoro lactams.[11] In our search for new electrophilic fluorination reagents we focus our attention on compounds containing the N-acylsulfonamide functionality for two reasons: 1) compounds of this type have been, to the best of our knowledge not reported as fluorinating reagents and 2) Acesulfam K (**2a**, X = K), a sweetener from Hoechst (Sunett®), would be an attractive starting material.

Indeed, fluorination of **2a** (X = H, Na, K) with a mixture of 5% fluorine in nitrogen at low temperatures gives a reagent, which can be used for electrophilic fluorinations. The isolation of the pure N-F compound (**1a**) is however, rather difficult and the material is not stable in air at room temperature. Similar results were obtained with the dimethyl derivative **1b**. In contrast to this, benz-1,2,3-oxathiazin-4(3F)-one 2,2-dioxide (**1c**) is a colourless, thermally stable solid with a m.p. of 61 °C, which is obtained in 83% yield by direct fluorination of **2c**. Selective fluorinations using **1c** (Table 1) can be carried out in most common organic solvents, even in nonpolar ones like n-hexane (see example 4). The spent reagent (**2c**) can be easily removed from the reaction medium by water extraction.

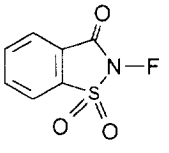
Benz-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide (**2c**, X = H) is a homologue of saccharin. Therefore, it was interesting to investigate whether a similar N-fluoro compound could be directly prepared from saccharin. In fact, a saccharin derived N-fluorosultam (**3**) has been already reported.[6] In this work, however, there is no comment on the fluorination of saccharin itself. Our attempts to prepare N-fluorosaccharin (**4**) by treating saccharin or its sodium salt with elemental fluorine diluted in nitrogen have been unsuccessful. Thus, it may be that in contrast to saccharin, **2c** gives a stable N-F compound (**1c**) due to less strain on the heterocyclic ring.



1c



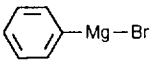
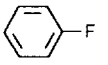
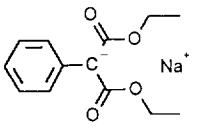
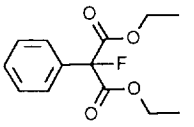
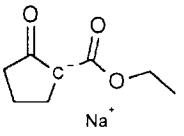
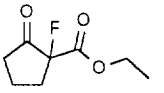
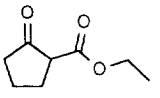
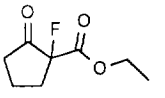
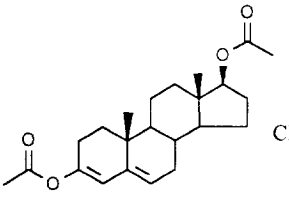
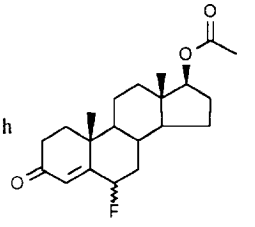
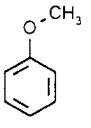
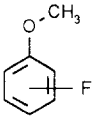
3



4

In conclusion, we have found that benz-1,2,3-oxathiazin- 4(3F)-one 2,2-dioxide (**1c**) is a stable, crystalline material, which can be used for the fluorination of both neutral and anionic nucleophiles.

Table 1: Examples of Selective Fluorination with **1c**

Entry	Compound	Conditions[a]	Product	Yield (%)[b]	Ref.
1		THF, 1 eq. **1c**, RT, 4 h		52	5
2		THF, 1 eq. **1c**, RT, 30 min		86	10
3		THF, 1 eq. 1c, RT, 30 min		77	14
4		n-hexane, 1 eq. **1c**, 65 °C, 8 h		66	14
5		CH_3CN, 1 eq. **1c**, RT, 4 h		59 (α:β 1:2.5)	15
6		neat, 1 eq. **1c**, 150 °C, 5 h		77 (o:p 56:44)	7

[a] RT = Room Temperature [b] Isolated yields, except for examples 1 and 6, which are ^{19}F NMR yields.

EXPERIMENTAL

Caution: Fluorine is a highly reactive and very corrosive material. Thus proper care should be taken when working with it.

Synthesis of N-Fluoroxathiazinone Dioxides (1). The starting materials **2** were synthesized according to procedures described in the literature[12] and thorougly dried before use. The N-fluoro oxathiazinone dioxides (**1**) were then prepared by low temperature fluorination of **2** in acetonitrile. The solvent was dried with CaH_2 and distilled just before use. The fluorinations were carried out at ambient pressure in a carefully dried glass reactor.[13] Although all the different derivatives of **2** (X = H, Na, K) can be used for the synthesis of **1**, the best yields were obtained with the sodium salts. Typical preparation: Excluding air and moisture, a suspension of **2c** (X = Na) (7.2 g, 32.6 mmol) and anhydrous NaF (0.1 g) in 130 ml of acetonitrile was treated with a mixture of 5% (v/v) F_2 in N_2 at -40 °C. The fluorination was discontinued after a slightly acidic KI trap, connected to monitor the off-gases, started to darken noticeably. To purge the system of residual fluorine, nitrogen was bubbled through for about 30 min at -40 °C and about 1 h at room temperature. After filtration of the mixture, the solvent was removed under vacuum leaving a light yellow solid. This material was treated with dried diethyl ether and the resulting suspension was filtered to obtain a clear solution. The colourless material obtained after evaporation of the solvent was recrystallized twice from diethyl ether / pentane yielding 5.89 g (83%) of white crystalline **1c**. M.p. 60-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): d = 8.23 (dd, J = 8, 2 Hz, 1 H), 7.85 (td, J = 8, 2 Hz, 1 H), 7.59 (td, J = 8, 1.5 Hz, 1 H), 7.42 (dd, J = 8, 1.5 Hz, 1 H); ^{19}F NMR (94.2 MHz, $CDCl_3$, 25 °C, $CFCl_3$): d = - 75.3 (bs, NF); MS (70 ev): m/z (%): 217 (61) [M^+], 120 (100), 92 (51), 57 (23).

Fluorinations with Benz-1,2,3-oxathiazin-4(3F)-one 2,2-Dioxide (1c). In general, enolates were fluorinated under standard conditions by first treating the carbonyl compound with sodium hydride at 0 °C, then adding a solution of **1c** and warming up to room temperature. Neutral compounds were fluorinated by simple mixing of the starting materials with **1c** in or without solvent at the given temperature. After aqueous work up the products were isolated by chromatography. The individual experimental details are given in table 1.

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