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Short communication

N-Fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[e]1,2-thiazin-4-one, a new and efficient agent for electrophilic fluorination of carbanions

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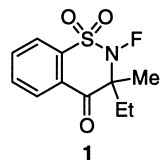
Dedicated to Professor Emeritus Yoshio Kobayashi on the occasion of his 75th birthday

Abstract

N-Fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[e]1,2-thiazin-4-one (**1**) was prepared in good yield by fluorination of the corresponding sultam (**3**) with $FClO_3$. The sultam (**3**) was prepared from saccharin (**2**) in 3 steps. The *N*-fluorosultam (**1**), a very stable crystalline solid, was found to fluorinate carbanions readily in good to excellent yields. © 1999 Elsevier Science S.A. All rights reserved.

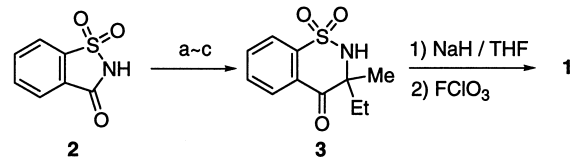
Keywords: *N*-fluorosultams; Electrophilic fluorination; α-fluoroketones

The replacement of hydrogen or hydroxyl with fluorine is an extensively used strategy for enhancement of biological activity in the design of analogues of biologically important molecules [1,2]. Electrophilic fluorination of carbanions is one of the most effective methods for this purpose because it permits the replacement of a C–H bond by a C–F bond in a single step [3–11]. Historically, electrophilic fluorination could be accomplished only by using toxic, corrosive, and/or explosive gaseous materials such as molecular fluorine, $FClO_3$ or CF_3OF. Usually, specialized equipment and techniques were required. In an important advance that helped overcome these limitations, Barnette found that the *N*-fluorosulfonamides can effectively fluorinate carbanions [12,13]. Although several *N*-fluorosulfonamides have been developed as electrophilic fluorination agents [14–19] since this report, there remains a need for additional fluorinating agents that are both readily accessible and give high chemical yields of fluorination product. In this paper, we wish to report the synthesis of a stable, crystalline compound, *N*-fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[e]1,2-thiazin-4-one (**1**), that effectively transfers fluorine to carbanions, exists as a stable crystalline compound, and, moreover, is readily and conveniently prepared in bulk quantities from inexpensive starting materials.



1

N-Fluorosultam (**1**) was readily prepared according to the route outlined in Scheme 1. Thus, saccharin (**2**) was converted into 3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[e]1,2-thiazin-4-one (**3**) in three steps that consisted of sequential alkylation, bromination, and ring expansion according to the procedure of Abramovitch et al. [20]. This sequence was carried out on a 10 g scale in more than 40% over all yield. Fluorination of **3** was first attempted by



2 **3**

Reagents: a) *sec*-BuLi / THF, b) Br_2 / benzene, c) KOH / H_2O

Scheme 1.

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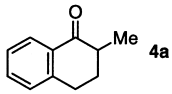
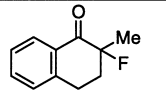
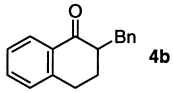
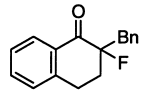
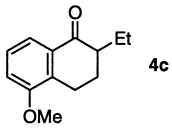
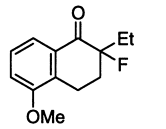
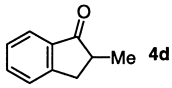
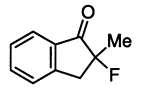
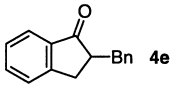
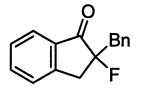
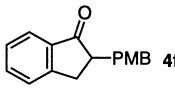
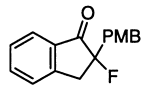
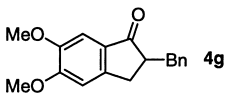
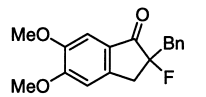
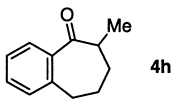
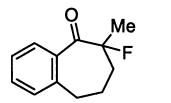
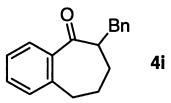
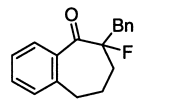
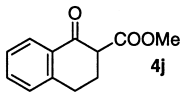
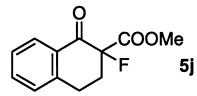
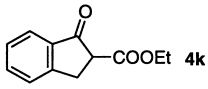
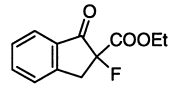
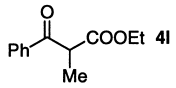
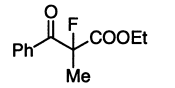
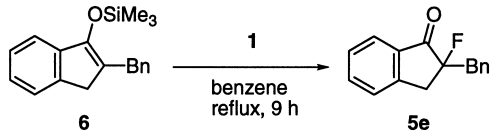
passing 10% molecular fluorine in nitrogen in a 1:1 solution of Freon-11 and chloroform in the presence of spray-dried NaF [21] at various temperatures. However, this procedure resulted in decomposition of **3**, even at −50°C. In contrast, fluorination of the sodium salt of **3** with $FClO_3$ in THF [22,23] readily gave **1**, obtained in pure form in 71% yield after silica-gel column chromatography and recrystallization from hexane. *N*-Fluorosultam (**1**) is a colorless, crystalline solid, mp 68°C (from hexane), which is stable over several weeks when stored at room temperature.

The results of electrophilic fluorination of a variety of enolates of ketone using **1** are summarized in Table 1. In experiments designed to optimize reaction parameters, we first examined fluorination of 2-methyl-1-tetralone (**4a**) under a variety of conditions. We found that the lithium enolate was a much more suitable substrate than the sodium

Table 1
Fluorination of ketones with **1**[a]

Entry	Ketone **4**	Conditions	Product **5**	Isolated Yield (%)
1	 **4a**	A	 **5a**	72
2		B		35
3	 **4b**	A	 **5b**	96
4	 **4c**	A	 **5c**	81
5	 **4d**	A	 **5d**	79
6	 **4e**	A	 **5e**	76
7	 **4f**	A	 **5f**	96
8	 **4g**	A	 **5g**	64
9	 **4h**	A	 **5h**	77
10	 **4i**	A	 **5i**	73
11	 **4j**	C	 **5j**	100
12	 **4k**	C	 **5k**	95
13	 **4l**	C	 **5l**	52

[a] Fluorinations were carried out using 1.5 eq. of base and 1.5 eq. of **1**. Bn: benzyl; PMB: *p*-methoxybenzyl.
Conditions: A: LiHMDS/THF/ − 78°C to −20°C; B: NaHMDS/THF/ − 78°C to − 20°C; C: NaH/THF/0°C.



Scheme 2.

enolate (entries 1, 2), producing the α-fluoroketone in good yield when subjected to fluorination with **1** in THF at −78°C to −20°C. Under similar conditions, lithium enolates derived from other ketones such as tetralones (**4b,c**), indanones (**4d–g**) and benzosuberons (**4h,i**) also gave the corresponding α-fluoroketones in good yields. The sodium salts of β-dicarbonyl compounds, including cyclic and acyclic ketones (**4j–l**), were also successfully fluorinated with **1** to give the products in good to excellent yields. It is noteworthy that fluorination of silyl enol ether (**6**) with **1** proceeded under neutral conditions to give **5e**, although the yield was modest (66%). Scheme 2.

In summary, we have synthesized *N*-fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[e]1,2-thiazin-4-one (**1**) and have found it to be an effective new agent for electrophilic fluorination of carbanions. The presence of an asymmetric carbon at the position adjacent to the nitrogen atom of **1** points to the obvious potential of development of asymmetric fluorinating agents [24–27] based on this structure. Such agents should be very useful for enantioselective fluorinations to produce chiral organofluorine compounds [28]. Accordingly, synthetic studies on asymmetric variants of **1** are now under investigation.

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