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Reactions of 1-fluoroalkyl triflates with nucleophiles and bases

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ABSTRACT

A series of 1-fluoroalkyl triflates are prepared, isolated and characterized. Their reactions with a large variety of nucleophiles are described. From these reactions are obtained 1-fluoroalkyl nitriles, azides, formates, acetates, ethers, phenylthio ethers, triphenylphosphonium salts, benztriazoles, benzimidazoles, xanthates, iodides, bromides and chlorides, most in excellent yield.

1. Introduction

1,1-Alkane bistriflates can be readily prepared in high yields from aldehydes by treatment with triflic anhydride in the presence of 2,6-lutidine at 0 °C in methylene chloride [1]. In previous work, Garcia Martinez and coworkers have reported that these highly reactive compounds can be readily converted to 1,1-dihalides [2,3] and 1-fluoro-1-haloalkanes [4], this latter chemistry proceeding through in situ formation of 1-fluoroalkyl triflates (Scheme 1).

Included in such studies of 1,1-bistriflates were reports from Garcia Martinez' group and that of Makosza of their conversion to 1,1-difluorides by use of $n\text{-Bu}_4{}^{+}(\text{Ph}_3\text{SnF}_2)^{-}$ and $\text{KF/Ph}_3\text{SnF}/n\text{-Bu}_4\text{N}^{+}\text{HSO}_4{}^{-}$, respectively as fluoride sources (Scheme 2) [3,5].

Because of our own interest in the development of effective methods for the preparation of *gem*-difluoro compounds, it was decided to take another look at the use of 1,1-bistriflates as precursors of 1,1-difluoroalkanes, and this work resulted in our recent report that triethylamine – 3HF was a good fluoride source for carrying out this conversion (Scheme 3) [6].

During the course of this study, conditions were also found for the preparation *and isolation* of 1-fluoroalkyl triflates in very good yield. For example, when nonane-1,1-bistriflate is allowed to react with 4 equivalents of $\text{Et}_3\text{N-3HF}$ in dichloromethane at 0 °C for 17 h, the monofluoro product, 1-fluorononyl triflate (**1a**) can be isolated in 91% yield (Scheme 4).

Having demonstrated the ability to prepare and isolate 1-fluoroalkyl triflates such as **1a**, it was decided to carry out a broad study of their use as precursors of monofluoro compounds of broad functionality.

2. Results and discussion

It was our initial thought that 1-fluoroalkyl triflates should be excellent precursors to 1-fluoroalkenes, especially since an α-fluoro substituent on an alkyl halide serves to enhance the E2 elimination reactivity of the compound relative to $\text{S}_\text{N}2$ substitution (Scheme 5) [7].

However, when 1-fluorononyl triflate was treated under identical conditions, ($\text{CH}_3\text{O}^{-}/\text{CH}_3\text{OH}$ at 50 °C, *no* elimination product was able to be detected, the only product deriving from double $\text{S}_\text{N}2$ substitution (Scheme 6). On the basis of the comparative results shown in these two schemes, we concluded that primary triflates must be very reluctant to undergo E2 eliminations. In order to unambiguously prove this, the reactivity of a simple *n*-alkyl triflate was examined the under identical conditions, and it was found that again, only substitution was observed (Scheme 7). Even its reaction with triethylamine leads only to substitution product.

To our knowledge, this particular synthetically important reactivity characteristic of *n*-alkyl triflates has not been specifically mentioned previously in the literature. However, there are a number of published examples where this property has been observed, with the lack of elimination allowing high yield substitutions of *n*-alkyl triflates in their reactions with nitrogen bases in the formation of ionic liquids and *N*-alkylpyridinium chromophores and semiconductor materials [8–12], as well as in radiofluorination experiments [13,14].

Interestingly, when DMSO is used as solvent in the reaction of 1-fluorononyl triflate **1a** with methoxide, double substitution to

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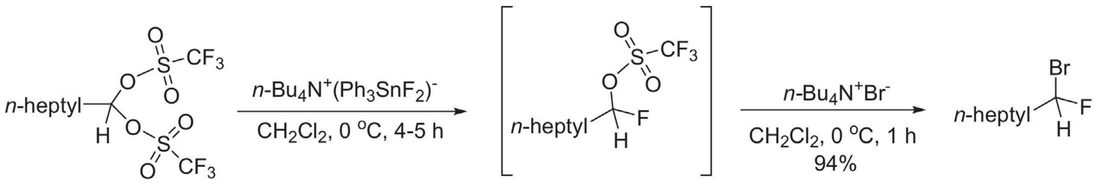


Scheme 1. Garcia Martinez' use of 1-fluoroalkyl triflates to prepare 1-halo-1-fluoroalkanes.

$$n\text{-C}_7\text{H}_{15}\text{-CH(OTf)}_2 \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt, 2h}]{[n\text{-Bu}_4\text{N}]^+[\text{Ph}_3\text{SnF}_2]^- \text{ (3 eq)}} n\text{-C}_7\text{H}_{15}\text{-CHF}_2 \quad 77\% \ [3]$$

$$n\text{-C}_7\text{H}_{15}\text{-CH(OTf)}_2 \xrightarrow[\text{10\% Ph}_3\text{SnF, 10\% }[n\text{-Bu}_4\text{N}^+][\text{HSO}_4]^-]{\text{KF (2 eq), CH}_2\text{Cl}_2\text{, rt, 30h}} n\text{-C}_7\text{H}_{15}\text{-CHF}_2 \quad 68\% \ [5]$$

Scheme 2. Conversion of 1,1 bistriflates to 1,1-diflurides via nucleophilic substitution.

$$n\text{-octyl-CH(OTf)}_2 \xrightarrow[\text{CH}_2\text{Cl}_2\text{ (0.25M)}]{\text{Et}_3\text{N-3HF (4 equiv)}} n\text{-octyl-CHF}_2$$

no additive, 40 °C, 2.5 h 81%

proton sponge (2 equiv), rt, 2.5 h 92%

Scheme 3. Conversion of 1,1 bistriflates to 1,1-diflurides using Et_3N-3HF.

form acetal **2** is not observed. Instead an almost quantitative yield of nonaldehyde is observed. Although this reaction is not of interest synthetically, we considered it a mechanistic curiosity. We believe that this reaction must proceed by means of initial nucleophilic attack of **1a** by DMSO, followed by a methoxide-assisted elimination to form the aldehyde, as shown in Scheme 8. The same conversion to aldehyde occurs in the absence of methoxide, under otherwise same conditions to provide 98% of aldehyde.

Another curious reaction was observed when 1-fluorononyl triflate (**1a**) was treated with DBU in dichloromethane, again in the hope of observing an elimination process. However, what was observed was a 48–50% yield of 1,1-difluorononane. What we are hypothesizing is happening here is that DBU undergoes a slow reaction that generates fluoride ion, which then reacts rapidly with remaining **1a** to form the difluoro product. Under this scenario, the maximum yield of difluorononane would be 50%, and that is what is observed. Although DBU is considered to be a relatively non-nucleophilic base, it is known to react readily with *n*-alkyl bromides and triflates [8]. Therefore it is proposed that DBU undergoes an S_N2 reaction with **1a**, followed by loss of fluoride, which then allows the reaction of fluoride with another molecule of **1a** (Scheme 9).

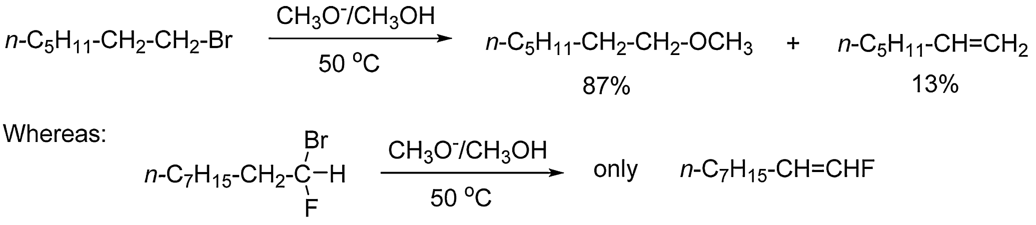
Having established that 1-fluoro-*n*-alkyl triflates readily undergo S_N2 nucleophilic substitution reactions, we turned our attention to exploring the diversity of such reactions. Most reactions were carried out in dichloromethane at room temperature, and almost all proceeded with excellent yields. Nucleophiles that were studied included cyanide, azide, acetate, formate, phenoxide, thiophenoxide, hexafluoroisopropoxide, benzimidazole, benztriazole, borohydride, xanthate anion, and the halides: fluoride, chloride, bromide and iodide. The exact conditions along with yields are given in Table 1.

Most of the reactions shown in Table 1 proceeded with excellent yields, with isolation being relatively easy. Many of the types of monofluoro compounds in the table, other than the halo, fluoro compounds, including the α-fluoronitriles [15], 1-fluoroalkyl azides [7], 1-fluoroalkyl acetates [16], and 1-fluoroalkyl benztriazoles [17] have only rarely been seen in the literature; others like the formate, the xanthate ester, the benzimidazole, the phenoxy, and the phosphonium salt derivatives appear to be unknown.

$$n\text{-octyl-CH(OTf)}_2 \xrightarrow[\text{CH}_2\text{Cl}_2\text{, 0 °C to rt, 18 h}]{\text{Et}_3\text{N-3HF (1.1 equiv)}} \underset{\textbf{1a} \quad 91\%}{n\text{-octyl-CHF(OTf)}} + \underset{5\%}{n\text{-octyl-CHF}_2}$$

(83% overall from aldehyde)

Scheme 4. Preparation of 1-fluorononane triflate.



$$n\text{-C}_5\text{H}_{11}\text{-CH}_2\text{-CH}_2\text{-Br} \xrightarrow[\text{50 °C}]{\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}} \underset{87\%}{n\text{-C}_5\text{H}_{11}\text{-CH}_2\text{-CH}_2\text{-OCH}_3} + \underset{13\%}{n\text{-C}_5\text{H}_{11}\text{-CH=CH}_2}$$

Whereas:

$$n\text{-C}_7\text{H}_{15}\text{-CH}_2\text{-}\overset{\text{Br}}{\underset{\text{F}}{\text{C}}}\text{-H} \xrightarrow[\text{50 °C}]{\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}} \text{only} \quad n\text{-C}_7\text{H}_{15}\text{-CH=CHF}$$

Scheme 5. Impact of α-fluoro substituent on E2 eliminations [7].